





## IBD and the IBDchip Project

**Inflammatory bowel disease** (IBD) includes Crohn's disease (CD) and ulcerative colitis (UC). Both are increasingly common, chronic illnesses, currently affecting more than 1 million patients in Europe. CD and UC affect patients early in life seriously impairing their quality of life and resulting in enormous personal, social and economic costs.

There is evidence suggesting that genetic factors play a key role in IBD pathogenesis, pointing towards a polygenic mode of inheritance for CD and UC. However, to date studies have only addressed the influence of single mutations on IBD, resulting in a poor prediction of clinical course or response to therapy in individual patients.

The IBDchip Project will develop an easy to use DNA array. This non-invasive tool will allow the simultaneous analysis of around 100 relevant mutations to predict the clinical evolution, the risk of developing IBD-related complications, and the likelihood of responding to certain drugs for each IBD patient.

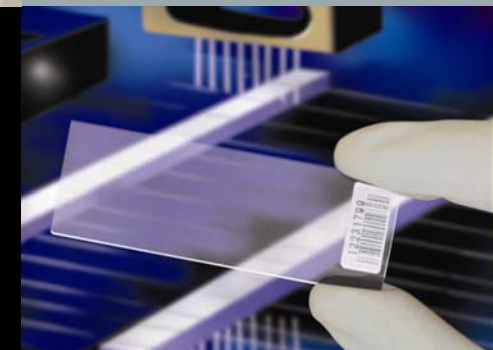
The IBDchip is a project in the LifeSciHealth Priority of the European Commission's Sixth Framework Programme. It will gather the efforts of European SMEs and opinion leaders in the field of IBD and genetics to meet the IBDchip Project's main aim, which is to provide doctors for the first time with a non-invasive predictive tool to optimize treatment in IBD patients, thus resulting in better clinical outcomes and costeffectiveness.

## Moving beyond the state of the art

The IBDchip will be a DNA-chip for molecular genotyping of diverse SNPs, since IBD is a highly polymorphic illness and a large number of genes may contribute to its behaviour. Whereas the first IBDchip prototype, currently undergoing a first, pilot, single-centre, proof of concept study only includes 61 SNPs (selected from an initial literature review as having shown some effect on either disease behaviour, development of complications, and / or patients' response to therapy in IBD) the final IBDchip prototype is expected to include more than 200 SNPs. In fact, reaching a consensus among the project partners, as opinion leaders in the field of genetics and IBD, on the final list of SNPs to be included in the IBDchip prototype will constitute the first and a key workstep of this project.

The new chip will take the state of the art forward by moving from just diagnosis of disease (Crohn's disease or ulcerative colitis) to individualized prognosis of clinical course, development of IBD-related complications and patients' response to a range of different IBD therapies available.

The project is also expected to move the IBDchip beyond the state of the art by developing a new laser technology system significantly smaller in volume resulting in cheaper and faster reading of the IBDchip.



»» *The IBDchip project purpose is to produce a fully functional prototype IBDchip which: has been proved to predict IBD clinical course, development of complications, and patients' response to existing therapies; has been technically optimized and tested for practicality in routine diagnostic settings; is ethically acceptable and economically competitive.*



## Contribution of IBDchip to the objectives of the LifeSciHealth Priority

The IBDchip project will contribute to the overall **objectives of the LifeSciHealth Priority of the EC's Sixth Framework Programme** for 2005-06 in the following way:

- Leverage the gene sequence and post-genomic research - “translational approach”
- Integrate genomics and established practices
- Integrating and building critical mass

The IBDchip project addresses the second strategic line of section 1 - “Application of Knowledge and Technologies in the Field of Genomics and Biotechnology for Health”. The specific topic that the project addresses within this strategic line is “Development of new diagnostics” and its goals:

- To provide an innovative new tool
- To use a non-invasive method
- To contribute to predict disease progression
- To enable doctors to interpretate *in-vivo* data so as to choose the optimum and most cost-effective therapy for each patient

## Strategic impact of the IBDchip project

### IMPACT ON COMPETITIVENESS

IBDchip will produce highly innovative, high value knowledge based products which will be first to market in a potentially very large sector both in Europe and overseas.

### IMPACT ON SOCIETAL PROBLEMS

After rheumatoid arthritis, IBD is the second most prevalent chronic non-fatal disease in Europe. The economic impact of IBD on society and health care systems is high due to its occurring during the economically productive years and its chronic nature. The IBDchip project will contribute to reducing the negative impact of IBD for individuals and society by: predicting disease behaviour; predicting the likelihood of needing surgery; providing better predictions of response to different pharmaceuticals and by improving “quality of life” for patients.

### IMPACT ON SCIENCE AND THE EUROPEAN RESEARCH AREA

The IBDchip project is the first time that knowledge about the full range of genetic factors will be captured and brought into the public domain and made available through conventional science dissemination routes to improve the teaching and practice of research centres across the European Union.

» *Epidemiological and genetic research has provided evidence for the existence of numerous genetic determinants influencing susceptibility to develop IBD, IBD clinical course, risk of developing IBD-related complications and likelihood of responding to IBD therapies. A better understanding of these factors will lead to a clearer understanding of pathogenesis and to better treatment.*

# Workpackages

## WP1

### FINAL SNP SELECTION AND CHIP DESIGN

#### OBJECTIVES

- To identify polymorphisms (SNPs) that predict IBD susceptibility, behaviour and response to therapy from the medical literature and directly from the laboratories of the involved investigators
- To design oligonucleotides for the chip that will robustly identify the IBD SNPs

#### DESCRIPTION OF WORK

Through systematic reviews of the published and unpublished literature and also from data from their own labs SNPs that predict IBD susceptibility and disease behaviour will be identified. Allele specific oligonucleotide probes will be designed to detect both alleles for each of the SNPs selected in the first phase of WP1. In general probe length is between 19 and 27 nucleotides with the discriminatory nucleotide in the central position. Once probes have been validated, a series of optimisation steps associated with sample and array processing will be performed.

#### DERIVERABLES

At month three of the project the final list of SNPs will be available and by month six of the project these will have been put onto the chip to create the first version of the IBDchip to analyse the samples in the prospective and retrospective studies.

## WP2

### PREDICTION OF PHENOTYPE AND COMPLICATIONS IN CD AND UC

#### OBJECTIVES

- To define what genetic factors (of those included in the IBDchip) are significantly associated with different relevant clinical outcomes (previously defined for CD and UC)
- To provide a predictive model (combining these genetic factors) which results in an optimal prediction for each one of the clinical outcomes

#### DESCRIPTION OF WORK

A major new retrospective multicentre study involving 1.000 CD and 1.000 UC patients with a standard diagnosis of CD or UC, with ten or more years since diagnosis and a complete follow-up history since diagnosis in one of the partner centres.

Worksteps:

- Collection of clinical data
- Collection of blood samples - DNA extraction
- Shipment of DNA samples to Progenika where DNA will be analyzed by means of IBDchip
- Statistical analysis

#### DERIVERABLES

Statistical predictive models derived from the analysis of patterns of DNA correlated with disease development. This WP will produce the following clinical results:

- For Crohn's disease, prediction of: more extensive disease (ileo-colonic or proximal); development of fistulizing phenotype; development of perianal disease; development of stricturing phenotype; need for surgery; appearance of extraintestinal manifestations
- For Ulcerative Colitis, prediction of more extensive disease (pancolitis); need for surgery; appearance of extraintestinal manifestations

## WP3

### RESPONSE TO THERAPIES

#### OBJECTIVES

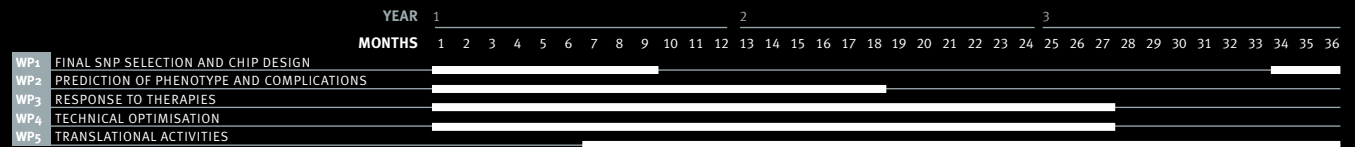
To produce an accurate predictive model for patients' response to a range of available therapies based on the prospective validation of data from WP 2 through further studies on Infliximab (including where possible data related to other anti TNF-alpha drugs Adalimumab and Certolizumab which will be in routine use for CD by the time the project is underway). This predictive model will be embedded on the prototype IBDchip.

#### DESCRIPTION OF WORK

The data from "Main Phenotype Study" (WP1) will form the basis of the prospective validation of the capacity of the IBDchip to predict response to pharmaceuticals. Prospective validation of the predictive models for response to azathioprine will be done as a part of "The Aztec Study". There will be another study on the response to Infliximab which will involve 200 CD and 200 UC patients. We will also include, where data is available, patients treated with other biological therapies i.e., Adalimumab and Certolizumab which should be in use for CD by the time the project starts. We will either analyse them separately (to assess response to each drug) or combine them with CD patients treated with Infliximab to assess overall response to anti-TNF-Alpha therapy.

#### DERIVERABLES

A codified, robust predictive statistical model consisting of a weighted combination of the genetic factors of the IBDchip that is best associated with response of patients with CD and UC to a range of pharmaceuticals incorporating both extensive retrospective and prospective data.



## WP4

### TECHNICAL OPTIMISATION

#### OBJECTIVES

To optimize the process of reading biochips and make the process ready for full, widespread commercialisation. This will be achieved by applying the Innopsys integration technology and know-how to develop a scanner with advanced new characteristics to make the reading process quicker, cheaper and more accurate.

#### DESCRIPTION OF WORK

- Integration of the optical system of the reader
- Integration of a photomultiplier in a specific box with a dedicated new electronic PCB
- Scanning system miniaturisation
- Developing a new CD actuator design for focusing on the slide
- Developing a unique embedded electronic PCB that will allow the treatment to be made directly inside the scanner
- Research and ensure compliance with all relevant medical device standards and regulations

#### DERIVERABLES

The final deliverable of this WP will be the first final prototype microscope slide scanner to be fully adapted to the new diagnostic and clinical tests markets and will it be ready by the end of month 27 of the project.

## WP5

### TRANSLATIONAL ACTIVITIES

#### OBJECTIVES

To clinically validate the IBDchip to prove that it can be used as a tool to aid clinical decision making in routine settings, that it is cost effective and that all ethical and legal issues are addressed during the project development phase In summary to make it as likely as possible that the prototype IBDchip will achieve widespread take-up and add substantial value in a wide range of routine clinical settings.

#### DESCRIPTION OF WORK

Worksteps:

- Assessment of performance of the IBDchip in a routine hospital diagnostic laboratory: this will be done at the Oxford Regional Genetics Laboratory in the first instance and then extended to other partner labs
- To map the clinical pathway for use of the IBDchip and to raise awareness of gastroenterologists
- To identify the ethical and legal issues associated with use of the IBDchip in Europe
- To estimate the cost-effectiveness of using the IBDchip compared with existing clinical practice. An economic decision model will be built to compare the costs and outcomes associated with using and not using the IBDchip in clinical practice

#### DERIVERABLES

The project outputs for this WP will be the reports, maps of clinical pathways and economic analyses that correspond to each of the worksteps.



## The consortium

The team offers a “holistic” range of complementary skills from research, through industrial innovation to the “translational” research necessary for maximum market impact. The three roles in the project are: **knowledge providers** - the hospital and university teams who will do the background research on the SNPs and also provide the DNA samples for the retrospective and prospective studies; **knowledge users** - the SMEs who will use the knowledge generated in the project to create innovative products, in this project, the IBDchip and the chip scanner; and **translational researchers** - ethicists, economists, and work practice analysts working alongside the other stakeholders to ensure that the final project outputs will be taken up widely and make maximum impact in routine clinical practice.



### PARTNERS

- 1 Institut d'Investigacions Biomèdiques Agustí Pi i Sunyer, Hospital Clínic, Barcelona (Spain)**

The Institute for Digestive Diseases at Clinic Hospital has been very active in research for the past 30 years and this has resulted in a leading position for the Institute in the fields of both Hepatology and Gastroenterology.

► Dr. Miquel Sans (coordinator)  
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- 2 Progenika Biopharma SA, Derio (Spain)**

Progenika produces oligonucleotide microarrays for the analysis of gene expression and for the diagnosis of genetic diseases.

► Dra. Marta Artieda Oseñaldea  
martieda@progenika.com  
www.progenika.com
- 3 Innopsys SA, Carbone (France)**

Innopsys' aim is to exploit its high-tech expertise and resources to develop competitive, high-performance industrial instruments.

► Stephane Le Brun  
s-lebrun@innopsys.fr
- 4 The University of Oxford, Oxford (UK)**

The Oxford Genetics Knowledge Park has the aim to facilitate and expedite the translation of genetics research into clinical practice.

► Dr. Derek Jewell  
derek.jewell@green.ox.ac.uk
- 5 Katholieke Universiteit Leuven, Leuven (Belgium)**

The gastroenterology Unit of the University Hospital in Leuven contains a very active centre for inflammatory bowel diseases.

► Dr. Severine Vermeire  
Severine.Vermeire@uz.kuleuven.ac.be
- 6 Vereniging voor Christelijk hoger onderwijs, wetenschappelijk onderzoek en patiëntenzorg, VUMC, Amsterdam (Holland)**

It promotes the study of immunogenetics as an integral part of health care disciplines.

► Prof. Salvador Peña  
as.pena@vumc.nl
- 7 University Hospital Schleswig-Holstein, Institute for Clinical Molecular Biology, Kiel (Germany)**

The Institute for Clinical Molecular Biology combines expertise in the positional cloning of complex disorders, functional genomics, cell biology and basic immunology with clinical excellence in gastroenterology.

► Stephan Schreiber (MD)  
s.schreiber@mucosa.de
- 8 General Faculty Hospital, Charles University, Prague (Czech Republic)**

Well known as a referral center for the treatment of IBD patients, and has expertise in the study of the role of genetic factors in IBD.

► Milan Lukas (MD)  
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- 9 Istituto Clinico Humanitas-IRCCS in Gastroenterology, Milan (Italy)**

The Division of Gastroenterology is a referral center of IBD patients for the North of Italy.

► Dr. Silvio Danese  
sdanese@hotmail.com



IBDchip is a project in the LifeSciHealth Priority of the European Commissions Sixth Framework Programme

For further information:  
[www.ibdchipproject.eu](http://www.ibdchipproject.eu)