

Cancer medicines: preclinical models and the challenges for therapeutics

One of the key challenges in the development of novel therapies lies at the interface of preclinical and clinical development, participants at the inaugural meeting of the "Development of cancer medicines" series heard. **Joseph Chamberlain** reports

Sue Burchill, of the University of Leeds, highlighted the problem that, despite huge investment in terms of money and time, current therapies are still lacking in efficacy and have excessive toxicity, thus driving a continued search for improved therapies. One of the key challenges in the development of novel therapies lies at the interface of preclinical and clinical development, specifically with the ability of preclinical models to predict clinical outcome.

With the advent of novel molecular targeted therapies, the traditional drug development model and the choice and role of preclinical models may need to be re-examined. It may be that it is not new models that are required, but that existing models may be better used, said Dr Burchill. As models become more complex, throughput of screening programmes decreases and overall development costs increase, although this may be balanced by a higher success rate.

Clinical challenges

Jeffrey Evans, of the University of Glasgow, put forward the perspective of the cancer clinician. He said that despite the advances in the understanding of molecular biology, surgery and radiotherapy remain the first choice for the treatment of many forms of cancer although, particularly in the advanced stages of disease, systemic forms of treatment are required.

The clinical challenges are exemplified by pancreatic cancer, which is one of the half dozen most frequent cancers of the West, and its incidence is rising. For this form of cancer, 90 per cent of occurrences are inoperable and the patients' prognoses remain bleak, making it probably the greatest challenge facing clinicians, said Professor Evans.

In the period 1991–94, 25 new agents were entered into 28 phase II clinical trials with little or no success. He suggested that new models that replicate the molecular biology of the human disease are needed because, although there exist successful agents that will kill cancer cells, they generally have narrow therapeutic windows. Many potential molecular targets are also unexplored.

Traditionally, in phase I studies, eligible patients at an advanced stage of disease are selected and given escalating doses according to an appropriate statistical scheme, until the maximum tolerated dose has been defined. Phase II looks to identify those drugs that show activity in at least 20 per cent of cases, while phase III defines efficacy in terms of

survival time, progression-free survival and quality of life in larger patient populations. With novel therapies it may be more meaningful to define the optimal biological dose rather than the maximum tolerated dose, while efficacy may be demonstrated by factors other than tumour size. Only if appropriate endpoints and surrogate markers of response have been defined based on suitable preclinical models will it be possible to design clinical trials in the most appropriate way and avoid the risk of discarding promising agents due to poor clinical trial design.

Not a factory process

The ideal of modern cancer research involves the study of the cancer genome to embark on appropriate diagnostics, prognostics and biomarkers in parallel with development of new therapeutic agents, resulting in personalised diagnosis and treatment. However, drug development is not a factory process, said Paul Workman, or the Institute of Cancer Research, Sutton, Surrey. It still requires much "individual inspiration and perspiration".

Despite media acclaim for Glivec (imatinib) in myeloid leukaemia, Professor Workman did not think the way ahead for molecular cancer treatment was so clear-cut. In phase I, there was only a 5 per cent success rate for cancer therapies compared with 11 per cent for all drug treatments. Drug development still proceeds only slowly and many fail expensively in the late stages. The use of biomarkers for patient selection has been sporadic, and multiple molecular abnormalities are common, thus complicating the selection of appropriate markers. The potential for many important pathways for drug intervention remains unexplored, and resistance is still a problem.

A lesson can be learnt from the study of pharmacokinetics for small molecule drugs, said Professor Workman. When many drugs failed in the clinical stages because of undesirable properties of absorption, distribution, metabolism or elimination, much effort was put into determining these characteristics in

the early stages of development. This focus on a specific problem resulted in better selection and modification strategies that ensured appropriate molecules were entered into clinical trials. What is wanted from better pre-clinical models then is an increase in the success rate and this should be done by better selection of targets, integrating the use of multiple technologies, improving the predictive properties of the model, raising the bar for entry into clinical trials, identifying sensitive cancers, identifying biomarkers for intelligent development, and anticipating resistance mechanisms.

Ultimately we would like to achieve the implementation of personal medicine, a drug for every molecular abnormality (or at least for key points in the pathways), the ability to predict and deal with resistance, and efficient combination therapy. Drug development is no longer a linear process, but is iterative and needs the input of different professionals, concluded Professor Workman.

Importance of drug delivery systems

Ruth Duncan, of the University of Cardiff, emphasised how drug delivery systems play an important part in the success or failure of developmental agents.

Activity of candidate compounds is obviously important but this is to no avail if delivery is poor. New workers in this field should benefit from the past 30 years of progress in delivery systems. Nanopharmaceuticals represent an emerging field where the nanoscale element may refer to either the size of the drug particle or to a therapeutic

Details

The Academy of Pharmaceutical Sciences of Great Britain and the British Association for Cancer Research hosted the inaugural meeting of the "Development of Cancer Medicines" series. The meeting took place in London on 30 November 2006

APS

The Academy of Pharmaceutical Sciences is an independent professional body which aims to provide scientific training through conference and seminar programmes, support focus groups for networking in specialised subject areas, collaborate with other organisations in Europe and the United States and represent views nationally and internationally.

The academy works in partnership with the Royal Pharmaceutical Society in a formal agreement to co-develop programmes for scientific events, including the British Pharmaceutical Conference science programmes. Further information on joining the academy and the benefits of membership can be found on its website apsgb.org.

delivery system. These therapeutic systems may be defined as a complex system consisting of at least two components, one of which is the active ingredient. In this field the concept of nanoscale is the range from 1 to 1,000nm. The definition includes polymer therapeutics, which share many characteristics with macromolecular prodrugs such as antibody conjugates of drugs.

Over the past decade, several polymer-protein conjugates have been taken to market and 11 polymer-anticancer drug conjugates have been progressed into clinical development. The most successful drugs of this type in the clinic have been rationally designed in respect of molecular weight, drug content, and the polymer drug linker. If the link is too labile the prodrug is not delivered. If the link is too strong the drug is not released. The link must be designed to degrade in a controlled way in the right place and this can only be achieved and tested with the appropriate models in place. While some of these properties can be explored with cellular systems, Professor Duncan pointed out that many questions pertaining to transport and access of drugs to the tumour, as well as toxicity and efficacy require the appropriate systemic models.

Use of disease-specific models

What should we learn from models, asked Anton Berns, of the Netherlands Cancer Institute, Amsterdam, in presenting research results on the use of disease-specific models. It was noted that tumours are only dangerous when they begin to metastasise. Thus, simple approaches to develop better models for improved therapy in human cancers should reproduce conditions for the tumourigenic process in man.

The same mutations then need to be introduced in supposed target cells, and then in appropriate subsets, and at the appropriate times in the life cycle of the experimental animal model. Furthermore, there should be some relevance to the tumour response. We should ask if the target is required for the survival of cancer cells.

Models should also identify the pathways that may be important in combination therapy. Several models were described which had these features.

One important observation was that the tumours that developed acquired a range of additional genetic changes leading to less clearly defined and more heterogeneous models. The most important role of models is whether they are predictive of the human situation and, despite considerable progress on the laboratory front, the jury is still out on this issue for many of the more sophisticated model systems, concluded Professor Berns

Multimode imaging methods

The challenges for developing anti-cancer agents include having a valid target or pathway, predictive models, and fit-for-purpose biomarkers, said Eric Aboagye, of Imperial College, London. Non-invasive imaging

techniques have a powerful role to play in this respect because they allow sophisticated longitudinal studies *in vivo*, assessment of the location of administered drugs, and their delivery and efficacy *in situ* within the tissues of interest.

Imaging using positron emission tomography, magnetic resonance or bioluminescence is used to increase the understanding of gene function in health and disease within the whole organism. The use of multi-mode imaging methods which combine various techniques can also help to improve the predictive value of disease-specific models and Professor Aboagye believes that imaging should be added to the classical pharmacological and biochemical tests, to better inform clinical trials.

Hollow fibre assay

Mike Bibby, of the University of Bradford, described the use of the hollow fibre assay for *in vivo* drug evaluation. This assay was originally developed by the National Cancer Institute as a screening filter between *in vitro* screens and *in vivo* xenograft assays, giving immense savings in time, money and use of animals.

The hollow fibre assay at full capacity allows screening of 50 or more compounds per week in a 10-day assay. In addition to requiring less than two weeks to complete, it requires at most only 450mg of material, as opposed to the multigram quantities required for xenograft studies. In addition, several such experiments can be conducted at the same time in the same animal.

Compounds that retard the growth of the selected tumour cell lines can then be recommended for the next level of testing. In the method, small hollow polyvinylidene fluoride fibres (typically 1mm in diameter, 2cm long) containing the tumour are inserted underneath the skin and in the body cavity of a

mouse. Mice are treated with experimental agents and fibres collected following the treatment period to determine the course of cell growth.

Professor Bibby demonstrated how the hollow fibre assay can be used to demonstrate drug-target interactions *in vivo*. It is an ideal follow-up to *in vitro* screens, can demonstrate a compound's *in vivo* pharmacology at an early stage, and is consistent with the target-orientated approach to drug discovery.

Genetic changes in cancers

Terry Rabbitts, of the University of Leeds, described how his work on the genetic changes in cancers can lead to better preclinical testing.

Targets can be at the gene, nucleic acid or protein level. Specific chromosomal translocations are found in leukaemias, sarcomas and carcinomas, affecting genes near the translocation breakpoints. The uniqueness of chromosomal translocations in tumours suggests that their products could be targets for anti-cancer agents. Chromosomal translocation proteins are intracellular molecules and thus targeting therapeutics to them presents difficulties. However, their involvement in protein complexes suggests an attractive target for therapy, as disruption of these interactions could be effective in producing anti-cancer effects.

The work has two strands — the development of the mouse models and the development of macromolecular drugs. Both strands lead to testing of the macromolecules in mice and ultimately to useful therapies in patients.

Monitoring responses

Gill Tozer, of the University of Sheffield, described approaches to monitoring responses to vascular-targeted drugs which can be classed into vascular-disrupting agents and anti-angiogenic drugs.

Vascular disruption is characterised by rapid shutdown of established tumour vessels, tumour growth delay and intermittent dosing, whereas anti-angiogenesis is characterised by prevention of new vessel formation, tumour growth delay and continuous dosing. Appropriate preclinical studies on vascular agents should define their toxicity, give evidence for a selective effect and mechanisms of action and provide guidance for timely clinical trials.

Methods for studying tumour vascular response include high-resolution microscopy of excised tissue and low-resolution methods using contrast agents to observe the flow of blood in the tumour.

Professor Tozer described examples of work on tubulin and non-tubulin binding agents as vascular disruptors and concluded that such animal studies provided means for testing effects of vascular targeting agents on vascular morphology and function, investigating mechanisms of action, determining the most appropriate vascular end-points and assessment times for clinical trials, and interpreting clinical imaging data.

Proper validation needed

All speakers took part in a comprehensive panel discussion. It was agreed that new technologies would only be better if properly validated.

Although there were similar approaches, there was a difference between the needs of an academic trying to understand the mechanisms of cancer and cancer therapy and the industrial researcher screening large numbers of candidate compounds.

A thorough understanding of molecular pathways seemed to be the most important feature, so the target can be evaluated for selection of the best model. However, a systematic approach should not preclude the prepared mind from serendipitous discovery.

It was extremely important to link the work and needs of the laboratory and clinical researchers.

The reduction in the use of large numbers of animals by implementing the new methods described was a welcome development not just for financial reasons but from an ethical viewpoint.