Surrogate endpoints IN CANCER TRIALS

Over the next 20 years systematic programmes of cancer risk assessment will be established and cancer-preventive drugs will be developed. The ability to prevent cancer will dramatically increase the number of people who will need to regularly attend clinics. This article discusses how we urgently need surrogate endpoints to enhance the speed of assessment in the development of drugs in this presently under-researched area and the potential benefits they can bring such as lowering costs, reducing time to NDA, bypassing need for phase II studies and reviving dead drugs.

By Professor Karol Sikora

The last two decades have brought remarkable progress in our understanding of the molecular basis of cancer. It is likely that the classification of tumours by their molecular phenotype will provide the key to predicting their natural history and response to treatment. Such systems will replace conventional histological approaches within the next five years. Functional genomics, proteomics, the development of novel animal models for human cancer and the ability to accurately verify biochemical targets has yielded several exciting platforms on which to develop novel therapies. The dramatic increase in the pace of discovery of new molecules for clinical trial requires innovative approaches for their clinical development.

To enhance the speed of assessment, it is now essential to identify surrogate endpoints to validate the effectiveness of a potential drug. Waiting for survival benefit is just too slow. A surrogate endpoint can be defined as a substitute measurement of benefit (derived from Latin *surrogare* – to substitute). A biomarker is a biological marker of an effect on a target and can in some circumstances be used as a surrogate. In the short term such assays will determine the activity on a specific molecular target *in vivo* and allow the construction of dose response curves, often in healthy volunteers. This is a radical departure from cytotoxic drug development. The use of such pharmacodynamic (PD) endpoints will replace the current phase I dose escalation schedules by which the maximum tolerated dose of a cancer drug is determined (**Table 1**).

Once the maximally effective dose has been identified, surrogate endpoints of effectiveness to halt tumour progression will be required. Such markers may include the release of specific tumour DNA fragments into serum, the quantitation of novel tumour markers or the identification

Table 1

Surrogate endpoint

a substitute measurement of benefit

- Biologically relevant
- Directly relates to disease activity
- Time course rapid
- Easy and cheap to measure
- Non-invasive

Table 2
Chemotherapy for advanced cancer

HIGH CR HIGH CURE	HIGH CR LOW CURE	LOW CR LOW CURE
HD	AML	NSCLC
ALL	breast	colon
testis	ovary	stomach
chorio	SCLC	prostate
childhood	sarcoma	pancreas
BL	myeloma	glioma

of downstream effects of tumour growth delay such as apoptosis, necrosis or the interaction with local blood vessels. Biochemical markers are being sought but other approaches such as positron emission tomography, nuclear magnetic spectroscopy, isotope scanning and a range of innovative non-invasive imaging systems will provide useful data on protein phosphorylation and even specific mRNA expression. It is conceivable that genetic indicator systems, introduced by direct injection into tumours, will yield information on both the effect of the drug locally and the response of cancer cells to it. Sophisticated array systems can monitor patterns of gene expression before and after therapy. Such techniques enhance the speed of early candidate drug selection and reduce the risk of later failure. They will almost certainly form part of future regulatory packages. The diverse nature of these highly specialised techniques will by necessity concentrate the early phase of drug development in a few centres of excellence rather than the current more diffuse pattern.

Leveraging the clinical-scientific interface in cancer research is a key component in accelerating the development of novel therapies. Creating innovative partnerships between an increasingly consolidated and globalised industry and major cancer treatment centres is now essential to enhance the speed of drug development. Currently more than 400 compounds are undergoing clinical trial for cancer, and this number can confidently be expected to reach more than 500 by the end of 2001. There has been a significant shift to the exploration of molecules with novel mechanisms of action during the last three years.

Cancer drug development in transition

Cancer drug development is entering a remarkable new phase. Although nearly all current anticancer drugs were discovered by serendipity[1], the effectiveness of chemotherapy in treating cancer has been relatively disappointing. Although several cancers can be effectively cured by chemotherapy, these are relatively rare. The common solid tumours such as breast, lung, prostate and colorectal cancer are only partially responsive to drug

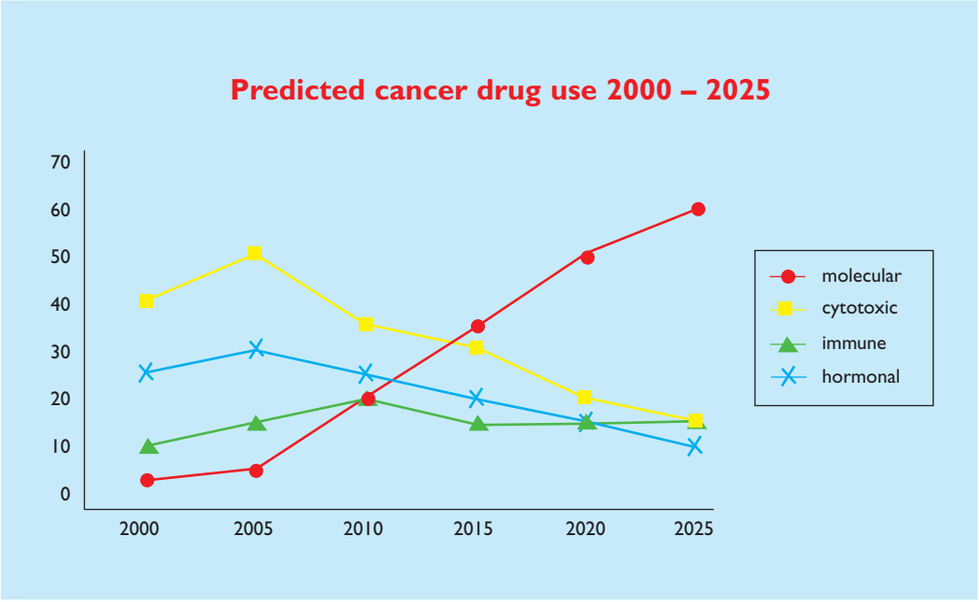

Figure 1
Predicted cancer drug use as a percentage of total use over the next 25 years. It is likely that drugs with novel molecular mechanisms of action will overtake cytotoxics in the middle of the next decade

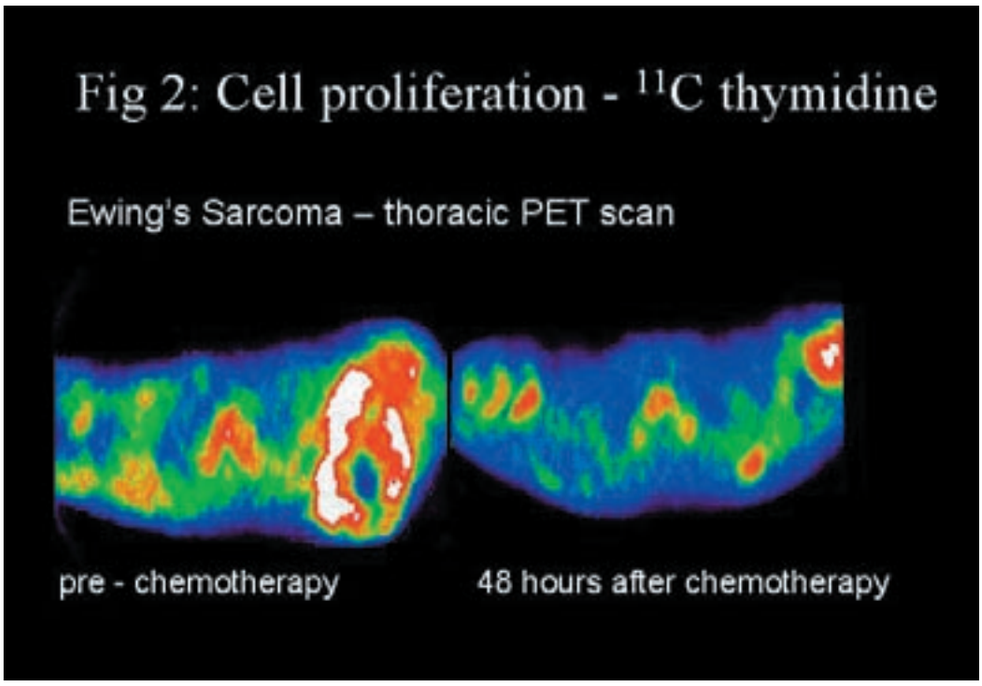

Figure 2
A ^{11}C thymidine PET scan performed before and after chemotherapy in a patient with a large thoracic Ewing's sarcoma. This agent is incorporated into DNA during mitosis and therefore the signal strength reflects mitosis. Although the tumour has not changed in shape or size as judged by conventional CT scanning, the PET scan shows that mitosis has been switched off within 48 hours of chemotherapy – an effective surrogate for subsequent tumour response.
(Courtesy of Professor Pat Price, MRC Cyclotron Unit, Hammersmith Hospital, London)

therapy. Drug resistance is either present at the start or is rapidly acquired through multiple molecular mechanisms. **Table 2** summarises the current position of chemotherapy in cancer treatment. Different views are held about the value of chemotherapy around the world with some countries adopting a more aggressive stance.

Exploratory compound flow

Over the last five years there has been an increasing shift to the discovery of drugs acting through defined molecular mechanisms. The Human Genome Project has created a dictionary of the genome[2]. And we can now also interrogate it through sophisticated bio-informatic systems. Not only do we have the library but we have the search tools. We can predict the three-dimensional structural biology of many proteins and create images of drugs *in silico* using computers to design small molecules which then can be synthesised in the laboratory to check their activity. A platform approach to drug discovery is creating a massive increase in new candidate molecules for cancer therapy. The protein kinases represent a good example of a platform used to develop a series of drugs which can affect processes as diverse as tumour blood vessel growth, cell division, natural cell death and growth control.

One of the problems currently is the large numbers of targets that have been identified in the cell to which new drugs can be developed. These targets extend from growth factors, cell surface receptors, signal transduction cog molecules, transcription factors, apoptosis stimulating proteins and cell cycle control proteins. Which one to target and to invest research funds into is a difficult decision[3]. Well defined targets are the starting point on the road to our future treatments. It is likely that classical cytotoxic drugs will continue to be used for the next 25 years although they will have a declining share of the total marketplace. This transformation is likely to start in the next two years with epidermal growth factor receptor and angiogenesis inhibitors. By 2015 successful molecular targeted approaches will overtake cytotoxics and transform cancer medicine (**Figure 1**). These new drugs will be individualised, chosen on the basis of molecular measurements on the patient's tumour and normal cells and taken orally for long periods of time.

The golden age of drug development

The classical way in which we develop cancer drugs is split into three phases. In phase I, the maximally tolerable dose is determined by gradually escalating the dose in patients with cancer[4]. From this we can determine a workable dose that patients can tolerate and yet is likely to have a therapeutic effect based on animal studies. We

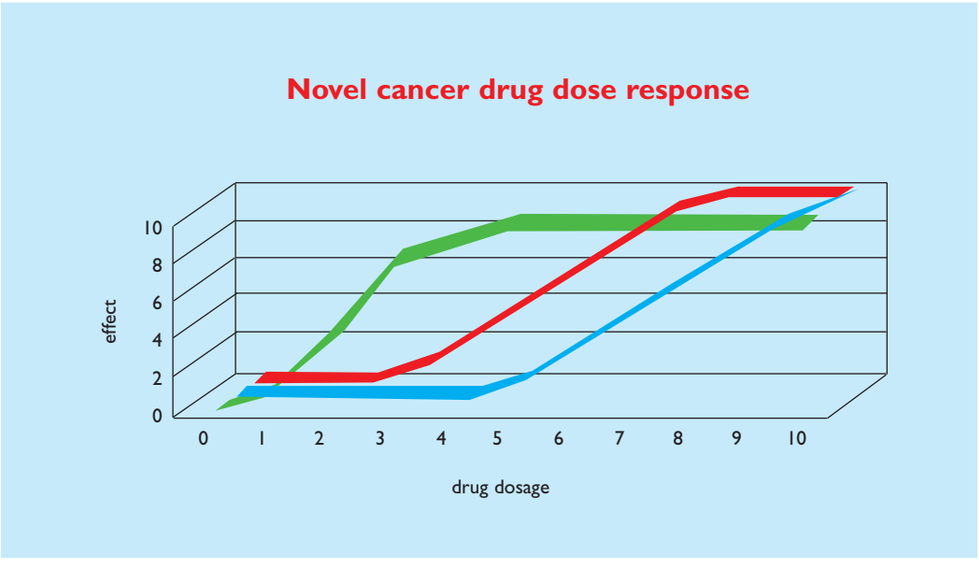

Figure 3
Classical phase I testing of a cytotoxic drug involves escalating drug dosage to the limit of toxicity (blue curve). Efficacy is usually seen (red curve) close to the toxic limit. With novel agents (green), efficacy may occur well below the toxic dosage

then carry out phase II studies in which a series of patients with cancers that can be easily measured by X-rays, photographs or biochemical changes are given the drug to see what effect it has on their cancer. This allows us to determine the response rate. Phase III is the final, longest and most costly phase. Here patients are randomised to receive either the new drug or the best available treatment and their long-term survival determined.

This traditional approach is not appropriate for many of our new agents. Toxicity may be minimal and effectiveness may be greatest well below the maximally tolerated dose. Furthermore tumours may not actually shrink but just become static so no responses are seen. As our new agents have been discovered by measuring their effect on a specific molecular target in the laboratory it should be feasible to develop the same assay for use in patients. This gives us a short term pharmacodynamic endpoint and tells us that we are achieving our molecular goals in a patient. Genomic technology has come to our aid. Gene chips allow us to examine the expression of thousands of genes simultaneously before and after administration of the drug[5]. If a second biopsy can be obtained for the tumour, then we can compare gene expression patterns in both tumour and normal cells in the same patient after exposure to a new drug. This enables us to get the drug to work in the most effective way. A particularly intriguing approach for the future is to use gene constructs, which signal easily measurable tiny light pulses when their molecular switches are affected by a drug.

We also would like to get information about how a drug distributes itself within the body and ideally get a picture of the changes it causes in a tumour. Functional imaging allows us to do just this. The aim is to understand the living biochemistry of a drug in the body. Here we label the drug with a radioactive tracer and then image using positron emission tomography (**Figure 2**). Such techniques promise to revolutionise our ability to understand drug activity and to select and improve on the way in which we choose anti-cancer drugs for further development. The next decade is likely to be a new golden age for cancer drug discovery, with many novel targeted molecules coming into the clinic.

The new paradigm of drug development

Novel cancer drugs interact with specific molecular targets. Because their target is known and an assay available for identifying drug-target interaction it should be possible to determine the PD endpoint in patients. Indeed healthy volunteers may be given low doses of the new drug to see if it does indeed affect its target in the planned way and to examine the time course of this interaction. This approach can then be used to determine the maximally biologically effective dose. Furthermore the effects of a drug on downstream biochemical pathways can lead to the identification of biomarkers which provide detailed information on the drug's behaviour.

Using PD endpoints in early drug development has several advantages. Firstly, it provides good

information of the likely dose required for the pivotal studies. The maximally tolerable dose as identified for a cytotoxic may be well above the maximally effective dose of a novel agent (**Figure 3**). If this is not recognised then the drug may go to market with far too high a recommended dose. This could lead to a commercial disaster once the optimal lower dose is identified. Furthermore there may be a bell shaped curve for effectiveness. By the time toxicity is reached, the effectiveness on a molecular target may be well below its peak.

Traditional phase II testing requires selecting patients with assessable disease with tumour response acting as a surrogate endpoint for effectiveness. Although there is a correlation between response and survival gain it is by no means linear. Furthermore some types of drugs may not cause tumour shrinkage at all. A good example are the anti-angiogenic agents which reduce infiltration of new blood vessels. This has led to the search for surrogate endpoints based on molecular targets in tumours. Ideally such endpoints should be biologically relevant, directly relate to disease activity, follow a rapid time course, be cheap and easy to measure and use non-invasive sampling methods to obtain an accurate time course. A range of clinical assays of molecular effect can now be developed (**Figure 4**).

Cancer prevention

We can identify the cause of three quarters of the world's cancers. It has been estimated that tobacco products cause approximately three million new patients with cancer a year. The majority will have lung cancer but other types of cancer associated with smoking are those associated with the mouth, the nose and throat as well as pancreas, kidney and bladder. The message is simple: stop smoking.

The second major cause of cancer is diet. This is estimated to cause another three million patients per year. Cancers in which a clear relationship to diet has been shown include those of the colon, breast, stomach, liver and several others. The problem with diet is that unlike smoking, we have to eat. The relationship between diet and cancer is extremely complex. It is not just the food that we eat but also the way in which the contents are digested, interact with each other and cause changes in hormone levels. We know certain foods protect against cancer whilst others stimulate it. Thus high-fibre, low-fat diets with a high content of fresh fruit and vegetables are protective. Conversely low-fibre, high-fat diets common in northern Europe carry significant cancer risks.

Infection causes a surprising 1.5 million cancers globally each year. Papilloma virus infection induces cervical cancer, the hepatitis virus – liver cancer (hepatoma), the Epstein Barr virus – lymphoma. All of these cancers are potentially preventable using vaccines. The difficulty here is persuading politicians to invest now for benefits in future generations. The commonest cancer in west Africa is hepatoma and for $2 extra at the time of childhood vaccination, hepatitis immunisation has been shown to reduce the incidence of hepatoma by 90%. Yet politicians avoid tackling

References

1 Weisse, A. From trench warfare to war on cancer. Hospital Practice 1992; 12: 141-148.

2 The human genome. Nature 2001; 409: 745-964.

3 Garrett, M and Workman, P Discovering novel chemotherapeutic drugs for the third millenium. Eur. J. Cancer 1999; 35 :2010-30.

4 Simon, R et al. Accelerated titration designs for phase I trials in oncology. J. Nat. Cancer Institute 89; 1138-44: 1997.

5 Debouck, C and Goodfellow, P. DNA microarrays in drug discovery and development. Nature Genetics 2000; 21: 48-50.

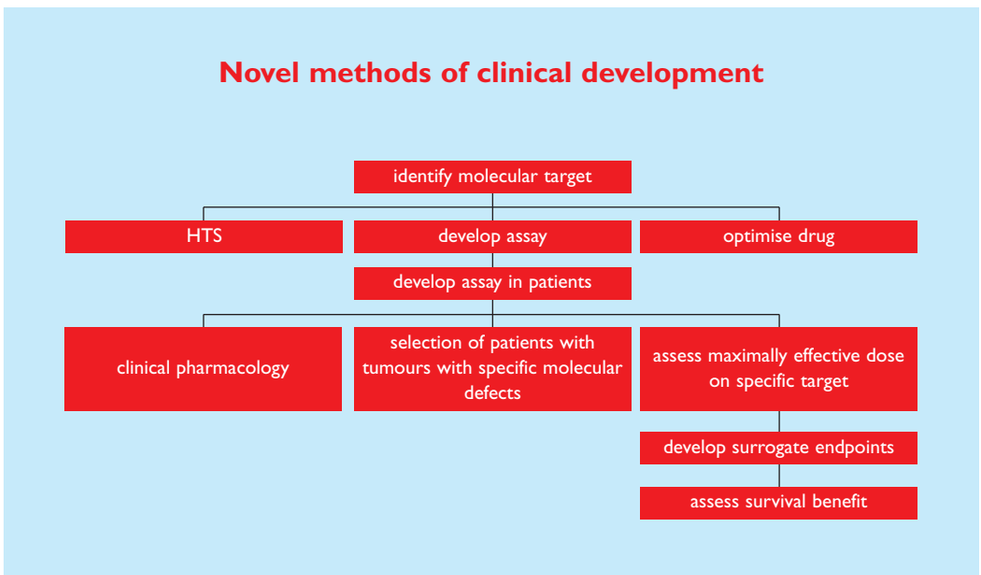

Figure 4
As novel cancer drugs have a known molecular target, it should be possible to devise clinical assays to measure their effect on that target in the clinic

Table 3
Potential benefits of surrogate endpoints

- Lower costs of drug development
- Reduce time to NDA
- Enhance milestone decision process
- Bypass need for phase II studies
- Increase response rate by patient stratification
- Revive dead drugs
- Guide early candidate selection

this issue as they see no gain until well beyond the end of their own careers. Instead they aspire to unrealistic but highly visible projects such as cancer centres and bone marrow transplantation units for breast cancer.

Over the next 20 years systematic programmes of cancer risk assessment will be established and cancer preventive drugs will be developed. From the newly sequenced human genome we will learn about the complex interplay of our genes and the environment. Individually tailored cancer prevention programmes will become available. Cancer preventive drugs and hormones are already available for certain high risk situations: tamoxifen for breast cancer and the cox 2 inhibitors for familial polyposis coli – a condition that if untreated will inevitably lead to colon cancer. Over the next few years this area will grow enormously driven by the ability to predict individual genetic risk; the elucidation of gene-environment interactions and the development of several drugs for prevention. The ability to prevent cancer will dramatically increase the number of people who will need to regularly attend clinics. We urgently need surrogate endpoints to speed up the development of drugs in this presently under researched area.

The future of cancer drug development

As we discover new targeted agents stratifying tumours by their specific molecular abnormalities will lead to better individual drug selection. Pharmacogenomics in cancer research will involve prediction of optimal therapy by genomics, transcriptomics and proteomics. Because the classical phase II response data may no longer be valid for agents that cause tumour stasis, it will be essential to identify surrogate markers to reduce the risk of later failure after costly phase III comparisons. Other advantages are listed in **Table 3**. It is likely that many of the new agents will be given orally over long periods of time. Their delivery will require the strategic development of integrated molecular solutions – bringing the sophistication of modern molecular biology as close as possible to the bedside of the cancer patient. This new way of working will bring with it immense challenge but a strong likelihood of considerably improved results across a wide range of cancer types. DDW

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