

## 'Living with IBD'

Three grants were awarded in 2002 for social and psychological research:

*The Integration of patients concerns into treatments for IBD: a qualitative study of opportunity and understanding:*

Professor Alan Radley, Loughborough University & Dr John Mayberry, Leicester General Hospital (£68,200)  
This study looked at how effectively patients' concerns were brought out in the context of outpatient clinic interviews, the skills required of the medical staff and the key factors that determined the patient's satisfaction. The findings were presented at a major European IBD Conference in 2004.

*Managing Inflammatory Bowel Disease at work: employee needs and employer awareness*

Dr Sarah Cox, Institute of Work, Health and Organisation, University of Nottingham (£44,785)  
This study found that the support and flexibility of employers were very important to the ability of patients to maintain satisfactory working lives and that this was more often available to white collar workers than others. The study has provided helpful information to improve the guidance available to employers and the findings have been presented at various occupational health meetings.

*IBD in Adolescence: using life stories to investigate and support everyday living.*

Dr David Middleton, Harriet Gross and Sally Sargeant, Loughborough University (£45,000)  
The project enabled young people to record an audio diary of their life with IBD and the report illustrates many of the issues that affect young people and the interplay between IBD and non-IBD concerns in adolescence. The report has been presented in a variety of professional and patient meetings to give insight into young people's needs.



# Environment

It seems self-evident that some factor in the environment must trigger Crohn's Disease in individuals who are perhaps rendered susceptible by their genetic make-up. An individual's risk may also be affected by priming of the immune system as a consequence of early immunological encounters. Examples might be exposure to common environmental microorganisms (the increasing sterility in which infants and children are raised is a new phenomenon, and one which our immune systems were not designed for) or specific infections. It is thought that these may lead the immune system to behave in an abnormal manner even years later – possibly leading to conditions such as IBD and asthma. The difficulty has been in identifying exactly what it is in the environment that affects susceptibility and triggers intestinal inflammation.

## Diet

Defining dietary constituents that affect susceptibility to IBD has been less straightforward than might be imagined.

Recent progress has been made by **Dr Andrew Hart in Norwich (2000)** who has studied data from a European Union funded study of 500,000 healthy individuals in whom dietary habits were recorded in detail. Over a period of five years there have been over 100 new cases of Ulcerative Colitis in this previously healthy population, allowing correlations to be made between diet and susceptibility to UC. Work by **Prof John Cummings (2001 and 2004)** and his group in Dundee has suggested that sulphur and sulphated foods might increase risk of relapse, and defined some foods associated with lower Disease activity. A correlation of UC activity with specific gut bacterial profiles was also observed. In terms of treatment it is well established that therapeutic 'elemental' liquid diets are effective in Crohn's Disease, but the reason for this is not clear. **Dr Tim Trebble (2001)** identified that reductions in polyunsaturated fatty acids were due to activity of Crohn's inflammation and not dietary restriction as previously supposed.

## Infection

Over a period of several years debate has raged as to whether and which infection might trigger either Crohn's Disease or UC. Some of this debate, based on legitimate scientific enquiry, has been held in the full glare of the media spotlight with some unfortunate consequences. In recent years studies have assessed a possible role for the measles virus – producing rather controversial results. It now seems clear that neither measles nor MMR vaccination are causally related to Crohn's.

Several groups have studied Mycobacterium paratuberculosis for a possible contribution to Crohn's. Even after 15 years of study – for example by **Prof Hermon Taylor (1992)** at St George's Hospital – the data remains conflicting. NACC's most recent contribution here has been to **Dr Nigel Cook (2001)** who has developed a sensitive molecular diagnostic test that can be used for screening dietary sources for possible contamination with this organism.

There is also considerable evidence that the bacteria that reside in the intestines of us all can in particular circumstances drive the inflammatory response of IBD. It may be that an (as yet undefined) trigger initiates the bowel inflammation, but that subsequent inflammation is perpetuated by the resident bacteria. Attempts to study these are complicated by their vast number and difficulty in identifying by conventional techniques of culture. This has recently been addressed by **Dr Stuart Bloom (2000)** who has used highly sensitive molecular techniques to characterise the bacteria that adhere to the mucus lining of the gut in IBD. NACC has also supported **Prof Gordon Duggan (2004)** in characterising a particular strain of adherent E. coli, which may contribute to chronic bowel inflammation. One of the hopes of the genetic work is that it will help to sub-divide the IBD populations into genetically distinct subgroups in which there will be less heterogeneity and hence more likelihood of being able to distinguish subtle trigger signals from background environmental 'noise'. The iden-



tification of NOD2 (which encodes a protein that binds bacteria within cells) as a Crohn's gene has certainly reaffirmed the idea that bacteria play an important role in causing Crohn's Disease.

## Gene / Environment Interactions

It is hoped that as the genetic and environmental determinants of IBD are identified, light will be shed on the specific mechanisms of Disease.

**Prof Jack Satsangi's group (2002)** have been funded by NACC to explore interaction between the two best characterised factors from each category: the NOD2 gene and smoking, and how they specifically affect one of the central effectors of gut inflammation called NfκB.

**Dr Satish Keshav (2003)** has investigated the effect of NOD2 mutations on the function of particular cell types thought to play a critical role in bowel inflammation.

**Dr John Mansfield's group (2004)** have attempted to identify specific microscopic difference in patterns of Disease between those Crohn's patients with NOD2 mutations and those without, and have also researched the influence of genetic variation on osteoporosis in IBD patients.

## Investigation

Diagnostic investigation aims to maximise information while minimising discomfort, inconvenience and expense. The stalwarts over the last 20 years have been contrast radiology, traditionally using barium, and endoscopic examination of the bowel. Both of these mo-

dalities have seen significant advances over the last five years allied essentially to technological progress – particularly with regard to imaging of the small intestine which is the primary site of involvement in up to two-thirds of people with Crohn's Disease. Hence MRI imaging and the futuristic concept of wireless capsule endoscopy are both establishing important roles in this regard. NACC has contributed to these important developments with regard to IBD by funding pilot projects undertaken by **Dr Jeff Berens in Norwich (2003)** with regard to image analysis in capsule endoscopy and **Dr Hugh Burnett in Manchester (2001)** who has undertaken a study comparing the previous gold standard of small bowel enema to new MRI protocols.

## Therapy

Bringing new treatments into the clinical arena is an expensive and time-consuming business for the pharma industry – but refining use of existing treatments and improving understanding of their role is an activity with which clinicians can engage. Azathioprine and 6-mercaptopurine are two of the commonest steroid-sparing agents used in IBD and their metabolism and side-effect profiles are now known to be heavily influenced by genetic factors.

This has been a major topic of investigation by **Dr Jeremy Sanderson (2003)** who has defined a number of new pathways in an attempt to predict response and tolerance of these valuable therapies. NACC has also recently funded **Dr Amanda Williams** to work in Bristol with **Dr Chris Probert** to evaluate a hypothesis that steroid therapy may itself cause later problems of resistant IBD.

Two recent grants have funded investigation of early-stage potential therapies: one a vaccine against Mycobacteria paratuberculosis which

may contribute to some cases of Crohn's Disease (**Hermon-Taylor 2005**), and the other a pump-priming grant to explore the possibility of gene therapy in IBD (**Keshav 2002**). **Prof Subrata Ghosh (2004)** is currently focussing on whether an increase in a particular group of nerve-ending receptors called the vanilloid receptor 1 in Crohn's Disease accounts for part of the pain pathway, and whether this might be amenable to specific therapeutic intervention.

## Complications of IBD

Crohn's Disease and Ulcerative Colitis can lead to the development of complications. These vary in severity but at the more complex end of the spectrum include malnutrition and intestinal failure, bowel stricturing and perforation, acute severe colitis known as toxic megacolon, and development of colon cancer. With regard to the latter NACC has funded two pilot studies in recent years to investigate how and why IBD-related colon cancer differs from 'sporadic' colon cancer.

**Dr Satish Keshav (2001)** demonstrated first an increase (related to active Ulcerative Colitis inflammation) then the loss (on cancer development) of a protein required for signalling from cells lining the bowel.

**Dr Qualtrough (2005)** has recently undertaken a pilot study of fascin to see if this protein identifies patients with IBD who are likely to go on and develop cancer. Clearly such a marker would be a valuable prognostic aid. NACC also funded **Dr Tim Card (2002)** who worked with Prof Richard Logan's group in Nottingham undertaking powerful analysis of over 16,000 IBD cases on a large GP research database. This work demonstrated that both Crohn's and colitis are associated with a small but significant increased risk of death greatest in relative terms in early adulthood.



Improving life for  
people affected  
by Colitis and  
Crohn's Disease

RESEARCH INTO

# Inflammatory Bowel Disease

## Unravelling the mystery of Inflammatory Bowel Disease



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2002-2006  
NACC RESEARCH AWARDS



## About NACC

NACC's aim  
Improving life for people affected by Colitis and Crohn's Disease

Founded in 1979, The National Association for Crohn's and Colitis and Crohn's Disease (NACC) now has approximately 30,000 members and 70 Groups throughout the UK. The Charity offers support and information to people of all ages who are affected by Colitis or Crohn's Disease, raises funds for vital research and also works to increase awareness and understanding of the illnesses.

## How you can help

Leading experts in IBD make decisions through the NACC Medical Research Committee. They ensure that only top quality research is supported in the search for a cure. Please help by returning this slip. The more funds we are able to distribute, the more quickly we can progress towards a cure.

I enclose a cheque payable to NACC for £ \_\_\_\_\_ for the Research Fund.

I would like to raise funds for the NACC Research Fund. Please send me details.

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SEND THIS SLIP TO: RESEARCH FUND, NACC, 4 BEAUMONT HOUSE, SUTTON ROAD, ST ALBANS, HERTS AL1 5HH TEL: 01727 830038

## FACTS AND FIGURES

- TOGETHER, UC AND CROHN'S DISEASE AFFECT ABOUT ONE PERSON IN EVERY 400 IN THE UNITED KINGDOM POPULATION
- THE MOST COMMON AGE FOR DIAGNOSIS IS BETWEEN 10 AND 40 (ALTHOUGH DIAGNOSIS CAN OCCUR AT ANY AGE)
- MEN AND WOMEN SUFFER EQUALLY.

# NACC research - INSIGHT IN IBD

NACC continues to make a significant contribution to the understanding of IBD through its own research awards. The results of NACC-funded research affect people with IBD on a daily basis. This review focuses on medical research supported by NACC since 2002 and shows how earlier work has influenced the direction of current research into the diagnosis, treatment and impact of IBD.

The total amount awarded by NACC between 2002 and 2006 was more than £1.5 million. Important advances during this period supported by NACC Research Award funding include, to name a brief selection:

- Dietary intervention in Ulcerative Colitis patients designed to lower intestinal sulphide levels and prevent initiation of Disease episodes or continuation of symptoms
- Identification of a susceptibility gene on the

HLA region on chromosome 6 responsible for colonic Crohn's Disease.

- Development of a test to predict unnecessary and unpleasant side effects to azathioprine.
- Genome partitioning to clarify unconfirmed associations and pinpoint the remaining susceptibility genes to enable the more rational use of existing treatments and the development of new therapies.
- Genetic investigation of NF-κB pathway in susceptibility to IBD.
- Steroid therapy investigation to understand why steroid therapy fails and whether 'over-use' leads to an increase of chronic Disease.

## Criteria for NACC Research Award success:

Much has already been achieved in understand-

ing the factors involved in the development of IBD. However, there remain many unanswered questions. Identifying the specific environmental triggers and genetic factors involved remains the mainstay of research, ultimately advancing knowledge for the benefit of those who live with the distressing effects of Ulcerative Colitis and Crohn's Disease.

## UPDATE

Applications for NACC Medical Research Awards meet a deadline in November of the year preceding the award presentations. An application form is available to download from the NACC website at: [www.nacc.org.uk/content/research.asp](http://www.nacc.org.uk/content/research.asp) All applications should include a detailed scientific statement of the research proposal.

## Successful outcomes from NACC-funded research included work on:

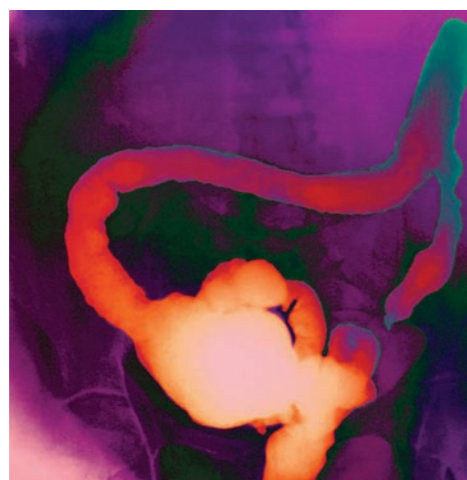
- Scientific discovery that may help IBD sufferers in the future (e.g. Dr Amanda Williams 2006 – investigation into the effects of steroid therapy).
- Practical benefits to IBD sufferers (e.g Prof John Cummings 2001 – dietary intervention approach to UC, Dr Jeremy Sanderson 2003 – thiopurine test to predict azathioprine side-effects).
- Fostering an interest by trainees in IBD (e.g Prof Derek Jewell and Dr Tariq Ahmed 2002 – HLA susceptibility gene).
- Supporting established units with existing scientific programmes (e.g Prof Chris Mathew 2005 – NFκB pathway susceptibility)
- Pump-priming new investigators who may be committed to IBD but need a chance to establish programmes and then attract other funding (e.g Dr Miles Parkes 2005 – genome partitioning).

### Inflammatory Bowel Disease (IBD)

actually describes two similar conditions: Ulcerative Colitis (UC) and Crohn's Disease. Both UC and Crohn's Disease are non-infectious, chronic (ongoing) conditions that are very distressing for those who live with them. The severity of the symptoms fluctuates unpredictably over time. Patients are likely to experience flare-ups in between intervals of remission or reduced symptoms. The cause or causes have not yet been identified in either illness. Both genetic factors and environmental triggers are likely to be involved.

**Ulcerative Colitis:** affects the rectum and sometimes the colon (large intestine). Inflammation and many tiny ulcers develop on the inside lining of the colon resulting in urgent and bloody diarrhoea, pain and continual tiredness. The condition varies as to how much of the colon is affected. UC can also cause inflammation in the eyes, skin and joints.

**Crohn's Disease:** can affect anywhere from the mouth to the anus but most commonly affects the small intestine and/or colon. It causes inflammation, deep ulcers and scarring to the wall of the intestine and often occurs in patches. The main symptoms are pain in the abdomen, urgent diarrhoea, general tiredness and loss of weight. Crohn's is sometimes associated with other inflammatory conditions affecting the joints, skin and eyes.



# Genetics of Crohn's and Colitis

One of the earliest clues for the clinician that an individual presenting with abdominal symptoms of pain, diarrhoea or bleeding may have Crohn's or UC is a family history of these conditions. Although by no means universal it is nonetheless true that **15% of people with IBD have a relative with Crohn's or UC** – significantly higher than the risk in the background population. The hope is that understanding which genes are responsible and the mechanisms involved will lead to significant insights into the causes of IBD – thereby allowing development of preventative strategies and better, targeted treatments.

## IBD DNA banks

The prerequisite for gene studies is to assemble large panels of DNA from individuals with Crohn's and UC. NACC has been instrumental in helping with these DNA banks by both encouraging participation of its members in the **multiply affected family collections** assembled by Prof Derek Jewell in Oxford and Prof John Lennard-Jones at St Mark's, and funding **case collections** by Dr John Mansfield, now in Newcastle, and Dr Miles Parkes in Cambridge. These DNA panels have formed the nucleus of key IBD genetic studies undertaken over the last ten years.

## Specific 'candidate' genes

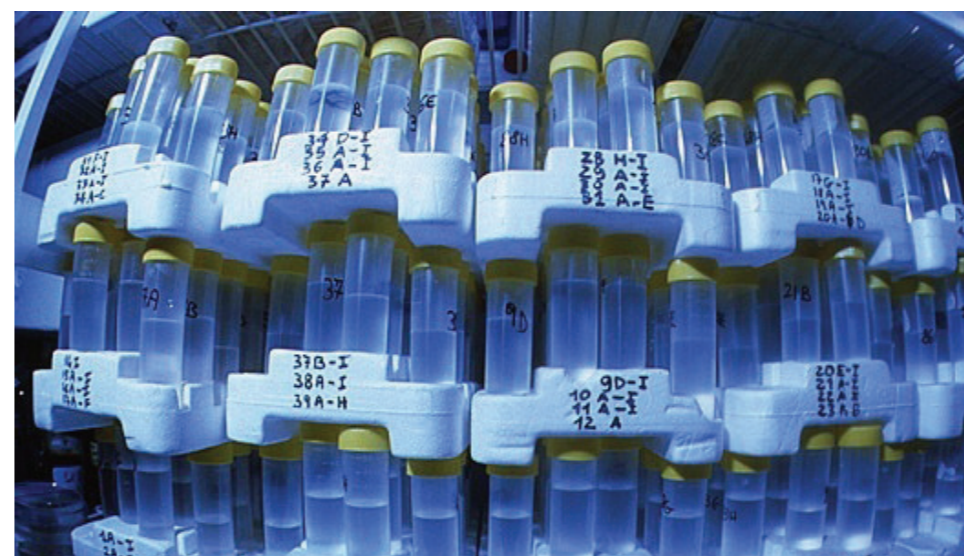
Of the 30,000 genes in the human genome some 'candidates' are more likely to contribute

## 'Hypothesis-free' Approaches

Another way to detect genes that cause IBD is to study large panels of variant markers ('**polymorphisms**') for which there may be no prior hypothesis regarding Disease-causation. By **genotyping** these in large collections of cases and controls, statistical signals can be detected for a small proportion of these markers suggesting that particular variants are more common in individuals with IBD than in controls, who do not have IBD. Initially these techniques were applied to multiply-affected family collections.

These studies have recently been followed up for markers on **chromosome 3** by Dr John Beckly with Prof Jewell (2003).

Subsequently they have been increasingly applied to case/control panels for example in



to IBD than others – particularly those known to encode proteins that play a key role in inflammatory pathways. Some of these have been subjected to detailed analysis to assess possible roles in IBD causation.

Dr Tariq Ahmed, working with Prof Jewell (2002), has published results of a detailed investigation of the role of variation in the HLA genes in Crohn's Disease and followed up this work characterising how this affects expression of genes in individuals who have required ileostomy.

Dr Sylvia Pender in Southampton (2001) investigated regulation of a family of genes whose products can cause damage to the bowel lining by digestion.

And Prof Chris Mathew (2005) at Guy's Hospital,

Cambridge (Dr Miles Parkes 2005).

NACC is also funding a major collaborative study (2006) combining **DNA collections** from Oxford, Cambridge, London, Edinburgh and Newcastle to genotype a large proportion of known coding variation (15000 markers) in 1000 cases of Ulcerative Colitis.

"Much has already been achieved in understanding the factors involved in the development of IBD."

London has studied the NF-κB pathway. NF-κB is a protein that binds to specific sites on DNA within cells and tightly regulates expression of many genes known to control inflammation.

Dr Miles Parkes (2004 and 2005) confirmed that genetic variation in the gene encoding **TNF** contributes to IBD susceptibility (TNF is a key messenger of inflammation in Crohn's Disease and is the target of infliximab therapy), identified **IBD5/OCTN** as contributing to UC and evaluated **NOD2**. Variation in this latter gene is known from landmark work undertaken in France and the US to play a major role in causing Crohn's Disease. **NOD2 mutations account for up to 20% of Crohn's Disease**, and further studies promise to provide profound insights into the mechanisms of bowel inflammation.

The laboratory work is being undertaken at the world-leading Sanger Institute in Cambridge by Dr Panos Deloukas, and complements a large Wellcome Trust-sponsored study into the genetics of Crohn's Disease ([www.wtccc.org.uk](http://www.wtccc.org.uk)).

Dr Geoff Warhurst (2002) has studied differences in gene expression (that is which genes are translated into protein product) that occur in the colon when it becomes inflamed compared to its uninfamed state – and particularly the role of **P-glycoprotein** which appears to determine how the lining of the bowel protects itself from potential damage from the normal gut bacteria.

# Biological mechanisms of IBD

The model which perhaps best encapsulates current opinion regarding the mechanism of chronic intestinal inflammation is one in which a genetically susceptible individual encounters an as-yet undefined environmental trigger (perhaps an infection, but possibly a drug which affects permeability of the bowel wall for example). This leads to inflammation in the bowel wall, which may initially be an 'appropriate' immunological response. But there is a failure of down-regulation (the 'off' switch) of the inflammatory response, which may now in part be driven by the normal gut bacteria. Ongoing intestinal inflammation results and the system is left primed for future flares.

This model is necessarily vague, and summarises what is an extremely complex and, at present, poorly understood process. Many facets of this have been explored by NACC-supported investigators over the last 20 years.

Recently this has included an assessment of **particulate permeability** undertaken by Dr Miranda Lomer (2002), in an attempt to identify whether particles as large as bacteria might be able to traverse the barrier of the intestinal wall in Crohn's Disease.

Prof Jonathan Rhodes' Liverpool group (2003) demonstrated that two specific but common varieties of bacteria (**E. coli and Bacteroides**) are able, by binding to the surface of cells lining the gut, to induce production of a chemical messenger ('IL-8'), which in turn attracts inflammatory cells into the bowel. Blockade of the release of this messenger might reduce the tendency to inflammation, and is a topic of on-going research.

Dr Geoffrey Warhurst (2005) has investigated the role of **P-glycoprotein**,

and demonstrated that loss of this protein can lead to early increased IL-8 production and subsequent development of colitis in mice. Genetic studies from Edinburgh have recently suggested that variation in this gene is associated with increased susceptibility to Ulcerative Colitis.

A number of groups have focused on interaction between the various types of inflammatory cells seen in IBD, and the pathways by which these lead to bowel inflammation.

Dr Peter Irving (2002), working with Prof David Rampton, showed that clumping of **platelets and white blood cells** in the circulation can itself increase their inflammatory capabilities in the intestine.

Dr Satish Keshav (2004) has investigated interaction between specific subsets of **circulating white blood cells** (some of which promote bowel inflammation, others which reduce inflammation) and the cells lining the intestine.

Dr Andrew Smith (2006) has recently been funded by NACC to investigate the hypothesis that Crohn's Disease may represent a rather **specific immunodeficiency state**, as suggested in an article published by this group in the Lancet in 2006.

This hypothesis stemmed significantly from work undertaken by Dr Marcus Harbord (2001) who demonstrated reduced infiltration by **neutrophils** (key inflammatory cells) into areas of induced inflammation in people with Crohn's Disease compared to healthy controls.

Two projects on-going are investigating possible specific roles for two further cell types in IBD – namely **eosinophils** (Dr Gordon Dent 2006) and **dendritic cells** (Prof Subrata Ghosh 2006). The latter are particularly focussing on NOD2 pathways first flagged in genetic studies as discussed on the previous page.



## 2002-2006 NACC RESEARCH AWARDS

### NACC Medical Research Awards 2001

- Dr H Burnett, Hope Hospital, Manchester: MRI - TrueFISP sequence. £10,800.
- Dr N Cook, Central Science Laboratory, York: NASBA - MAP. £6,000.
- Dr J Cummings, University of Dundee: sulphur dietary intervention - sulphur compounds. £69,971.
- Dr S Keshav, Royal Free Hospital, Phosphoinositide-3-kinase g. £5,947.
- Dr S Pender, Southampton General Hospital: matrix metalloproteinase genes. £74,202.
- Dr T Trebble, Southampton General Hospital, n-3 PUFA. £5,521.

### Grants Awarded for 2002

- Dr Timothy Card, University Hospital, Nottingham: Large population based study. £28,542.
- Dr Peter Irving, Barts and The London School of Medicine and Dentistry: Platelet-Leucocyte Aggregation. £79,809.
- Professor Derek Jewell, (Dr. Tariq Ahmed) Department of Gastroenterology, Oxford: HLA susceptibility gene. £44,838.
- Dr Satish Keshav, Royal Free & University College Medical School, London: Chimeraplast-mediated gene therapy. £5,800.
- Miss Miranda Lomer, St Thomas' Hospital, London: (particulate) permeability. £5,992.
- Professor Jack Satsangi, University of Edinburgh: NOD-2 mutations and nicotine NF-κB. £76,775.

### Grants Awarded for 2003

- Dr Jeff Behrens, University of East Anglia, Norwich: Wireless Capsule Endoscopy. £5,995.
- Dr Barry Campbell, University College Department of Medicine, Liverpool: IL-8, E.coli, Bacteroides. £76,790.
- Dr Satish Keshav, Royal Free and University College, London: 'NOD2 gene and Paneth cells'. £74,723.22.
- Dr Mark Pritchard, Liverpool University, Liverpool: gastrin/CCKB receptor. £29,887.
- Dr Jeremy Sanderson, St Thomas' Hospital, London: Predictive Pharmacogenomics of Thiopurine. £36,812.
- Dr Geoffrey Warhurst, University of Manchester, Manchester: Colonic gene expression. £5,920.

### Grants Awarded for 2004

- Professor Gordon Dougan, Imperial College London: E.coli. £77,741.
- Professor Subrata Ghosh, Hammersmith Hospital, London: Vanilloid receptor 1. £42,500.
- Professor Derek Jewell, University of Oxford: Chromosome 3 for susceptibility gene. £84,827.
- Dr Satish Keshav, Royal Free & University College Medical School, London: Tissue-specific and circulating effectors. £85,000.
- Dr Miles Parkes, Addenbrookes NHS Trust, Cambridge: Genetics. £41,455.
- Dr J Mansfield, Royal Victoria Infirmary, Newcastle-upon-Tyne: Genetic Variation. £38,000.

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### Grants Awarded for 2005

- Professor Christopher Mathew, King's College, London: NF-κB pathway. £89,946.
- Dr Miles Parkes, Addenbrooke's Hospital, Cambridge: Genome Partitioning. £25,501.
- Dr David Qualtrough, University of Bristol, School of Medical Sciences, Bristol: Fascin cancer risk. £5,756.00.
- Dr Geoffrey Warhurst, University of Manchester Hope Hospital, Salford: P-glycoprotein. £67,339.
- Professor John Hermon-Taylor, St George's Hospital Medical School, London: Prime/boost MVA/Ad5 vectored vaccine (MAP). £89,242.

### Grants Awarded for 2006

- Dr Gordon Dent, Keele University, Staffordshire: Eosinophil/epithelium interactions. £3,000.
- Prof Subrata Ghosh, Hammersmith Hospital, London: NOD2 - dendritic cells. £95,242.
- Dr Andrew Mark Smith, Rayne Institute, University College London: Macrophages and Inflammation. £20,000.
- Dr Amanda Williams, University of Bristol, Bristol: Steroid therapy. £89,987.

TOTAL: £1657.854.22