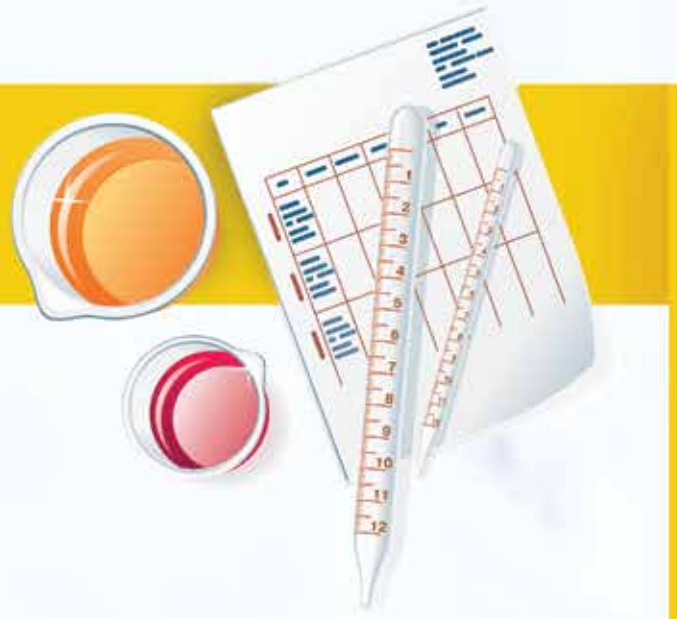
PROFESSOR JOHN HICKMAN

Driving drugs to trial



Coordinating the development of new models for drug target validation sees **Professor John Hickman** and eight other pharmaceutical laboratories working with a world-class team of European biologists, clinicians and computational scientists. Here, he talks about their progress to date

What do you think should be done to increase the return on investment for the drug industry to ensure companies remain involved?

The most expensive part of drug discovery is currently phase II and III trials. It is here that two thirds of novel drugs, considered to be efficacious in pre-clinical models fail to show benefit to patients. My opinion is that the pre-clinical work is under-resourced because budgets are too focused on clinical trials. This phase of drug discovery needs to be re-tooled.

Whole sub-industries outside the industry itself serve this pre-clinical discovery cascade and naturally have interests in maintaining the status quo. I think it is critical in the future that budgets are front-ended to the early stages of drug discovery (pre-clinic) so that early and better informed 'go/no-go' decisions can be made in the laboratory based on much better assays, diminishing the risk of subsequent and expensive failure. There are ethical questions too about clinical studies that are being performed with a 90 per cent failure rate.

Do you belive that there is something wrong with current pre-clinical drug discovery methods?

To be fair, Industry has adopted methodologies from much of current cell and molecular biology, so maybe this is to blame! Pathology is complex; most cellular and molecular biology dissects and reduces this complexity to permit investigations of single components of the healthy or pathological cell. In laboratories, cells are grown in isolated cultures or in immune-deprived mice, not connected to the plethora of extracellular signals and appropriate cell-to cell contacts that set the context for normal or even pathological function. The results from these reductionist systems are, to various degrees, insufficient approximations of reality.

Successful collaboration is a key part of the project. Is this simple to achieve?

The project is goal orientated and long term. Bringing together different industrial cultures with those of academia has been interesting. Some of the industrial partners are under pressure to show rapid returns which are unrealistic, whilst some academics are under pressure to publish papers as senior authors – a difficult task whilst working in a consortium. Both parties need to think rather differently and see PREDECT as one project in a portfolio of activities under their direction. This is not easy.

What has been the primary focus of the first 18-24 months of PREDECT?

The first period – the honeymoon of the marriage between the industrial and academic partners – has been used to establish technologies and lines of communication so that progress and problems can be shared and tackled together. The great advantage of Innovative Medicines Initiative projects to industry is that teething problems of some quite difficult technical platforms, such as tissue slicing, can be resolved as a team. This prevents duplication of effort across industry and advances projects more efficiently and rapidly.

A major achievement of this first period was also to put the central molecular pathology platform together: all partners will submit material for analysis and archiving as tissue microarrays (TMA). Standard operating procedures have had to be put in place for fixation and this has posed some challenges for platforms such as three-dimensional (3D) cultures. The TMAs will be stained for tens of proteins, first requiring in this period validation of antibodies. Archived TMAs are traceable through an electronic record and can be visualised in the participants' own laboratory

via web-based microscopy. In addition, PREDECT has growing expertise in advanced imaging which, in the long-term, may allow live cell imaging of complex 3D cultures.

How do you see the project evolving over the remaining years?

In the next year, PREDECT will have a slew of results allowing us to fine-tune the analysis of many proteins expressed in slices and complex 3D cultures. This will permit comparisons with expression in a tumour *in situ*, and ultimately allow us to interrogate aspects of cell circuitry in the resting state and when perturbed by drugs with known mechanisms of action.

Where the word 'validation' will be very important is in the validation of the new platforms themselves. Will they perform better than existing *in vitro* platforms? Can we persuade management in industry to use them to inform go/no-go decisions? One interesting challenge may be to take 'failed' drugs and show that these platforms would have predicted this failure. We have three years left to try and reach that point.

Deconstructing tumours

Concerned about current tools and methods used to deliver results in pre-clinical drug target validation, a European public-private partnership known as **PREDECT** is aiming to improve platforms for drug discovery

THE GLOBAL MEDICAL field is facing huge challenges associated with discovering novel drugs. The poor rate of success in finding effective new drugs is ubiquitous and is leaving the healthcare industry in a quandary. One of the greatest difficulties comes from the fact that the return on investment from drug discovery programmes is struggling to meet spiralling costs and high failure rates.

In efforts to pioneer a new approach to this pervasive problem, the EU's Innovative Medicines Initiatives (IMI) was born out of a collaboration between the EU and the European Federation of Pharmaceutical Industries and Associations (EFPIA). IMI addresses problems of innovation in many areas of the healthcare sector. Programmes started in March 2008, and three projects on cancer in 2010. The focus of one of the cancer initiatives is on creating novel, robust and reproducible *in vitro* models that deliver state-of-the-art platforms for both target validation and drug discovery. Known as PREDECT, it is an alliance between nine academic institutions, three SMEs and nine EU pharmaceutical companies who are looking at ways to break new ground for *in vitro* models that embody, with improved reliability, the complexity and heterogeneity of human tumours.

ADVANCING TARGET VALIDATION

Validation of potential drug targets is a critical part of developing novel pharmaceuticals. The pre-clinical data that is gathered through laboratory tests is responsible for propelling a drug to clinical trial. However, currently available methods for pre-clinical experiments are incorrectly validating many targets and drugs, meaning that drugs proceed to clinical trials but fail – a hugely expensive and time consuming process. In order for industry to reduce the time and cost involved, a more effective way to confirm the likelihood of success at an early stage is required.

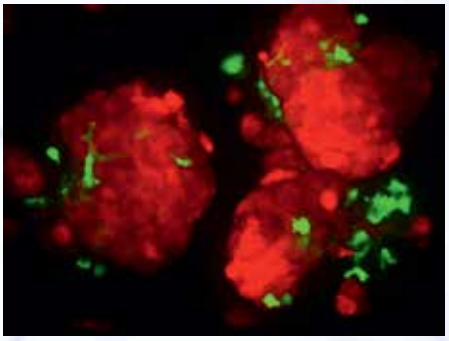
Early target validation, using cellular and molecular biology tools, is a necessary and important first step in the process of drug discovery. However, one of the challenges facing modern target validation is that the models used can become oversimplified. Professor John Hickman, responsible for coordinating PREDECT, describes the problem with current target validation as starting with data coming from a heterogeneous, complex human tumour which is then translated into oversimplified laboratory models: "The key element that is often lost in the process of target validation is the perception of the target as being part of a complex circuitry," he explains. "Simplifying that circuitry too much probably increases the possibility of positive target validation."

Hickman and his colleagues in PREDECT believe that industry needs to perform target validation with as much as possible of the circuitry intact, which calls for improved models and a realisation of the limitations of current laboratory models in regards to their ability to incorporate dynamic complex disease states. "Early decisions to stop projects, based on data from more representative models, may greatly reduce attrition rates in the most expensive phases of drug discovery, during subsequent phase II and III clinical trials," he concludes.

BREAKING DOWN THE PROBLEM

The PREDECT team co-coordinated by Dr Ralph Graeser at Janssen in Belgium, and with academic coordination from Emmy Verschuren in Helsinki, is exploring how to 'deconstruct', step by step, a complex tumour to create models whose characteristics – circuitry, protein and gene expression – can be compared with a real tumour. For the first stages of this process, three major tumours – breast, prostate and lung – are being investigated by deconstructing their intricacies *in vitro*. This is being undertaken at different levels of decreasing complexity. At each level, features of the models are being determined which still represent the original complex tumour *in situ*.

One of the guiding principles of this initiative is the concept that tumours are pathological



Development of complex 3D models of prostate cancer cells (red) co-cultured with fibroblasts (green). © Malin Akerfelt and Matthias Nees (VTT Turku, Finland)

organs which grow in three dimensions. To build on this idea, they are studying the generation of thin (about 250 microns) slices where the tumour cells are left connected with the surrounding tissue or stroma, capturing all of the immune, endothelial and mesenchymal cells. The question which they are asking is how the complexity of the cells can be retained in a slice and whether or not the cells have a functioning biochemical profile that is similar to the tumour of origin. One concern is that the procedure used to make the slice can stress the cells for a long period. PREDECT will look at varying complexities of circuitry within cells of a slice, as well as other three-dimensional models.

Samples will be harvested and archived as tissue microarrays (TMAs), which can then be analysed through multiplexed immunohistochemistry methods and advanced imaging techniques.

PREDECT

OBJECTIVES

- To compare the pathological and molecular profiles of novel *in vitro* platforms with those of human tumours
- Ultimately, to create more appropriate *in vitro* platforms for target validation and drug discovery

KEY PARTNERS

For a full list of partners, please visit **www.predect.eu/about/participants.**

FUNDING

Innovative Medicines Initiative

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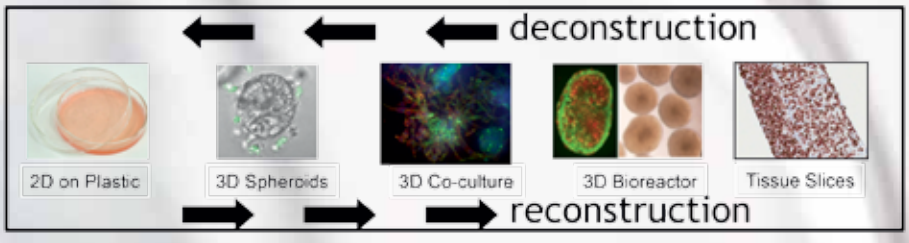
PROFESSOR JOHN HICKMAN is an internationally known scientist who trained in Pharmacy and received his PhD in Organic Chemistry in 1971. In 1989 he received his Doctorate of Science and after a postdoctoral fellowship at the Institute of Cancer Research, London, he held university posts in Molecular Pharmacology in Liverpool, Birmingham, Manchester and Yale.

Amongst many achievements, as a Director of the Cancer Research Campaign's (now Cancer Research UK; see p13) Experimental Chemotherapy group in Birmingham, he was lead pharmacologist for the discovery of the important and highly successful drug Temozolomide, now used to treat brain tumours. In Birmingham, he was a founding Director of Aston Molecules, a biotechnology company subsequently purchased by OSIP in New York. And the Manchester Biotechnology Incubator was co-initiated by him at the University of Manchester. Its restaurant bears his name – 'Hickman's'.

Hickman moved to Paris in 2000 to direct cancer drug discovery at Servier. During his tenure, four novel molecules have been advanced for development. He has published over 150 articles, with his most highly cited paper on apoptosis receiving almost 1,000 citations. Since his retirement in 2010, he has coordinated the PREDECT project, in addition to other consulting projects.



Some of the platforms created as complex tumours are either deconstructed or reconstructed in the PREDECT project

"Our decision to use immunohistochemistry and microscopy addresses the challenge of analysing a heterogeneous mass of cells," elucidates Hickman. "It also addresses the question of the importance of phenotype compared to genotype."

A primary challenge in deconstructing tumours is the need for substantial quantities of human sample material which is generally not readily available. One of the long-term objectives of PREDECT is to develop genetically engineered mouse models (GEMM) of cancer which mimic the complexity of human tumours. The possible isolation of both stromal and tumour material from these models is being investigated as well. It is hoped that this approach will offer a continuous resource of material for tissue slices and novel cell lines for three-dimensional (3D) spheroid models. The process is already underway, creating and characterising GEMM models of oestrogen receptor-positive breast cancer, prostate cancer and non-small cell lung cancer.

IMPROVING DECISION MAKING

The driving goal of PREDECT is to generate *in vitro* laboratory models that better represent the intricacy and heterogeneity of a cancer and retain as much intact circuitry as possible. Hickman believes that this will offer industry improved *in vitro* models which can be used to better validate or invalidate targets at the beginning of the drug hunting process rather than nearer the end. These industrial tools should then be adaptable to the subsequent steps of drug discovery. "Provision of a range of models of varying complexity, such as tumour tissue slices and models where tumour cells grow in three dimensions together with other types of cells, will hopefully permit industry to make better informed decisions on whether to launch and progress drug discovery programmes," he explains.

The new models are anticipated to be more expensive and more work-intensive than current models, but it is also expected that resources can be shifted from the budgets for currently expensive, and failing, clinical trials to pre-clinical studies. Any decision to proceed can then be based on far sounder evidence and the expected likelihood of success at the clinical trial stage will be greater.

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This is a highly exciting project that offers potential to reduce the currently unsustainable levels of attrition for novel cancer drugs by providing early and robust decisions for industry. As a result, PREDECT has important implications for the pharmaceutical and healthcare industries in the way in which current and future research and development programmes progress.

The goals of PREDECT

- Improving *in vitro* models of human disease, through the development of complex, reproducible and robust models that more closely mimic the cellular organisation of tumours (eg. in three dimensions) and the cellular heterogeneity within human malignancies
- Cross-validating, in a reciprocal way, these novel complex *in vitro* models against relevant *in vivo* models which more closely reflect characteristics of human cancer pathology, particularly tumours arising in transgenic mice
- Using a systems biology-based approach to integrate and compare -omics data derived from novel models and public databases, to generate testable *in silico* models of the biochemical circuitry associated with potential drug targets