

## Cancer Degradome

**Project title:** Extracellular Proteases and the Cancer Degradome: Innovative Diagnostic Markers, Therapeutic Targets and Tumour Imaging Agents

**Thematic area:** Life Sciences, Genomics and Biotechnology for Health

**Instrument:** Integrated Project

**Co-ordinated by:** Professor Dylan Edwards, University of East Anglia

**EC contribution:** 10.4m€

**Duration of project:** Four years from 2004

**Number of partners:** 32

**Subject of case study:** Professor Dylan Edwards, University of East Anglia.

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**Project website:** <http://bioweb2.bio.uea.ac.uk/cancerdegradome/welcome.html>

### The Challenge

In many European countries, cancer is now the leading cause of potential years of life lost to disease. The ageing of European populations is progressively increasing the number of new cancer cases.

The critical defining feature of a malignant tumour is the presence of cancer cells that have penetrated into surrounding normal tissue, escaping into the circulation and establishing secondary tumours elsewhere in the body. This cellular invasion and metastasis involves the action of extracellular proteases from multiple enzyme classes (metalloproteinases and serine, threonine, thiol and aspartic proteases), constituting the Degradome – the complete repertoire of proteases through which cells and tissues regulate their local environment.

First generation anti-protease drugs were found disappointing in clinical trials but it has become clearer that the diverse extracellular proteases have complex roles with distinct functions at different stages of tumour development and progression and, thus, may have conflicting effects on malignancy.

### The Project

The European Cancer Proteases Consortium is undertaking multidisciplinary research into innovative cancer therapy and diagnosis based on the Degradome for the common human malignancies breast and prostate cancer (with some additional work on skin and colorectal cancer). The project covers a wide range of research techniques including cell and animal models of cancer, analysis of patient tissues, molecular profiling and modelling, synthetic chemistry, and molecular imaging (MRI and PET) of tumours. Throughout the research there is emphasis on access to shared technologies, data analysis and knowledge dissemination.

As some proteases inhibit rather than facilitate cancer growth, the project aims to develop enzyme-specific initiatives – adopting a genome-wide approach to the Degradome in order to identify key proteases and design selective inhibitors to target different aspects of malignant transformation.

There are three main objectives:

- Define new molecular targets for drug design; developing novel specific interventions based on knowledge of the pathophysiological roles of target proteases - understanding how and when to intervene.
- Identify new profiling technologies, molecular diagnostic and prognostic indicators of disease status and patient risk that can improve health care delivery based on an individualised approach to therapy.
- Provide new ways to enhance clinical visualisation (functional imaging) of tumours.

## **The Consortium**

The consortium comprises 32 organisations in 13 countries (including five SMEs, mainly technology providers spun out from public sector institutions). It is coordinated by the Biomedical Research Centre at the University of East Anglia (Professor Dylan Edwards, Project Coordinator; Aileen Hogan, Project Manager).

Partners participate in five clusters:

- Degradomics and Interactomics
- Functional genomics – animal and cell based models
- Molecular pathology – human tumours and diagnostic markers
- Molecular pharmacology and drug development
- Tumour imaging.

## **Perspectives from the Project Coordinator**

### Achievements and impact at the European level

Outputs from the consortium already include an impressive number of pioneering scientific publications and patents (the latter covering, for example, new agonists and antagonists of critical events in cell migration and angiogenesis; new contrast agent for imaging by magnetic resonance angiography; and novel 3-dimensional approach to visualisation and quantification of tissue damage in histological analysis). These scientific outputs have been accompanied by extensive effort in training and support for researcher mobility.

From the perspective of the project coordinator, the major current achievements that distinguish the Degradome consortium include:

- Bioinformatics analysis – mapping proteases to define the scale of the Degradome and generating the tool kit for further work;
- Use of gene knockout animals models by many of the partners to probe the function of proteases;

- Use of X-ray crystallography and saturation mapping of protein structure by systematic mutagenesis to provide detailed knowledge of structure and function of targets.

Scientifically, it can be concluded that the project is already very successful in terms of the demonstrable progress in each of the initial objectives (novel therapeutic approaches, diagnosis, imaging). The challenge for coordination during the remaining lifetime of the project is to ensure that the broad range of discovery deliverables already accomplished supports increasingly focused outputs in the final year. For example, having established proof of concept for druggable targets, the consortium will need to capitalise on its small molecular weight compounds as relatively selective inhibitors of target proteases by developing the appropriate linkages for commercialisation.

Project coordination is a major demand on the time of the coordinator, but there are also particular rewards. One benefit for the coordinating laboratory is a raised visibility with other leading laboratories; in the EU and elsewhere (successful links have been built with a US consortium). The experience in coordinating Cancer Degradome (the first Framework Programme 6 Integrated Project to be coordinated at the University of East Anglia) has also stimulated interest within the host institution such that other research groups have been attracted to participate at the EU level.

The continuing interest by the European Commission in cancer proteases is highly welcome and the Degradome coordinator hopes to build on lessons learnt in Framework Programme 6 to engage with Framework Programme 7. From the current details in the Framework Programme 7 work programme, there seem to be several opportunities that may usefully support the further focusing of current research effort, possibly mobilising resources in smaller consortia to deliver European added value.

### Managing a large consortium

The Degradome Integrated Project is large and wide-ranging. The provision of a dedicated project management resource by the coordinating laboratory has been essential to maintain the philosophy of inclusiveness introduced at the outset. To date, the project has been particularly successful in fostering existing relationships between partners and in building interactions within the work clusters. The continuing challenge is to facilitate interaction between the different clusters and to develop new synergies across the project partners.

In terms of the interaction between the consortium and the European Commission, the scientific working relationship is good. What has been found more difficult is the apparent inconsistency in Commission financial reviewing decisions over the course of the project. As a "tip for improvement", project management would be aided by more transparency and clarity in the Commission's financial review.

### Sharing best practice

The Framework Programme 6 SSA (SPARK <http://www.spark-fp6.com/> ) in the LifeSciHealth priority that has supported interaction between managers of different projects has become very useful in sharing experience of good practice in management and has led to new interactions between UK project managers –

particularly valuable in coping with the challenges presented by the large IPs. The Commission might now do more to encourage equivalent interaction between project coordinators to facilitate discussion of common coordination issues and, also, to encourage strategic interchange of relevant scientific interests between projects. Inter-project interaction could be further enhanced, perhaps, by creating a mechanism whereby a lead academic plus lead SME scientist from consortia met collectively to share experience and foster the academic-biotech industry interface.