

5-Year Strategic Plan

2005 – 2010



A vital link in the food chain ifr.ac.uk



The Institute is located 6 kilometres west of Norwich on the Norwich Research Park, adjacent to the John Innes Centre and Sainsbury Laboratory, and the Norfolk & Norwich University Hospital, and ten minutes walk from the campus of the University of East Anglia.

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Vision

IFR's Vision is to be a world-leading contributor to harnessing food for health and controlling food-related disease

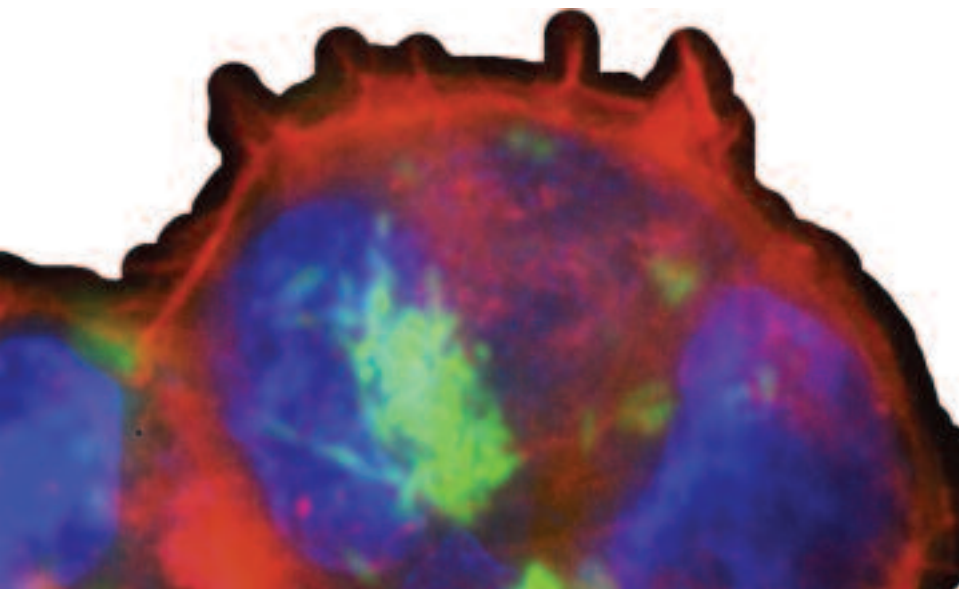
Mission

IFR's Mission is to

- Undertake international quality scientific research relevant to food and human health
- Work in partnership with others to provide underpinning science for consumers, policy makers, the food industry and academia

Objectives

- **Biology of the Gastrointestinal Tract – Understanding gut health and function**
How the gut responds to what we eat in both a negative and positive sense, how it functions and malfunctions
- **Nutrition, Diet and Health – Understanding how our diet influences our long-term health**
Cell, organ and whole body response to what we eat – the path to systems biology [post-genome integrative biology]
- **Food Safety**
How foodborne pathogens interact with the body and their elimination from the food chain
- **Food Innovation – Maintaining food quality with a healthy diet**
Meeting consumer need without affecting acceptability or compromising safety
- **Integrating tools and technologies – the Partnerships**
The technology to support the science and the tools to interpret the data and apply it in human health and wellbeing



Salmonella bacteria infecting epithelial cells (with red membrane and blue nucleus). These cells line the human gastrointestinal tract and are a target for invasion by *Salmonella*. By highlighting the bacteria with Green Fluorescent Protein, IFR scientists can see where they are expressing particular genes during infection.

Image: Dr Isabelle Hautefort (IFR)

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Preface

Our VISION (see Frontispiece) states our aspirations. With this Strategic Plan we are establishing a change in emphasis of our scientific direction. We are focussing our research across a range of food and nutrition-related disciplines with the goal of providing evidence for how food can be a means of improving the health of individuals and of preventing or reducing the risk of food-related diseases.

Our OBJECTIVES indicate the research areas we shall use to achieve the vision. The heart of this strategy will be to understand the biology of the GI tract as a holistic integrated biological system influenced simultaneously by signals from food components, systemic metabolism and an immensely complex colonic microbiota. Recent developments, particularly those emanating from the genomics revolution, give confidence that we can define how microbial communities play a central role in the maintenance of GI tract health and use commensal bacteria to promote health, preventing and curing disease states. They also enable us to advance our fundamental understanding of how phytochemicals are absorbed and metabolised by humans, particularly as they define the chemical nature and concentration of phytochemical-derived human metabolites that may offer health benefits.

Post-genomic developments in biology also enable a more fundamental understanding of the basis of nutrition, and we are developing a new programme of fundamental research in molecular nutrition and nutrigenomics. This will include understanding the need for and role of micronutrients. IFR expects to play a significant role in moulding the national strategy for nutrition.

The institute will continue to work on both commensal and pathogenic food bacteria, for the latter focussing on

Salmonella, *Campylobacter* and *Clostridium*. The aim of this work will be to understand their molecular biology and physiology within the host as well as ways of eradication from the food chain. In addition, the Institute's expertise in research into the basic physics and biology of the formulation of food will be used to develop improvements to such formulations in the light of nutritional needs. Our understanding of the GI tract will be accompanied by research to understand the physical chemistry of food behaviour in the gut.

Our vision for the future includes:

- Management of diet-related precancerous field changes in the GI tract mucosa and the effect of nutrition and gut microflora.
- Exploitation of dietary factors to suppress intestinal neoplasia in humans.
- Control of allergy and inflammatory disease via a new understanding of the interplay between the mucosal immune system, GI tract microflora and food associated allergens.
- Smart probiotics based on recombinant commensal bacteria and novel micro-encapsulation systems to deliver biologically active compounds to the gut will impact on allergy, food intolerance, inflammatory disease and cancer.

- New biomarkers of health and early maladaptive response to diet will be used to identify risk of disease.
 - Definition of genetic and epigenetic variables that explain individual differences in response to diet and quantification of individual variability in groups of the UK population.
 - New knowledge led exploitation of the protective compounds in fruits and vegetables and other foods that can help us to remain healthy.
 - Definition of “vulnerable” groups and individual genotypes with specific dietary requirements so as to reduce disease risk and morbidity.
 - Improved barrier and encapsulation systems in foods to deliver micronutrients and retain processability, stability and shelf-life.
 - The elimination or effective control of all existing bacterial pathogens in the food chain via new interventions and new vaccines.
 - Provision of fully quantitative microbiological food safety.
 - New foods that provide consumer benefit and diet related health advantages without compromising microbial safety.
 - Prediction, prevention or proactive management of the emerging new microbiological food safety issues.
- New insight into the effect of host stress on pathogens and strategies that avoid reliance on antibiotics in the food chain.

IFR's distinctive contribution to BBSRC's mission and strategic plan objectives

The above addresses well the requirements within BBSRC's mission “to advance knowledge and technology, and provide trained scientists and engineers, which meet the needs of users and beneficiaries (including the... food, healthcare... industries), thereby contributing to the economic competitiveness of the United Kingdom and the quality of life”.

With its proposed programme the Institute addresses issues within all of the main objectives of the current BBSRC Strategic Plan, especially within its ‘Healthy Organism’ priority area.



Professor DCS White, Director
August 2005

Delivery

The Research and Innovation Programmes

Our eight PROGRAMMES collectively contribute to the four broad areas of science in our Objectives; they are coherent activities, with not only individual identities, but also important interfaces and inter-relationships.

Programme G1
Gastrointestinal Biology and Health

Programme G2
Gut Microflora

Programme H1
Phytochemicals and Health

Programme H2
Micronutrients

Programme H3
Personalised Nutrition

Programme F1
Structuring Food for Health

Programme S1
Pathogens: Molecular Microbiology

Programme S2
Pathogens: Physiology and Predictive Ecology

Central to our strategy is to have a fundamental research base of the highest international quality, essential to address the needs of our various stakeholders. From this will emanate contributions to the store of scientific knowledge and understanding. We are further committed to technology transfer and the exploitation of our research, seeing this as an integral part of our activities, embedded throughout the work of the Institute.

The Partnerships

The research objectives in the portfolio of Programmes depend on the continued development and the maintenance of state of the art capability in several areas of scientific technology. Where these have broad impact for our future success they are managed as **Partnership** activities with direct support for the facility and skill base combined with Programme interaction.

Partnership BS
Bioinformatics and Statistics

Partnership TSB
Technologies for Systems Biology

Partnership RCS
Risk and Consumer Science

Partnership IMG
Imaging

The Innovation Agenda

The Institute is committed to developing further its entrepreneurial culture, considering IP potential at the inception

of a project and managing this potential alongside the scientific objectives.

Exploitation Platforms

Part of our strategy is to define a small number of activities that offer good potential for commercial development, termed **Exploitation Platforms**, and to develop these as businesses within a *Business Development Group*. These are, and will be, developments that have evolved from within the Programmes and have reached a stage where the opportunity of greater concentration of effort in their exploitation becomes viable and worthwhile. Which specific areas form the portfolio at any one time

will change, dependent upon the opportunities offered. Currently there are four:

Exploitation Platform MG
The Model Gut

Exploitation Platform MRI
Magnetic Resonance Imaging

Exploitation Platform NCYC
National Collection of Yeast Cultures

Exploitation Platform SFC
Sustainability of the Food Chain

Science in Society

The Institute has a tradition of professionally-supported outreach that dates back over 40 years and has been at the cutting edge of developments away from public 'understanding' towards concepts of awareness and involvement. Responsive to stakeholders, it thus invests in activities which maximise delivery of impartial, science-based information to inform debate and assist in the quality of

decision-making. Staff exploit the broadcast, print and e-media as a most effective tool for specialist through to mass communication of our science and innovation. IFR staff have an active relationship with the UK Parliament and contribute not only to national 'Science in Society' events but also more locally-based activity. We actively support school science programmes, in particular through the Teacher-Scientist Network.

Support

The Institute's *raison d'être* is science. The scientific effort is compromised if inappropriate time is spent on non-science functions. Effective management of a £15M pa turnover charity is only possible with a well-qualified, professional support team. IFR strategy is to ensure that it

has the skills and staffing necessary for effective delivery of services to science. As part of this strategy the Institute is assessing its needs going forward, and moving towards a joint services and administrative group with the John Innes Centre.

Programmes

Introduction

The **Gastrointestinal Biology and Health (G1)** Programme is one of overarching importance because the gut represents the interface between the human body and food.

The programme has a broader focus on gut biology and aims to advance our understanding of the gut as an integrated biological system, by interacting, especially with the **Commensals and Microflora (G2)** Programme to address this objective.

G1 focuses on host cell and tissue biology, particularly with reference to diet-related diseases of the colon, primarily cancer. The focus of G2 is on molecular microbiology of the complex microflora that are characteristic of the natural microbial world, and in particular on the role of commensal bacteria. The interface between these Programmes is in immunology, representing an exciting area of opportunity where advances in fundamental biology will translate into major applications. It is central to our initiative in GI tract biology and seeks to define the function of the gut microflora including inter-microbial communication and cross talk between microbes and the host, especially the mucosa and mucosal immune system.

The G1 Programme also contributes to our objectives in Nutrition, Diet and Health, but this area is predominantly addressed by two established and one proposed new Programme. Our very strong niches in micronutrition are represented by Programme H1 **Phytochemicals & Health** that investigates and exploits the properties of bioactive chemicals that are characteristic of plants and Programme H2 **Micronutrients** that deals with minerals and vitamins. The new Programme, **Personalised Nutrition (H3)**, reflects the growing importance of knowledge of the human genome and of individual genotype in underpinning the development of personalised nutrition.

In order to deliver our vision for health promotion via the diet we need a greater understanding of how the gastrointestinal tract (from the oral cavity to the colon) interacts with food structures to deliver macro- and micro-nutrients. This will be realised by interaction between the **Gastrointestinal Biology & Health (G1)** Programme and the **Structuring Food for Health (F1)** Programme, the latter capitalising on our established strengths in the biophysics of food structure to study how food structures can be manipulated to optimise delivery of macro- and micro-nutrients to the mucosa, including the mucosal immune system. The latter aspect is key to understanding and managing food allergy.

Pathogens: Molecular Microbiology (S1) focuses on the fundamental biology of two significant food-borne bacterial pathogens *Salmonella* and *Campylobacter*. Extensive use is made of functional genomics, and the resultant skill base in post-genomic technology is used in other Programmes. It is complemented by the **Pathogens: Physiology & Predictive Ecology** Programme (S2) which has a focus on the behaviour of pathogens within food, and builds on our unique expertise in the biology of *Clostridium botulinum*. The interface between the S1 and S2 Programmes is important in facilitating the broad exploitation of functional genomics and in grounding fundamental molecular microbiology with a practical food microbiology dimension. Food structure influences pathogen behaviour, and hence there is a synergy with the **Structuring Food for Health (F1)** Programme, to consider the impact of healthier (e.g. low salt) foods on microbial food safety. The **Commensals & Microflora (G2)** Programme also contributes to our food safety vision, providing a proactive dimension to the eradication of pathogens from the food chain.

Each Programme is subdivided into a number of projects. The titles of these are listed. In addition there are four cross-Programme projects, listed in both Programmes.

G1: Gastrointestinal Biology and Health

This Programme is focused on the maintenance of healthy function in the gastro-intestinal tract mucosa. It addresses its vulnerability to malfunction and disease states, including allergic reaction and cancer. It aims to understand the response of the gut epithelium to food allergens and the GI tract microflora and to define the central role of inflammation in the development of disease. The ultimate goal is to develop strategies for the maintenance of gut health and the prevention of disease based on new insights into the biology of the gastro-intestinal tract.

5 Year aims

- Identify the mechanisms underlying the effects of diet and the colonic microflora on epithelial cell proliferation and differentiation.
- Identify diet-related precancerous changes in the GI tract using post-genomic approaches, and develop new insights into the causal relationship between systemic and local inflammatory signals and GI tract cancers.
- Characterise the interaction of components of the gut epithelium and immune system with gut microbes and food allergens, leading to the control of allergic reactions and inappropriate inflammatory responses.
- Determine how the structural and physicochemical properties of food allergens influence their availability for transport at the mucosal surface.

The alimentary tract is specialised for the efficient absorption of nutrients and fluid, but the mucosal surfaces also provide both physical and immunological barriers against infectious agents and toxins in the gut contents. These dual functions are achieved by the epithelial cells lining the lumen, and the cells of the gut-associated lymphoid system, which maintain a tightly regulated repertoire of tolerance and immune responses to intraluminal antigens. The objective of this Programme is to characterise the effects of food components and the gut microflora on the epithelial physiology and immune responses of the mucosa. Success

depends on joint work via a Cross-Programme Project with the related Programme **Commensals & Microflora** (G2), enabling integration of research on intestinal epithelial physiology, gut immunology and gut microbiology. The Programme is of major significance for public health, and it directly addresses the future strategic needs of food manufacturers, for whom "gut health" is an important target for functional foods.

Diseases of the gut are major causes of ill-health and premature death in the UK and other western countries. The alimentary tract is particularly vulnerable to a number of inflammatory conditions and cancers. For example, colorectal

G1: Gastrointestinal Biology and Health

carcinoma is about four times more common in industrialised countries than in the developing world, and it is the second most common cause of death from cancer in the UK. The incidence rates for oesophageal adenocarcinoma and its precursor lesion, Barrett's oesophagus, are rising steeply throughout North America and Europe. Currently, these conditions are more common in the UK than in any other country. Our work depends on established active collaboration with clinical groups, including work with the Norfolk and Norwich University Hospital (NNUH) focused on the relationship between aspects of nutrition and oesophageal adenocarcinoma.

Using a combination of proteomics and analyses of aberrant CpG-island methylation, we have established that precancerous field changes are detectable in the human colonic mucosa, well in advance of the appearance of morphological lesions. This key finding provides the hypothesis drive for our future work on the vulnerability of the gut to cancer, and provides novel surrogate biomarkers with which we will investigate the adverse and beneficial effects of diet. We will continue our pioneering work on the use of human DNA residues in faecal samples to measure the methylation of genes involved in precancerous field changes (epigenetic drift). Already, we have shown that this approach has the potential to provide biomarkers of

vulnerability, suitable for use at the population level. We plan to use a combination *in vitro*, animal and human-intervention techniques, together with proteomics and other post-genomic methods, to characterise and define the effect of diet on pre-cancerous field effects in both colonic and oesophageal mucosa. We will explore the hypothesis that the vulnerability of the alimentary tract to cancer is causally linked to obesity-related systemic inflammatory signals, and determine the extent to which dietary factors such as polyunsaturated fatty acids, phytochemicals and fermentable substrates can be used to modify epithelial cell proliferation and apoptosis, and hence to suppress intestinal neoplasia in humans. This work involves interaction with **Phytochemicals & Health** (H1) and **Micronutrients** (H2). The integrated, evidence-based approach to gastrointestinal cancer prevention provides a novel niche for IFR that is distinct from most other centres where the emphasis is on tumour biology and therapy.

Having recently demonstrated that certain bacteria can up-regulate the number of fully operational M cells by inducing production of the cytokine MIF by the host gut immune system, we will use this observation as a starting point from which to explore the role of lympho-epithelial cross-talk in gut function. We will also build on our niche

expertise in the biology of dendritic cells, which acquire antigens from the gut lumen, and shape the response of T cells in the gut-associated lymphoid tissue and beyond. We have established the critical role of systemic and gut-derived dendritic cells in food allergy, and demonstrated that the characteristics of apoptosis in dendritic cells from allergic mice differ markedly from those of non-allergic mice. We will extend our work on the role of both gut-derived and systemic dendritic cells in the genesis and maintenance of allergic reactions to food in humans. In collaboration with **Commensals & Microflora** (G1) we will test the hypothesis that probiotic bacteria can restore a balanced immune response in allergic subjects. We will also use molecular approaches to investigate the role of colonic dendritic cells in modulating T cell responses to the microflora.

Building on our recent work on the transport of allergenic proteins across the intestinal epithelial barrier, we plan to develop this area as a Cross-Programme project with **Structuring Food for Health** (F1). Initially, we will focus on how the structural and physicochemical properties of proteins, and particularly their interactions with lipids in the food matrix, determine their availability for transport at the mucosal surface.

Programme Leader:
Professor Ian Johnson

Project Leaders

Professor Ian Johnson

Cross-Programmes

Dr Alan Mackie

Professor Claudio Nicoletti

G2: Commensals and Microflora

This Programme is concerned with non-pathogenic, 'commensal' bacteria and the analysis of complex microbial communities, notably those inhabiting the gastrointestinal tracts of humans and animals. It aims to define how microbial communities play a central role in the maintenance of gastrointestinal (GI) tract health. It involves novel approaches to the biocontrol of pathogens and has an emphasis on lactic acid bacteria and bifidobacteria.

5 Year aims

- Provide new insights into complex GI tract microbial communities including their molecular profiling and communication and cross-talk within and between these communities and the host.
- Apply functional genomics to selected species of the commensal lactic acid bacteria, including bifidobacteria.
- Develop a predictive approach to metabolic engineering, based on insights into genomic plasticity and metabolic flux control.
- Develop novel, biologically-based antimicrobials to prevent and cure infectious diseases and microflora imbalances without recourse to conventional antibiotic treatment.
- Develop and exploit 'SMART' probiotics for man and animals to eliminate pathogens, alleviate inflammatory disease and deliver vaccine antigens.

The complex microbial communities that inhabit the gastrointestinal tract play a vital role in maintaining gut health and homeostasis but the mechanisms involved are poorly understood. The role of cross-talk and communication both within the microbial community and with the host are of central importance. We will use molecular approaches to advance understanding of these processes and seek to exploit the knowledge gained. Success depends on joint work with the related Programme **Gastrointestinal Biology & Health** (G1) enabling integration of research on gut microbiology, gut immunology and

intestinal epithelial physiology. Our focus on the biology of the lactic acid bacteria and bifidobacteria is relevant to the food fermentation and probiotics industries and supports these sectors of functional and fermented food manufacturing. We maintain a niche activity in the development and exploitation of natural antimicrobials that contributes to the proactive dimension of our food safety mission.

We will maintain a well established expertise in the molecular genetics of lactic acid bacteria. We have completed a collaborative project to determine the genome sequence of the prototype strain

G2: Commensals and Microflora

Lactococcus lactis MG1363 that was developed at IFR. We will develop functional genomics with an initial focus on metabolism, especially in the context of metabolic engineering. There is an excellent opportunity here to use *L.lactis* as a relatively simple model with which to probe genomic plasticity and the rules that govern metabolic flux control. We will extend our interest in fundamental molecular microbiology of commensal bacteria to other species of relevance to the programme, including *Lactobacillus* strains with demonstrated ability to compete with pathogens, and *Bifidobacterium* species with an established association with positive health status in the gastrointestinal tract. For selected strains we intend to facilitate new whole genome sequencing projects.

The GI tracts of humans and animals harbour large and complex populations of micro-organisms that play a vital role in the maintenance of health. We will develop and apply molecular methods to probe the population dynamics of these complex microbial communities. Complex microfloras represent an attractive target for metagenomic projects and there is international interest in a major project to determine the sequence of the human gastrointestinal tract microbial metagenome. We will seek to be involved with such an international initiative but also explore innovative approaches to shortcut this bulk

sequencing process and sample community DNA.

One of the most interesting and challenging aspects of microbiology is the behaviour of individual species in the context of their natural environment and this will be a focus for future work on the microflora of the gastrointestinal tract. We will explore the interactions and communication processes that take place between bacterial species in the context of the complex microflora, and probe the two way communications that take place with the host. In this regard we will focus on i) the impact of bacteria on the gut epithelium and the mucosal immune system and ii) the impact of stress-related hormones such as noradrenaline on the bacterial community. This activity will interface with and complement work in

Gastrointestinal Biology & Health

(G1). In particular, we will investigate the cross talk between GI tract bacteria and the host immune system, focussing initially on the interplay between lactic acid bacteria and dendritic cells.

Work in this Programme impacts on food safety as commensal bacteria have the potential to compete with, and exclude, pathogens. We will continue to investigate their potential for pathogen control and eradication. Specifically, we will seek to understand the process of host colonisation focusing on surface structures, including adhesins and the interaction of bacteria with host epithelial cells and the host immune

system. The control of pathogens can be improved by the exploitation of a range of naturally occurring antimicrobial agents, including bacteriocins, lantibiotics and bacteriophage. With respect to lantibiotics we will isolate novel molecules from nature using new molecular screening approaches and perfect existing structures by peptide engineering. We will build on our strong IP position in the exploitation of bacteriophage endolysins as novel targeted antimicrobials and for bacterial detection. The immediate focus will be on the cloning and characterisation of new endolysins that are active against clostridia. We will investigate their potential in the context of the gastrointestinal tract, with the intention of controlling disease states caused by *Clostridium perfringens* and *C. difficile*.

We will build on our strengths in the exploitation of lactic acid bacteria as GI tract delivery vehicles for a range of biologically active molecules. This includes targeted antimicrobial compounds, modulators of the immune system such as anti-inflammatory cytokines and vaccine antigens. This approach offers a range of biotechnological opportunities with enormous potential to address GI tract disease states, allergic and intolerance reactions, the maintenance of GI tract health and the elimination of pathogens in both man and food animals.

Programme Leader:
Professor Mike Gasson

Project Leaders

Professor Mike Gasson

Dr Arjan Narbad

Dr Claire Shearman

Cross-Programme

Professor Mike Gasson

H1: Phytochemicals and Health

This Programme is concerned with the relationship between phytochemicals in the diet and the prevention of chronic disease. The focus is on flavonoids, folates and glucosinolates and their potential to reduce the risk of cardiovascular disease (CVD) and cancer in healthy individuals and high risk groups. The provision of dietary advice to policy makers and the development of foods with enhanced levels of protective phytochemicals provide practical application of the research.

5 Year aims

- Elucidate the metabolic processes and pathways of phytochemical absorption, metabolism and excretion.
- Quantify the role of human genetic variation in determining folate status, and the effect of folates on influencing risk of CVD and cancer.
- Identify polyphenol metabolites that influence the risk of CVD.
- Determine the processes by which glucosinolate metabolites influence the risk of cancer, and how this is modulated by human genetic polymorphism.
- Develop plant-based and processed functional foods to deliver bioactive phytochemicals that reduce cancer risk.

In this Programme we investigate the relationship between the levels and types of plant secondary metabolites in the diet and the incidence of chronic disease. We will elucidate biological processes at the molecular, organism and population level and thereby provide the evidence for dietary recommendations, not only for healthy individuals but also high risk groups. The emphasis is on a relatively small number of phytochemicals, including selected flavonoids, folates, and glucosinolates. Major activities are: analysis of plants and foods for phytochemical composition; analysis of human plasma and urine for phytochemical metabolites; cellular and tissue studies to investigate mechanisms of action; human

intervention studies, including the role of genetic polymorphisms in determining metabolism of phytochemicals and their health benefits. The Programme objectives depend on a systems biology approach. To date, we have invested most heavily in gene expression studies with Affymetrix™ whole genome human arrays and in future will use both proteomics and metabolomics.

There are two main strategic objectives: The first is the manner by which phytochemicals (mainly flavonoids and folates) can maintain and improve vascular health. Gene and protein expression will be studied in endothelial cell cultures to understand fundamental mechanisms. This will be combined with physiological and biochemical

H1: Phytochemicals and Health

assessments on individuals within dietary intervention studies. These include individuals at high risk of CVD, such as those with Type 2 diabetes. The second strategic objective concerns the manner by which certain phytochemicals can reduce the risk of cancer. This largely involves studies with glucosinolates and their derivatives, and involves research with a variety of cell types and, where unavoidable, animal models. This work involves interaction with **Gastrointestinal Biology & Health (G1)**. We have a particular focus on the prevention of prostate cancer. This involves studying global gene and protein expression in healthy and cancerous tissue, combined with long term intervention in men at high risk of prostate cancer using glucosinolate-enriched broccoli. As part of these studies, we investigate the interaction of isoflavones and organic forms of selenium with glucosinolate degradation products in perturbing gene and protein expression and physiological processes. This work involves interaction with **Micronutrients (H2)**.

We will determine the absorption, bioavailability and metabolism of flavonoids, through both cell culture studies and human intervention studies with flavonoid-rich foods. We will determine the means by which flavonoid metabolites perturb gene and protein expression in human immune and endothelial cell cultures, and quantify changes in biomarkers of

cardiovascular health in healthy and high risk groups following dietary intervention with flavonoid-rich foods. High risk groups will include those with Type 2 diabetes, those with elevated plasma cholesterol and those with intermittent claudication.

We will quantify changes in biomarkers of cardiovascular health in healthy and high risk groups following dietary intervention with a high food folate diet, a folic acid supplement and a 5-methyltetrahydrofolate dietary supplement. The potential importance of genetic polymorphisms of 5-methyltetrahydrofolate reductase, methionine synthase and methionine synthase reductase will be explored. We will further develop and validate our *in vivo* kinetic model for folate absorption and metabolism in humans, and specifically seek to elucidate whether the initial site of folate and folic acid biotransformation following ingestion occurs at the absorptive mucosal membrane, or within the liver.

We will quantify changes in gene and protein expression and physiological processes in colon, breast and prostate cell cultures induced by glucosinolate metabolites such as isothiocyanates (ITCs), and quantify synergistic and antagonistic interactions with other dietary compounds and their human metabolites. We will seek to identify other metabolites in broccoli extracts that may be of biological importance in influencing risk of carcinogenesis. In collaboration with **Micronutrients (H2)**,

we will study the interaction between ITCs and selenium in mediating gene and protein expression in cell cultures, and quantify pathways of selenium metabolism in humans. We will investigate the manner by which sulforaphane, the predominant ITC obtained from broccoli, can induce the expression of the transcription factor KLF4 in cell cultures and, in collaboration with **Gastrointestinal Biology & Health (G1)**, animal models and explore its consequences for downstream gene and protein expression. We will quantify the consequences of human polymorphism at the GSTM1 locus on the metabolism and biological activity of isothiocyanates in humans. We will undertake a five year human intervention study with men at high risk of prostate cancer to study how a high broccoli diet can perturb gene expression in prostate tissue, and whether these changes are consistent with a reduction in risk of carcinogenesis, and to what extent the changes are influenced by GSTM1 genotype.

In partnership with industry, we will develop functional foods, including high glucosinolate broccoli, and processed products that provides several phytochemicals that interact in a synergistic manner to reduce cancer risk.

Programme Leader:
Professor Richard Mithen

Project Leaders

Paul Finglas
Dr David Hughes
Dr Paul Kroon
Professor Richard Mithen

Cross-Programme

Dr Tony Michael

H2: Micronutrients

This Programme aims to understand the relationship between micronutrient intake and health, diet-gene interactions and the reasons for individual variability. The emphasis is on iron and selenium, reflecting public health concerns. A combination of cell and molecular biology and human metabolic studies are used to study dietary requirements for optimal health, prevention of chronic disease, and the effect of common polymorphisms.

5 Year aims

- Generate information on dietary requirements for key micronutrients that promote optimal health and reduce the risk of marginal deficiency or excess.
- Develop biomarkers of dietary exposure and nutritional status
- Investigate the role of micronutrients in preventing chronic disease by examining diet-gene interactions and the effects of common polymorphisms on metabolism

The overall aim of the Programme is to understand the relationship between micronutrient intake and health and the reasons for individual variability. It requires multidisciplinary research of a fundamental and strategic nature to address gaps in our understanding of micronutrient metabolism and dietary requirements, and to provide an evidence base for policy, advice on healthy eating and the development of improved foods with respect to micronutrient supply. This research is crucial to a range of stakeholders, including the UK Food Standards Agency and the food industry's growing investment in nutritional aspects of food, with potential for evidence-based health claims and the opportunity of developing products tailored for specific phenotypes and genotypes. In addition, we will continue to advise industry on bioavailability and fortification issues and undertake studies on micronutrient bioavailability and bioactivity.

Public health issues are core to this Programme, therefore we have a major emphasis on iron and selenium, for which we have an established international reputation. With respect to iron homeostasis, we will continue to explore the effects of dietary and systemic factors on bioavailability. We are attempting to develop an immunoassay for hepcidin, a newly discovered iron regulatory protein, and we will investigate the expression of hepcidin (at the level of transcription and post-translational processing) in pregnancy, a physiological condition that is associated with increased iron requirements. Building on our work on iron overload disorders (haemochromatosis) we are collaborating with the N&NUH to set up a non-invasive method for quantifying liver iron stores using MRI. Our hypothesis is that carriers of *HFE* mutations (heterozygotes) have subtle changes in iron metabolism which are

H2: Micronutrients

associated with higher transferrin saturation, and if this results in tissue iron loading there may be an increased risk of free-radical mediated damage.

We will continue to investigate the effect of different forms and doses of selenium on bioactivity, in particular mechanisms of anti-cancer activity. Interacting with **Phytochemicals & Health (H1)** and **Gastrointestinal Biology & Health (G1)** we are investigating the effect of low selenium status, and the role of selenomethionine and Se-MC (found in allium and brassica vegetables) on immune function, and the role of selenium in CpG-island methylation in colon cells. In order to fully understand the impact of dietary selenium on human health, we will be developing methods for measuring selenium species in foods and body tissues.

We will use a range of post-genomic and stable isotope techniques to develop biomarkers of zinc status, working in collaboration with colleagues with established programmes in developing countries where zinc deficiency is a major problem. Conversely, we hope to employ metabolomics to develop biomarkers of high environmental

exposure to elements such as manganese, a particular problem in some parts of Europe.

In all our studies, we aim to unravel mechanisms of absorption, excretion and bioactivity, and to characterise the extent to which individuals can maintain homeostasis under different dietary conditions. The genetic control of mineral metabolism is investigated in cell culture model systems and human tissues using transcriptomics and proteomics. Individual variability is approached by examining differences in physiological requirements and genotype.

We are collaborating with colleagues at the University of East Anglia and the St Thomas' Hospital Adult Twin Register, the most extensively phenotyped database in the world, to study diet-disease relationships in the context of an individual's genetic background. Diet-gene interactions will be studied by analysing dietary patterns and disease risk in a co-twin case control study, starting with the relationship between vitamin D and health, and leading on to further dietary assessment to test diet-disease hypotheses. We plan to work with **Personalised Nutrition (H3)** to

establish an NRP cohort for prospective dietary intervention studies examining diet-gene interactions and the effects of common polymorphisms on metabolism and risk of chronic disease.

Wherever possible we will use external funding to develop practical strategies for the prevention of micronutrient deficiencies. For example, we are working with the food crops community in the UK to help optimise the selenium content and species in plant crops in order to improve the selenium status of the UK population. We are also involved in a worldwide biofortification programme, funded by the Bill and Melinda Gates Foundation, coordinated by HarvestPlus, whose aims are to increase the iron, zinc and vitamin A content of staple foods in developing countries. We are currently developing an assay for plant ferritin, a recently recognised route for increasing the iron content of plant foods, and contributing expertise on micronutrient bioavailability.

Ways to enhance delivery of micronutrient uptake will be addressed with the **Structuring Food for Health (F1)** programme.

Programme Leader:
Professor Susan Fairweather-Tait

Project Leader

Professor Susan Fairweather-Tait

H3: Personalised Nutrition

This future Programme will focus on the role of the individual human genotype and its impact on phenotype with respect to the interplay between diet and health. It will build the science needed for the realisation of the 'personalised nutrition' concept.

5 Year aims

- To understand the relationship between human phenotype and the response of the body to nutrients, with particular reference to those areas of diet-health being developed in other Programmes.
- To provide guidance to policy-makers on life-stage nutritional guidelines.
- To provide guidance to policy-makers on life-style nutritional guidelines.
- To provide guidance to industry on food formulation for target groups.
- To contribute to upstream engagement with stakeholder groups on personalised nutrition concepts.

Nutrition and health research is focussed on the prevention of disease by optimising and maintaining cellular, tissue, organ and whole-body homeostasis. This requires understanding, and ultimately regulating, a multitude of nutrient-related interactions at the gene, protein and metabolic levels.

Much of the variability in risk of chronic disease results from interactions between individual genomic variation and environmental exposures, including diet. Identification of specific gene-nutrient interactions opens up possibilities for a more individualised approach to dietary recommendations based on genotype and a more effective strategy for disease prevention through dietary modification. In a limited number of cases diet-gene interactions are well-defined. For example, single nucleotide polymorphisms (SNPs) in the methyl tetrahydrofolate reductase gene interacts with dietary folate and

riboflavin to determine homocysteine status. Also, the haemochromatosis gene (HFE gene) affects susceptibility to iron overload. However, for most diet-gene interactions, their impact on whole body metabolism and functional nutrient status, and the subsequent effects on chronic disease risk, are poorly characterised.

A particular focus of this Programme will be to explore interactions between nutrients and candidate genes in order to elucidate mechanisms underlying the effect of diet on chronic diseases. There is a need to identify SNPs in key target genes which result in proteins with altered function as well as to determine how variations in the nutritional 'environment' of candidate genes and/or proteins modify the phenotype. Further research is needed on variations in post-transcriptional and post-translational modifications of protein expression that modulate, or are modulated by, the effects of dietary components.

In combination with whole body approaches to investigate mechanisms underlying development of high-risk phenotypes, these will provide powerful strategies that have not yet been fully exploited in diet-health research. Approaches using human, animal or cell models will be developed to:

- a) identify nutrient-sensitive gene polymorphisms and epigenetic modification;
- b) elucidate the molecular, cellular and metabolic pathways through which interaction between dietary components and individual genomic variation leads to development of high-risk phenotypes.

This is a new Programme, for which we plan to recruit an international-leading scientist to lead and deliver research. The details of the Programme will depend upon the exact research drivers identified by the person appointed.

F1: Structuring Food for Health

This Programme will seek to describe the rules that govern the assembly of natural and fabricated food structures and their subsequent disassembly in the gastro-intestinal tract. It will advance understanding of the way that food structure and processing affect macro- and micro-nutrient release and allergenic potential. This will contribute to the delivery of acceptable and healthy food choices that are necessary for reducing diet-related diseases and developing knowledge-based ways of reducing allergenicity of foods.

5 Year aims

- To understand how to control the behaviour of synthetic and natural biopolymeric food structures in the gastrointestinal tract and hence improve systems to deliver biologically active components, particularly nutrients.
- To investigate how manipulating the properties of the interfacial layer can alter the structure and texture of food colloids with a view to developing novel approaches to improving the nutritional quality of food emulsions.
- To gain new insights into how food structures, particularly aggregated networks and protein-stabilised colloidal structures, may alter the allergenic potential of foods.
- To understand the molecular events surrounding the uptake by the gut mucosal barrier of colloidal structures stabilised by food allergens.

Many diet-related diseases result from unbalanced intake of macronutrients including biopolymers (starch and non-starch polysaccharides), fats and protein. It is also emerging that the food matrix and processing itself may radically affect allergenic potential although this remains unexplained. During digestion and uptake food structures (formed largely from macronutrients) undergo a complex series of physical processes together with chemical and enzymatic changes. Food structure therefore ultimately influences delivery of nutrients to the

human body and subsequent physiological (including allergenic) activity. It is our objective to understand the rules governing the assembly of natural and fabricated (including nano-scale) food structures, their subsequent disassembly during digestion and the impact this has on nutrient (including food allergen) release and uptake in the gastrointestinal (GI) tract. We will take a materials science approach to understanding these processes, based on skills in biophysics, biochemistry and molecular biology, and internationally recognised expertise in biopolymers and

F1: Structuring Food for Health

food colloids which, together with close interactions and synergies with **Gastrointestinal Biology & Health (G1)**, is unique.

We will determine the underlying physical principles controlling the assembly, breakdown and behaviour of synthetic and natural biopolymeric food structures. This will allow us to control their behaviour in the gastrointestinal tract and design structures which control release of active ingredients (e.g. aromas, flavours, micronutrients). It will also provide an understanding of the effect of the environment of the GI tract on the properties of plant cell walls and the release of nutrients contained within plant cells. We propose that the attractive interaction between oppositely charged biopolyelectrolytes (and biopolyampholytes e.g. gelatin, bovine β -lactoglobulin) can be used to assemble environmentally responsive network structures. We will investigate the assembly of biopolymer network structures formed from polysaccharide polyelectrolytes (e.g. pectin, alginate), and protein biopolyampholytes. Intermolecular interactions which affect the assembly process and the environmental responsiveness of the structures as a function of pH, ionic strength and enzymatic degradation will be determined.

We will investigate the influence of interfacial and colloidal structures of

multiphase foods on their stability and texture (rheology), digestibility and bio-accessibility of nutrients. In conjunction with the Imaging Partnership, we will study how changing the properties of the interfacial layer can alter the structure and texture of food colloids with a view to developing novel approaches to improving reduced fat food emulsions. This will be realised by investigating factors determining the stability of multiple emulsions, and the colloid functionality of interesterified triacylglycerols which possess reduced energy content. In addition approaches to controlling satiety by modulating rates of lipid digestion through manipulating interfacial properties of emulsions will be investigated in partnership with the Model Gut Exploitation Platform.

Many food structures (including protein-stabilised colloidal structures) are developed from unfolded proteins which interact to form aggregated networks. These networks, and their association with lipid, confer uncharacterised adjuvant effects relevant to understanding how structural features and physicochemical properties of proteins affect allergenicity. The molecular events involved in allergenic protein network formation in colloidal structures and their behaviour in the gut will be investigated using model allergenic proteins drawn from the

prolamin and cupin superfamilies. Assessing effects on allergenic potential will capitalise on international collaborations with world-leading clinical researchers, particularly through the IFR-led EU Integrated Project 'EuroPrevall'. The understanding generated will allow the development of knowledge-based food allergen management and will underpin regulatory assessment of the allergenic potential of novel foods and processes. Lastly, in collaboration with the **Gastrointestinal Biology & Health (G1)** Programme we will seek to increase our understanding of the molecular events surrounding the uptake of colloidal structures stabilised by food allergens by the gut mucosal barrier, using model systems (including *in vitro* epithelial cell culture systems for M cells and dendritic cells) developed within G1.

Through collaboration with industry the outputs of this Programme will lead to the delivery of the healthy food choices to consumers necessary for reducing diet-related diseases, and will underpin the development of personalised interventions (foods and/or nutraceuticals) required to improve health, based on the future outputs of **Personalised Nutrition (H3)**.

Programme Leader:
Dr Clare Mills

Project Leaders

Dr Clare Mills

Dr Steve Ring

Dr Pete Wilde

Cross-Programme

Professor Ian Johnson

S1: Pathogens: Molecular Microbiology

This Programme is focused on the fundamental molecular microbiology of two major causes of food poisoning which have distinct lifestyles: *Salmonella* and *Campylobacter*. The emphasis is on the use of functional genomics to advance understanding of pathogenesis and environmental stress response. This new insight will be used to develop novel interventions to control pathogens in the food chain.

5 Year aims

- Improve understanding of pathogenesis and environmental stress response in *Salmonella* and *Campylobacter*.
- Identify how *Salmonella* and *Campylobacter* thrives in food-relevant niches, including novel environments such as bacterial biofilms.
- Create DNA microarray compendium databases of gene expression profiles for *Campylobacter* and *Salmonella*.
- Define the mechanisms driving genomic variation and virulence in *Campylobacter* for the differentiation of disease-causing strains in epidemiological studies.
- Develop novel intervention strategies to eliminate *Salmonella* and *Campylobacter* from the food chain.

We aim to reduce the incidence of food-borne disease by discovering new approaches to eliminate bacterial pathogens from the food chain, and protect humans from infection. We will advance the fundamental biology of *Salmonella* and *Campylobacter* using a functional genomics approach. We will build on well-established research in molecular microbiology that emphasises the basis of bacterial virulence and the response of bacteria to their environment, including the effects of stress. Understanding these phenomena will provide new insights into bacterial food poisoning and generate novel, knowledge-led interventions that will reduce the load of bacterial pathogens in the food chain.

The availability of whole genome sequences and related post-genomic technologies allow us to answer holistic questions about gene expression at the level of the entire bacterial genome. IFR is a world leader in the DNA microarray analysis of *Salmonella* gene expression. We will maintain and build on our state-of-the-art functional genomic capability and apply it to advance the fundamental biology of *Campylobacter* and *Salmonella*, which represent distinct scientific challenges. *Salmonella* is well characterised with a good genetic toolbox that facilitates the pursuit of more difficult questions, such as its behaviour inside the host. In contrast, *Campylobacter* is poorly understood and technically more challenging. These

S1: Pathogens: Molecular Microbiology

two pathogens have evolved very different strategies for success, adding to the importance of understanding their respective fundamental biology in relation to infection.

We will continue a range of studies to assess the effect of a variety of environmental stresses on gene expression in *Campylobacter* and *Salmonella*. Because of their relevance to infection we will focus initially on oxidative stress, iron stress, phosphate starvation and nitric oxide stress, and the most relevant bacterial regulons.

Campylobacter is a particular challenge. Unlike *Salmonella*, which has a relatively stable genome, *Campylobacter* uses genomic variation as a key mechanism to survive stressful environments and avoid host defences. Here, DNA sequencing, gene expression analyses and proteomics will be exploited alongside targeted gene knockouts. The basis of pathogenicity of individual *Campylobacter* isolates is poorly understood and knowledge-led control strategies do not yet exist. Our *Campylobacter* research is supported by exclusive access to a recently-completed genome sequence that identifies important new genes. We will address: the genetic diversity and biodiversity of *Campylobacter* strains using functional genomics; the role of *Campylobacter* 2-component systems in infection, colonisation and bacterial adaptation to stress and survival in food-relevant

environments; the role of *Campylobacter* plasmids in virulence, drug resistance and survival; our approach benefits from our established DNA microarrays and our well-defined *Campylobacter* proteome map.

IFR is a world leader in the analysis of *Salmonella* gene expression during infection of cultured mammalian cells, and we recently succeeded in obtaining gene expression profiles from *Salmonella* during colonisation of the mouse gut. Gene expression profiling of bacterial pathogens during colonisation is allowing us to understand basic biological processes, such as core metabolism, that occur within the animal gut. Interacting with **Gastrointestinal Biology & Health (G1)** and **Commensals & Microflora (G2)**, we will investigate cross-talk between pathogenic bacteria and the host.

We will develop novel methods for analysing co-regulation of gene expression by building and interrogating our own Compendium Databases, which will contain several hundred gene expression profiles of *Salmonella* and *Campylobacter*, and use this to drive a new Systems-led approach. In collaboration with the **Technologies for Systems Biology (TSB) Partnership** we will build a detailed understanding of the interplay and cross-talk between key bacterial regulatory proteins using AQUA, a method for accurately quantifying proteins. This will allow us to establish

the stoichiometry of key proteins both *in vitro* and during infection.

Research is integrated with that in **Pathogens: Physiology & Predictive Ecology (S2)** and this will establish IFR as a world leader in the application of knowledge-led approaches to food safety. In particular, it facilitates a molecular approach to practical issues of food protection. Together we aim to discover the basis of *Salmonella* attachment to vegetable surfaces and biofilm formation on abiotic surfaces. We will determine the mechanism used by *Salmonella* to survive acidic environments following treatment with organic acids used as food preservatives. Similarly, we will investigate the mechanisms by which *Campylobacter* survives in food-relevant niches. We now understand gene expression during lag phase and will exploit this information to find new ways to prevent *Salmonella* from initiating growth.

Outputs from the Programme will contribute to the elimination of *Salmonella* and *Campylobacter* from the food chain. We have recently identified a novel *Salmonella* target gene which could reveal an unexplored aspect of the infection process that could be sensitive to antimicrobial or vaccine-based approaches.

Programme Leader:
Professor Jay Hinton

Project Leaders

Professor Jay Hinton

Dr Bruce Pearson (Acting)

Cross-Programme

Professor Tim Brocklehurst

S2: Pathogens: Physiology and Predictive Ecology

This Programme will develop knowledge-led approaches to microbiological food safety, based on advanced understanding and improved prediction of pathogen behaviour in food. It includes well-established, internationally competitive work on quantitative microbiology and the microbial physiology and molecular biology of *Clostridium botulinum*.

5 Year aims

- Better understanding and improved prediction of pathogen behaviour in food, leading to knowledge-led approaches to food safety (e.g. new ways to remove *Salmonella* from ready-to-eat vegetables).
- Advance the functional genomics and physiology of *Clostridium botulinum* delivering improved microbiological food safety with respect to the foodborne botulism hazard.
- Better understanding of lag time variability leading to improved prediction of *C. botulinum* growth
- Provide a platform for fully quantitative microbiological food safety.
- Develop novel approaches for stochastic modelling of single cells in mixed populations.

We will advance understanding of the behaviour of pathogens in food and improve its prediction, contributing to our vision for the elimination of existing bacterial pathogens from the food chain and the prevention of emerging bacteriological food safety problems. The latter might occur, for example, through a reduction in the use of preservatives, the increased sales of chilled foods or the introduction of new food types and processing technologies. A distinctive feature of this Programme is its multidisciplinary nature. There is an emphasis on microbial physiology and microbial ecology together with strong predictive microbiology and an element of molecular microbiology. We will deliver the IFR mission on food safety by interfacing with fundamental

molecular biology in **Pathogens: Molecular Microbiology (S1)** and quantitative microbiological risk assessment in the Partnership **Risk & Consumer Science (RCS)**.

The Programme includes our well established niche expertise in anaerobic microbiology, especially the control of *Clostridium botulinum*. The proposed work will extend understanding of the physiology and molecular biology of this important pathogen. We will contribute to UK food safety by delivering an improved capability to predict the behaviour of *C. botulinum* in food environments. We will establish why lag phase is so variable for *C. botulinum*, identify which stages of lag are most variable, and develop a better prediction of lag time under food-relevant

S2: Pathogens: Physiology and Predictive Ecology

conditions. We have an outstanding opportunity to advance the molecular microbiology of this species based on our generic expertise in functional genomics, our involvement in the recently completed genome sequence of *C. botulinum* and our building the first DNA microarrays for this pathogen. Initially we will focus on neurotoxin formation and its regulation, and later on the lag phase of growth and sporulation. This new understanding will lead to knowledge-led approaches to microbiological food safety. In addition, the DNA microarray built at IFR will be used to characterise genomic strain variation in *C. botulinum*.

An important output of this Programme will be the transfer of information to key stakeholders. For example, we will continue to support industry and regulators by undertaking contracts to quantify combinations of environmental factors that control growth in foods of spore-forming bacteria such as *C. botulinum*, *C. perfringens* and *Bacillus cereus*, including the use of predictive modelling and quantitative risk assessment (collaboration with **Risk & Consumer Science** (RCS) Partnership).

We aim to provide a platform for fully quantitative microbiological food safety. Work on the modelling of food microbial systems will develop novel approaches for stochastic and dynamic modelling. Work on the prediction of lag time of single cells will continue, and will be extended to include microbial interactions between single cells in mixed cultures. In addition, we are using molecular approaches to extend understanding of lag time in collaboration with **Pathogens: Molecular Microbiology** (S1). With funding from the UK Food Standards Agency, and the food industry, we will continue to build on our previous activities and drive forward the more traditional deterministic, predictive microbiological approaches. *ComBase* and *Growth Predictor* are widely-admired flagship activities, and an important innovation will be to develop web-based delivery. A longer term plan is to characterise, in a quantitative manner, the network of complex microbial ecology in food (a future interaction with **Commensals & Microflora** (G2) will extend this approach to the gastro-intestinal tract).

We will extend understanding of the ecological interactions between bacterial foodborne pathogens and food structure, leading to an improved understanding of the mechanisms of bacterial survival and growth *in situ*. Interacting with **Pathogens: Molecular Microbiology** (S1), we will use transcriptomics to study *Salmonella* following attachment to food surfaces, and during resuscitation following exposure to physical processing (including new processing technologies). Derived information on the physiological and genetic response of *Salmonella* to inimical food environments will be used to develop "knowledge-led" food preservation and decontamination systems. *Salmonella* is the largest cause of bacterial-associated infection associated with salad vegetables in the UK. We will develop knowledge-led intervention strategies to remove *Salmonella* from ready-to-eat fruit/vegetables, and optimise combinations of physical processes to inactivate pathogenic bacteria.

Programme Leader:
Professor Mike Peck

Project Leaders

Dr József Baranyi
Professor Mike Peck

Cross-Programme

Professor Tim Brocklehurst

The Partnerships

The (Internal) Partnerships

The research objectives in the portfolio of Programmes depend on the continued development and the maintenance of state of the art capability in several areas of scientific technology and expertise. Where these require major resource (in either capital or personnel) and have broad impact for our future success they are managed as internal 'Partnership' activities with direct support for the facility and skill base combined with Programme interaction.

Partnerships will work in two modes: *Partnership Mode* and *Development Mode*.

- In *Partnership Mode*, the staff and resource of the partnership will be a component of the research activity of one of the scientific Programmes. The total resource required for any interaction will vary, but will only require a proportion of the total available. This way of working will enable best practice to be disseminated across the Institute.

- In *Development Mode*, the staff will be developing the expertise of that Partnership, for publication and exploitation as appropriate.

We have introduced four internal Partnerships: 'Technologies for Systems Biology', 'Bioinformatics and Statistics', 'Imaging' and 'Risk and Consumer Science'. In the latter case both consumer science and risk analysis are important for the realisation of our Vision.

Technologies for Systems Biology

The delivery of our science strategy depends on the use of a Systems Biology approach. Here we will focus on maintenance and development of a state-of-the-art capability in transcriptomics, proteomics and metabolomics and the promotion of best practice across the range of our activities.

5 Year aims (Partnership Mode)

- To maintain and develop the state of the art in post-genomic and metabolomic technologies in support of Institute research.
- To develop comparative proteomics for the facile determination of protein abundance changes and post-translational modifications.
- To develop functional metabolomics and metabolite profiling as a facile, sensitive and rapid technology to underpin most metabolic and physiological work at IFR.
- To assess the effect of metabolic engineering on the transcriptome-proteome interface.

Technologies for Systems Biology

Functional genomics and a Systems Biology approach are integral to much of our forward science strategy. We have invested heavily in both DNA microarray technology and proteomics. We are building an equally strong capability and technology base in metabolomics. This Partnership will ensure we maintain a state of the art capability across these and future platforms such that all Programmes

can take full advantage of an integrated skill base.

In this Partnership we benefit from a vigorous collaborative portfolio with the John Innes Centre and UEA, and with international groups such as the new RIKEN plant sciences centre in Yokohama, Japan.

Partnership Leader:
Dr Tony Michael

Core Activities 2005-06

Functional Genomics and Systems Biology
Comparative Proteomics
Metabolomics
Transcriptomics: microarray manufacture

Leaders

Dr Tony Michael
Dr Fran Mulholland
Dr Ian Colquhoun
Dr Colin Hanfrey

For the Development Mode within this Partnership we will undertake exemplar programmes of research as a Cross-Programme activity with **Phytochemicals & Health (H1)** that use functional genomics and Systems Biology approaches in order to ensure

that the provision remains at the cutting edge and is disseminated throughout the Institute. These include the transcriptomic, proteomic and metabolomic analyses of GM plants for safety evaluation and a focus on post-translational regulation.

5 Year aims (Development Mode)

- To characterise the components of the regulation and biosynthesis of phytochemicals and phytomaterials using functional genomics and Systems Biology.
- To engineer metabolically the major phytochemical and phytomaterial pathways in plants.

Bioinformatics and Statistics

The predictive and systems engineering approaches made possible by the new post-genomic technologies requires teams of 'wet' biochemists and biologists to work in partnership with 'dry' scientists - mathematicians, computer scientists and software engineers. The purpose of the Bioinformatics and Statistics Partnership is to meet this requirement by providing this resource base, with key skills in mathematics, statistics and data handling.

5 Year aims

- To develop advanced expertise in the extraction, analysis and visualisation of data from the post-genomic technologies in support of Systems Biology approaches adopted in the science Programmes.
- To provide a long-term, core resource base in statistics and data handling skills in support of the Institute's research activities.
- To provide the mathematical skills to enable predictive approaches to our science, thereby generating holistic understanding of the systems we study.
- To act as a hub for dissemination and encourage best practice in mathematics and informatics, and to act as a node of interaction with external centres of expertise.

The explosion of data collected from the high-throughput and massively-parallel experiments in post-genomic technologies and metabolomics has changed the way in which biological research is undertaken. IFR has traditionally had a major investment in the instrumental techniques of analytical chemistry (GC/MS, LC/MS, MS, NMR), and has now embraced the post-genomic arena (transcriptomics, proteomics). The data produced by all of these are multi-dimensional (several thousand numerical values generated from each specimen examined). It is recognised that advanced computational methods (data mining and modelling) are essential in the analysis of these kinds of data sets.

The Institute's considerable strength in analytical science and chemometrics, with the necessary skills base in statistics and modelling, forms the base from which the future data analysis needs will be met. The Partnership will adopt a 'hub-and-spokes' model: an open-access resource base, from which individuals will be devolved to client groups. The activities of the resource base will include:

- Data analysis input into projects, particularly where the amount of effort needed is substantially less than 100% staff time, and so would be difficult to recruit into directly.

Bioinformatics and Statistics

- Pump-priming: carrying out short-term, exploratory analyses with researchers where the goal is to produce proposals that include further long-term informatics funding, to be based with the science teams.
- Assistance to scientists carrying out their own analysis; day-to day support with statistics and software problems.
- Acting as a hub for dissemination and encouraging best practice

The Partnership will foster collaboration with computation groups external to IFR. In particular, the Computer Science department at UEA has oriented itself towards biology with considerable complimentary strengths to our own, and we shall expand on the many existing collaborations. We will expand on the work we already undertake with the Sanger Institute, the European Bioinformatics Institute and the Cambridge Computational Biology Institute.

Partnership Leader:
Dr Kate Kemsley

Project Leader

Dr Kate Kemsley

Imaging

Understanding food structure is the key to the delivery of high quality, safe and nutritious foods. The leading-edge microscopic methods available at IFR allow us to visualise heterogeneous food structures and to image and interpret such structure at the molecular level. We have pioneered the use of probe microscopy in food science. These techniques have already led to new solutions to previously intractable problems and have contributed to the commercial delivery of higher quality, lower cost food products. IFR has 30 years expertise in the light and electron microscopy of food and plant materials and well established collaborations in the use of these methods within IFR and the NRP. Our intention is to maintain, expand, develop and exploit this expertise base in microscopy across the scientific programme at IFR.

5 Year aims

- To maintain, develop and exploit state-of-the-art imaging methods for food and plant material.
- To identify and exploit new structural factors contributing to improved nutritional characteristics of starch-based foods.
- To exploit expertise in the imaging of interfacial structures for the rational design of food foams and emulsions and to test models of the digestion of fat-based foods.
- To develop novel applications of force microscopy in food science.
- To provide resource in imaging techniques and to train staff in the routine application of imaging methods.

IFR has developed most of the methodology used in the imaging of food systems by probe microscopy and, in particular, atomic force microscopy (AFM). We will use this unique expertise base, in collaboration with Programmes, Exploitation Platforms and external grants, to tackle original research problems relevant to the IFR strategy. AFM is still an emerging tool and the need for expertise in sample preparation and image interpretation is of utmost importance for the successful exploitation of the use of these methods. The use of AFM at IFR has been focussed in the past on a few well-

chosen problems, chiefly based in the materials science area. Now that the methodology has been validated, and the methods of contrast determined, there are potentially much wider applications of these imaging methods, and the newer techniques of force measurement, across the multidisciplinary research portfolio at IFR. We intend to seek out such research opportunities and to develop the methodology to tackle them if necessary. New methodology will be developed in response to the needs of Programmes or Exploitation Platforms and as part of feasibility studies aimed

Imaging

at underpinning external grant applications. As the methods become established we will provide resource or training for their wider use across IFR.

The considerable expertise base in light and electron microscopy will also be used in collaboration with Programmes and Exploitation Platforms to carry out original research on food structure.

Although light and electron microscopy are well established methods, their successful use to tackle problems in complex systems, such as food materials, requires considerable expertise and innovation in sample preparation, in the avoidance of artefacts and in the interpretation of the final images. The Partnership will

provide this expertise base. Once methods are validated and are capable of being applied routinely then training will be provided to allow application of such methods by other scientists. Training and resource will be provided for the use of established methods for characterising food materials.

The Partnership will provide advice to on the future needs and options for future investment in microscopic methods within IFR or through collaboration within the NRP. We will continue to develop integration of our expertise and facilities with colleagues at JIC and UEA.

Partnership Leader:
Professor Victor Morris

Project Leaders

Patrick Gunning

Professor Victor Morris

Dr Mary Parker

Risk and Consumer Science

The developments arising from the research in the natural science Programmes have implications for society, particularly with respect to the impact of the potential combination of personalised nutrition and functional foods and nutraceuticals. Further, eating and drinking are inherently risky activities. It is crucial to the health and wealth of the nation that appropriate attitudes and behaviours associated with microbial food safety and healthy eating are understood and facilitated. This is the central tenet of this Partnership, which encompasses a multi-disciplinary skill-base appropriate for exploring the concepts of risk and behaviour within the boundaries of IFR's research remit.

5 Year aims

- To establish IFR as an internationally recognised centre for social research in the domain of food choice.
- To establish IFR as an internationally recognised centre for the application of complexity sciences to societal problems related to food and develop a unified view of uncertainty and complexity in relation to food safety information and food safety research.
- To develop a theory of 'risk perception' and a battery of validated measures of the relevant factors identified within the theory.
- To build and implement accessible, web-based, communication systems that can deliver IFR food safety expertise, from the Partnership, directly to stakeholders.
- To build and implement representations that interface advanced food safety assessments with established codes and schemes that support improved food safety practices (e.g. Codex, HACCP).

In *Partnership Mode* research will be undertaken with members of the science Programmes to understand the implications for, and attitudes of, society to the capabilities that could flow from the research being undertaken. In addition, research supporting quantitative risk assessments for complex food borne hazards will be undertaken with the Programmes concerned with food safety.

In *Development Mode*, members of the Partnership will undertake research into food choice, risk perception and risk assessment.

Why individuals eat what they do and the subsequent health consequences of those choices is a major national and international priority now and for the foreseeable future. This subject can and is being approached from many perspectives: biological, genetic and

Risk and Consumer Science

economic. The psychological and sociological perspectives of food choice and health are essential dimensions in aiding our understanding.

The sciences of complexity show us that we are embedded in a world fundamentally different from that which has previously characterised modern science, with its emphasis on prediction and control. Complexity techniques are already employed at IFR with regards to understanding collective dynamics (from microbial populations to sand piles), comparison and combination of distinct food safety information sources, and modelling with network methods. We plan to mesh this existing in-house expertise in mathematics/complexity with IFR's psycho-social and biological expertise to develop and apply the science of complexity to current social problems related to food.

Research on 'risk perception' has demonstrated that people do not perceive risks solely in terms of likelihoods of harm or death (the definition used by risk assessors), but instead perceive the concept in a more

complex, multi-dimensional manner. One problem is the absence of standardised measures of the key constructs/factors; another is the lack of *theory* to *explain* and *predict* what hazards, in what circumstances, will be perceived as particularly risky and what will not. The presence of a 'risk' indicates a need for responsible parties to communicate relevant information to those who might be adversely affected. Unfortunately, 'risk communications' tend to have only limited success. Public *engagement* is seen as an antidote to trust-related communication difficulties: it is assumed that by involving people (e.g. the public) in some manner in agenda setting/decision making/policy making, this will enhance trust (in the sponsor), increase learning, reduce resistance, and even lead to better decisions/policies. Empirical evidence for these benefits is, however, lacking; indeed, there are various difficulties with engagement processes that suggest these are not universally appropriate. We will develop a model that indicates in what contexts *communication* as opposed to *engagement* should take place

(and *vice versa*), and identify the appropriate characteristics of communication/engagement mechanisms.

Research supporting quantitative risk assessments for complex food borne hazards centres on improved quantification of uncertainties, improved understanding of complexities and stronger support for communication and management of information. It concerns the development of strong mathematical descriptions, and improved quantitative understanding, for the hazards and risks that are associated with food consumption. A secondary development involves construction of a consistent framework, and a range of user-friendly tools, that facilitates strong communications between IFR food safety research expertise and appropriate stakeholders. Additionally we aim to provide a basis for embracing, and targeting, IFR food safety research and continued food safety data acquisition.

Partnership Leader:
Dr Nigel Lambert

Project Leaders

Dr Gary Barker

Dr Nigel Lambert

Dr Gene Rowe

The Innovation Agenda

IFR is required to exploit and apply the outputs of its research for the benefit of its stakeholders. We are developing our “innovation culture” alongside the existing science culture, addressing the OST Objective “to increase the performance of the science and engineering base in exploiting the results of its research”.

5 Year aims

- To provide evidence-based research required to underpin changes in policy and regulation.
- To increase the proportion of income that emanates from knowledge transfer and commercial exploitation to 15% within five years, by undertaking collaborative work with the food, nutraceutical and pharmaceutical industries, and by exploiting our research by licensing and other means.

The Innovation Agenda is concerned broadly with how we exploit the research and development in the Institute beyond the normal, fundamental outputs (publication, lectures, seminars, attendance at international meetings and so on). IFR has two important routes for exploitation and knowledge transfer:

- providing the evidence base for development of relevant *Government Policy* particularly in relation to the *Health of the Nation* and prevention of disease;

- promotion of *Wealth Creation* both for the nation by knowledge transfer to industry and also ourselves by generation of an income stream from KT and exploitation. For this we will protect our Intellectual property (IP) and exploit it, by licensing our inventions to industry and by the creation of spin-out companies where appropriate. We will work closely with PBL. Whilst our past developments have concentrated largely on the food industry, we see ourselves interacting increasingly with the nutraceutical and pharmaceutical industries. We expect to contribute to regional, national and European *Economic Development*.

Technology and Knowledge Transfer

We are committed to the development of technology transfer and the exploitation of our research initiatives. An enhanced *Business Development Group* (BDG) will work with the Programmes and Partnerships to develop and exploit our IP. The BDG will also promote the work of the Institute and develop our interactions with industrial partners. This will be in part through activities of the pre-existing *Food & Health Network* (F&HN) ^{*} acting both in its horizon-scanning mode via the *F&HN Clusters*, and also through developing *F&HN Direct* and thereby

interactions with individual companies. Knowledge transfer takes place through a variety of routes in addition to F&HN. We publicise science advances internationally via our 'Science+Innovation' quarterly, through specialised media releases, press conferences, articles for the trade and technology press and through our website. Staff are encouraged to take part in political and industrially-relevant fora in order to ensure visibility for the IFR 'science-voice'.

- www.foodandhealthnetwork.com

ISO 9001:2000 Registration

Our continued registration to the QA standard ISO9001:2000 provides independent recognition of our effectiveness as a research provider, of particular importance for our work with

the Food Standards Agency, Government Departments and Industry. It also sets an internal standard of working.

Policy Development

The Institute will continue to play an important role in the development of national, European and International policy, principally via the UK Food Standards Agency and Government Departments, and particularly in the areas of nutrition and food safety. It is Institute policy to encourage the involvement of senior staff with advisory committees that support the work of Policy stakeholders.

The Exploitation Platforms

Part of our strategy is to define a small number of activities that offer good potential for commercial development. These will be underpinned to the minimum extent necessary to sustain their transition into externally supported ventures and the challenge will be to build successful business plans for their further development. Current Exploitation Platforms are in 'Sustainability of the

Food Chain, 'The Model Gut' and 'Magnetic Resonance Imaging (MRI)'. In addition, IFR hosts the National Collection of Yeast Cultures (NCYC). We are committed to maintaining this as a national resource in support of the UK science base but we will exploit the Technology Platform concept in building a visionary approach to its business development.

The Exploitation Platforms

5 Year aims

- A developed Platform culture, with special reference to business and market research activities, and interactions with relevant IFR research and support activities.
- Nationally and internationally recognised Platforms for innovation in the food, nutraceutical and pharmaceutical arenas with a highly developed network of collaborative and paying customers generating significant business opportunities and revenue.

Specific

- To aggressively identify licensing opportunities for the Model Gut technology in collaboration with PBL, i.e. sale under licence of stand-alone, and application of specific units, incorporate lower bowel fermentation into the Model, and provide models for other industries
- To characterise 100 commercially important yeast strains per annum with high precision, develop the marketing of NCYC services via the Internet, and expand the NCYC customer base - increasing income from existing customers by 20% in the first year and 10% per annum thereafter, and adding 5 new customers per annum, each spending over £1,000 per annum on NCYC services.
- To develop an on-line sensor for quality control problems and a bench-top medical scanner and guide developments of tailored commercial versions.
- To reduce 'waste' in the food-chain, thereby contributing to sustainability, via improvements in recovery, recycling and recovery.

Exploitation platforms 2005-06

The Model Gut
 Novel Magnetic Resonance Imaging Technologies
 National Collection of Yeast Cultures
 Sustainability of the Food Chain

Leader

Dr Martin Wickham
 Dr Brian Hills
 Dr Ian Roberts
 Dr Keith Waldron

External Collaboration

IFR will enable the maximum output and benefit from research and our skills base by collaborating with others to maximise the investment made in IFR.

5 Year aims

- To collaborate with other relevant BBSRC institutes within an overall BBSRC strategy.
- To exploit the synergies and benefits of being a partner in the Norwich Research Park.
- To contribute to the success of Norwich Research Park (Enterprise) thereby enhancing our ability to exploit our activities.
- To collaborate with partners in fundamental, strategic and applied research wherever doing so increases our capability to achieve our mission, in particular with University Departments and Institutes with complementary expertise, with the Food Research Associations and with Industry.
- To build on the considerable base of European partners within the various Framework programmes to which we contribute.
- To expand our interactions on a world-wide basis.

BBSRC-sponsored Institutes

The Institute has considerable synergies with research being undertaken in other BBSRC Institutes, and will continue and expand on these collaborations to deliver best an overall BBSRC research agenda. These include the John Innes Centre, whose activities in both plant and microbe science are complementary to ours, with the Institute for Animal Health whose mission in animal health marries well on a number of areas with our focus on human health, and the Babraham Institute with our mutual interests in immunology.

Norwich Research Park

IFR is a member of the Norwich Research Park, whose other members are the John Innes Centre, the Sainsbury Laboratory, the University of East Anglia and the Norwich and Norfolk University Hospital. There is also a Bio-Incubator and a number of start-up and spin-out companies,

making the NRP a vibrant place to do business as well as research. The considerable synergies, both in major technical and equipment resource and in science and engineering, present excellent opportunities for adding value to the work of all players.

National collaborations

There are a number of organisations that are of especial relevance to enabling maximum mutual benefit by collaborations. These include a number of University Departments, the Rowett

Research Institute, Camden and Chorleywood Food Research Association, and hospitals with interests in preventative medicine in diet-related diseases.

Europe

The Institute has developed major activities within Europe in a variety of ways. We are partners in a number of EU Framework Programmes, co-ordinating three major activities whose life extends well into the timescale of this Strategic Plan. We are members of a number of others. We are a founder member of Foodforce, a consortium of European Food Institutes (not more than one per nation) and from within

this have played a significant role in promoting the development of a European Technology Platform "Food for Life". These activities are all important in placing IFR in a European context and providing wider opportunities than are available within the UK alone; this is of particular importance with the food industry, whose R&D agenda is much more buoyant in the EU than the UK context.

Science in Society

The findings from scientific research undertaken at IFR impinge in the medium or long term, and either directly or indirectly, on the lives of individuals, groups of people and communities world-wide. The research that we carry out cannot be undertaken in a vacuum, and is not value-free. Engagement with stakeholders, both in the UK and nationally, will continue to be pervasive throughout IFR's science Programmes, Partnerships and Exploitation Platforms.

5 Year aims

- To protect and enhance IFR's international reputation as an impartial commentator on food and nutrition issues.
- To enhance IFR web communication, in response to stakeholder requests, by redeveloping 'food information sheets'.
- To contribute to the British Association's Annual Festival of Science (and in particular that hosted by Norwich Research Park in 2006).
- To continue outreach with public audiences through events and activities such as Open Days.

The Institute has a tradition of professionally-supported outreach that dates back over 40 years. In this we work closely and collaboratively with colleagues on the Norwich Research Park, at sister Institutes, with the BBSRC and other research councils and with charities such as Cancer Research UK and the British Nutrition Foundation. Our Communications staff work closely with social scientists in the **Risk & Consumer Science** Partnership.

We were among the pioneers in a variety of approaches that now seem 'the norm' – encouraging the media to report scientific conferences, writing lay summaries of scientific documents, working with consumer magazines, and providing science communication training courses for younger staff to name just a few.

Given the continuing interest in food safety and health issues at all levels in society, the challenge is for us to balance work at the cutting edge of developments in upstream engagement, with responsiveness to stakeholder needs. We will thus continue to invest in activities which maximise the delivery of impartial, science-based information to inform debate and assist in the quality of decision-making. We will ensure that staff exploit the broadcast, print and e-media as a most effective tool for specialist through to mass communication of our science and innovation.

IFR staff will continue to have an active relationship with the UK Parliament, providing speakers for debates and events (for example the Westminster Food & Health Forum), responding to consultations and supplying briefings for Members.

We contribute not only to national 'Science in Society' events but also more locally-based activity. Over the years we have tested a number of novel formats for public engagement and practical work in this area is informed by IFR's Social Scientists.

We actively support school science programmes, not only through the provision of activity packs where our policy remains that of seeking opportunities for national impact (for example, Amazing Maize) but in particular through the Teacher-Scientist Network. About 20 staff and students are involved in these 1:1 linkages, supported by The Gatsby Foundation.

Support

Scientific effectiveness is optimised when underpinned by professional support. IFR provides a safe, secure and optimal working environment to enable the Institute to fulfil its science mission and provides scientists with financial, project management and business guidance.

5 Year aims

- To develop and support strategies to assist scientists in the generation of income in line with the Institute's Plan.
- To develop new initiatives to support scientists in delivering Technology Transfer, Knowledge Transfer, and Science in Society objectives.
- To introduce an FEC model into the Institute during the financial year 2005/06 in line with the requirements of key stakeholders for clarity of project costing.
- To develop and implement a five year Estate Strategy for the Institute, providing options for the future use of the IFR estate and optimised accommodation for the Institute's scientific and business requirements.
- To seek opportunities for improving efficiency and managing costs through joint operations with the John Innes Centre and other operations on the Norwich Research Park.

Science Support Operations aim to provide a safe, secure and optimal working environment to enable the Institute to fulfil its science mission and to provide scientists with financial, contractual and project management support and guidance. Science support is provided from two units, Finance and Contracts and Site Operations. Finance

and Contracts deals with all issues of financial governance and control including all aspects of project costings, financial reporting and governance issues. Site Operations is responsible for other activities such as Estates Management, Human Resources, Health and Safety, Information Technology, Enterprise, Quality Assurance and Communications.