Surrogate endpoints in cancer drug development

Karol Sikora

Over the next three years a large number of novel, mechanistically targeted drugs will enter clinical trials for cancer. The remarkable progress in understanding the molecular biology of cancer has provided an enormous range of validated targets for drug discovery. Following lead optimisation and suitable pharmaceutical formulation these compounds have undergone rapid screening in preclinical models. Innovative methods of clinical development are now essential to ensure optimal dose determination and scheduling. The discovery of novel surrogates for efficacy is essential in this fast moving area and requires imaginative partnerships between academic groups and the pharmaceutical industry.

Karol Sikora
Mereside
Alderley Park
Cheshire
UK SK10 4TG
tel: +44 1625 513768
fax: +44 1625 516904
e-mail: karol.sikora@astrazeneca.com

▼ Cancer drug development is entering a remarkable new phase. Recent developments in molecular biology (Box 1) have led to a host of new validated targets. *In silico* drug design allows the construction of thousands of virtual compounds, the most promising of which can be rapidly synthesized [1]. This complements robotic HTS of well organized chemical and natural compound libraries and has led to a platform approach to drug discovery – the creation of specific inhibitors for each member of a gene family such as the protein kinases [2]. This approach has been remarkably successful and a range of small molecules is now available that affects processes as diverse as cell cycle control, mitotic spindle separation, apoptosis, signal transduction, angiogenesis and tumour invasion. Over the past five years there has been a shift away from the search for new cytotoxic drugs to drugs acting through defined molecular mechanisms known to be aberrant in cancer. There are currently nearly 500 molecules undergoing clinical study and this could well reach 1000 by 2003. Clearly, new methods to identify and prioritize the most promising candidates are necessary because there only limited resources to take these compounds into expensive and time consuming Phase III studies. Figure 1 shows the potential timeline for the introduction of new technology to the marketplace. The crucial years are predicted to be 2005–2010.

The traditional approach to cytotoxic drug development is not appropriate for many of these new agents for several reasons. First, as their precise molecular mechanism is known it should be possible to develop a pharmacodynamic (PD) assay for their molecular effectiveness in patients. This can be used to determine the maximally effective dose for use in further studies [3]. This approach will replace the classical Phase I study which has in the past been used to evaluate the maximal tolerated dose (MTD; Box 2). Although PD endpoints have been used, for example, with DNA binding drugs, in the past, specific relevant assays were simply not available. Second, it might not be possible to rely on tumour response in Phase II as a guide to survival benefit. Many of the new agents will cause disease stabilization and not shrinkage [4]. Thus it will be necessary to commit to expensive randomized Phase III studies without having the confidence generated by a successful Phase II programme. The key to success in this mechanistically based future will be the collection

Box 1. Reasons for the dramatic increase in molecular therapies

- Sequencing and bioinformatics
- Expression vectors for target production
- Predictive ability of three-dimensional structural biology
- Robotic HTS
- Combinatorial chemistry
- Platform approach to drug discovery
- Huge increase in number of targets

1359-6446/02/$ – see front matter PII: S1359-6446(02)02434-0

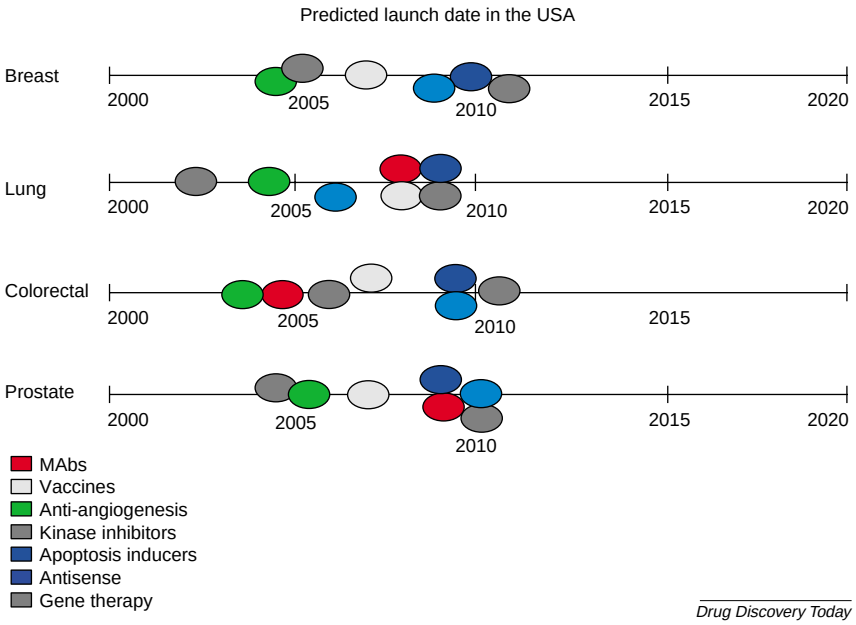

Figure 1. Predicted New Drug Application (NDA) dates with the US food and Drug administration for novel cancer drugs. 2005–2010 is forecast to be the crucial period.

of far more data in the early phase of drug development by the use of surrogates of both molecular target effects and clinical efficacy.

Definitions

There is a lack of consistency in how certain terms are used despite several attempts to formalise definitions [5]. A 'surrogate endpoint' is defined as a substitute measurement of benefit, derived from Latin – *surrogare* – to substitute. Tumour shrinkage is an effective surrogate for clinical efficacy as measured by long-term survival. The complete disappearance of a tumour on an X-ray image carries a better prognosis than only a minor effect after giving chemotherapy or radiation [6]. Similarly the generation of data showing a long average time to disease progression with therapy can in some cases be a surrogate for long-term survival. In addition, the decline of a serum biochemical tumour marker suggests a tumour response that might lead to a better outcome. Although some tumour markers are reliable surrogates for ultimate outcome [human chorionic gonatotrophin (HCG) in choriocarcinoma and testicular teratoma], changes in others such as prostate specific antigen (PSA) or carcinoembryonic antigen (CEA) are less tightly correlated to subsequent survival [7].

A 'biomarker' can be defined as a biological marker of target effect. By definition, it will always be a surrogate for the effect of a drug on its molecular target. In certain cases it could also be a surrogate for tumour response and subsequent prolonged survival, although this will need verification. A biomarker can be biochemical or reflect a physiological byproduct such as hypotension or platelet aggregation. It can involve a complex imaging process such as positron emission tomography or the genomic analysis of tumour biopsies before and after therapy. Tumour markers are just a subset of biomarkers that are sometimes useful in predicting prognosis. Biomarkers are commonly used outside oncology to monitor the effectiveness of a therapy. Serum cholesterol, glycated haemoglobin and blood pressure are biomarkers for statin therapy, control of diabetes and anti-hypertensive treatment, respectively. They are also effective surrogates for the probable long-term consequences of the relevant disease. Unfortunately we currently lack such tightly correlated biomarkers, which will become essential if we are to make cancer a chronic illness controlled by long-term medication.

'Functional imaging' can be defined as the imaging of a biological process. Recent advances in technology have made it possible to begin to visualize mitosis, apoptosis, inflammation, receptor targeting and blood flow as well as the structural changes associated with tumour regression. Novel computer technology can integrate structural and functional images giving detailed information on drug effects [8,9].

A 'predictive marker' allows the stratification of patients by their likelihood of response to an agent. It can be determined by immunohistology such as the presence of

Box 2. Phase I cancer drug development

Old approach
- Determine maximal tolerated dose
- Recommend Phase II dose
- Describe toxicities
- Examine pharmacokinetics

New approach
- Determine maximal effective dose
- Examine pharmacokinetics and pharmacodynamics
- Describe toxicities
- Stratify by molecular pathology

hormone receptors or HER2 expression, or by some more complex interactive assay to determine the effect of an agent on a clinical sample such as the SF2 assay for radiosensitivity [10]. Predictive markers are particularly feasible when the precise molecular mechanism of a drug is known and its target variably expressed across the spectrum of cancer. The regulatory label for a drug can restrict its use to patients with tumours that express a specific marker. Examples include Herceptin and HER2b-overexpressing breast cancer [11]; Gleevec and the bcr–abl translocation in chronic myeloid leukaemia [12]; and the expression of CD20 in non-Hodgkin's lymphoma for the use of the monoclonal antibody, Rituximab [13].

'Molecular profiling' is the holistic profiling of a tumour using several technologies to determine its probable natural history and optimal therapy. The beginnings of such correlations have been used in assays for the expression of specific gene products in increased, reduced or mutated form. Examples include erbB1, erbB2, ras and p53 [14]. The emerging technologies of genomics, proteomics and metabolomics can produce enormous datasets to correlate with tumour behaviour patterns and response to different therapies [15–17]. Although current data are fascinating, it will take several years before 'personalized medicine' becomes a reality for the majority of cancer patients.

The next decade will bring novel technologies in all these areas together with increasingly sophisticated bioinformatic tools. Figure 2 plots the value versus the uncertainty over the next ten years for these approaches.

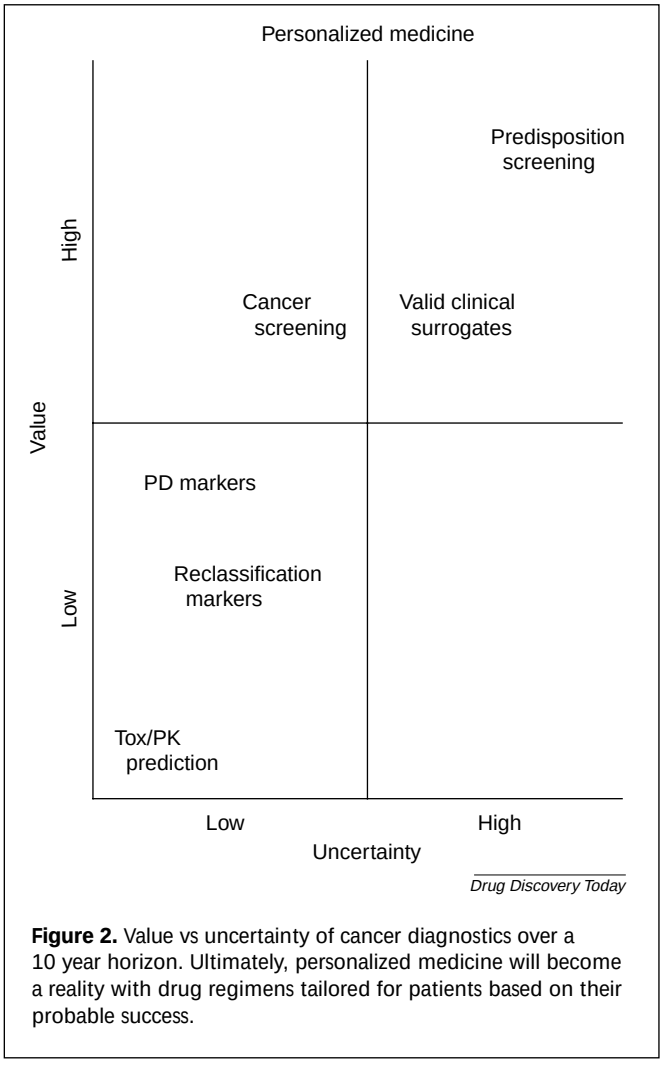

Figure 2. Value vs uncertainty of cancer diagnostics over a 10 year horizon. Ultimately, personalized medicine will become a reality with drug regimens tailored for patients based on their probable success.

A toolkit for early cancer drug development

Biomarkers, surrogate endpoints, functional imaging and predictive markers can be developed to form an essential toolkit for early drug development. The target molecules for novel anticancer agents can be grouped by their function. In this way, a set of biomarkers can be developed for each function (Table 1). The practical value of each component can be evaluated in cell lines and animal tumours to determine its effectiveness in producing accurate dose–response information – a pre-requisite for determining PD endpoints. For safety, an escalating dose scale will still be necessary when a compound first enters the clinic. However, the toolkit can be used to avoid the need to determine the MTD.

Conventionally the safe starting dose is one-tenth of the LD_{10} value in the most sensitive of three species. This can

Table 1. Creating a toolkit for cancer drug development

	Cell cycle inhibitors	Apoptosis stimulators	Signal transduction inhibitors	Anti-inflammatory compounds	Anti-invasive agents	Anti-angiogenic compounds	Differentiating agents
Biomarker	+	+	+	+	+	+	+
Surrogate	–	–	–	+	+	+	–
Imaging	+	+	–	–	–	+	–
Predictor	–	–	+	+	–	–	–

+ Indicates a priority requirement for optimal drug development. All classes require effective, preclinically validated biomarkers to determine pharmacodynamic endpoints in the initial clinical studies.

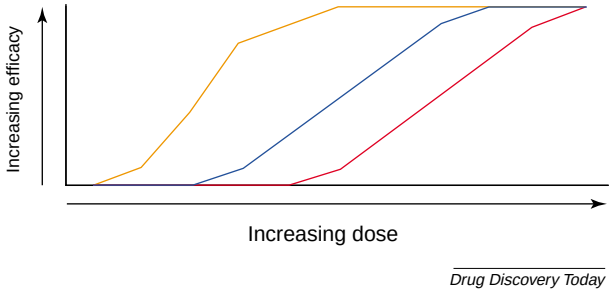

Figure 3. Efficacy vs toxicity of novel and cytotoxic drugs. The blue sigmoid curve represents increasing toxicity with increasing dose. The red curve is the efficacy of a cytotoxic. Response rates only become substantial if toxicity is accepted. With a novel, molecular targeted approach drugs might follow the orange curve – their maximally effective dose is well below that causing serious toxicity.

then be increased using an accelerated titration method until the maximal molecular effect can be obtained on the drug's target [18]. This dose could produce no toxic effects whatsoever. Choosing the correct dose based on PD data permits proof-of-principle studies to proceed with confidence. It reduces the number of patients required for a Phase I trial, thus speeding up this phase and avoiding many patients receiving a sub-therapeutic dose. Furthermore, it reduces the risk of operating at a dose higher than peak effectiveness if the effect of the drug peaks at a certain concentration. It also avoids a later potential commercial disaster if the drug priced for a high dose close to toxicity is demonstrated to work just as well at a much lower one (Fig. 3).

For most novel agents the toolkit for measuring biomarkers of cell function will in future be validated in healthy volunteer subjects. This is a radical departure for trials of cancer agents and an area where oncologists traditionally have no expertise. This enhances the speed of data acquisition by forward planning and avoiding the need to identify cancer patients in real time as stacking for a defined future time-point would be unethical given the probable progress of the disease.

The different components of the early development toolkit have different costs, risks and potential information yield. The investment payback will depend on how crucial the information is to the successful development of drugs against a defined target. Thus biomarkers of molecular effect are a requirement for all drugs. Surrogate endpoints of clinical benefit are particularly important for drugs whose long-term administration is necessary to achieve either tumour stabilization such as anti-angiogenic agents or prevention of metastasis where the cost in both time and effort of pivotal studies is immense. Success in achieving surrogate benefit here gives the confidence to commit long-term financial resources by effectively reducing the risk of failure. Functional imaging studies are particularly helpful where optimising the effect of a drug requires precise scheduling – for example, cell-cycle inhibitors and pro-apoptotic agents [19,20]. By obtaining real-time images of mitosis and apoptosis in patients, logical decisions about enhancing selectivity can be made more easily.

Some biomarkers might well be surrogates for clinical efficacy under certain defined conditions. Biomarkers have different levels of specificity. Some can be used for a class of drugs affecting a biological process such as angiogenesis [21,22]; others could be highly specific for the effects of a single agent. The toolkit, therefore, consists of a series of biological process drawers in which there are drug specific boxes.

Surrogate endpoints for toxicity

Successful drug development requires both efficacy and safety. Useful biomarkers and surrogates for safety are also possible provided that the molecular mechanism of any deleterious effect can be identified. The most widely used surrogate in choosing which molecules to take further are the assays that predict the possibility of sudden death resulting from cardiac dysrythmias. Certain drugs are associated with a rare but lethal ventricular fibrillation called Torsade de pointes. This is caused by an effect on the ion channel pumps in cardiac tissue resulting in abnormal repolarization. Because of its rarity, it can be impossible to detect during the clinical development of a drug and so only manifests itself once the drug is marketed to a larger population. Several surrogates are now available to predict the risk of this syndrome [23]. These include dog cardiac telemetry, electrophysiological effects on isolated cardiac muscle or Purkinje fibres and the effect of a drug on the pumping mechanism of the human ether a-go-go gene product (hERG) [24].

The determination of genotoxicity by a range of assays for the potential of a drug to damage DNA has also proven useful in screening early stage compounds for potential problems [25]. This area will be of increasing interest as early studies of novel cancer drugs could well be carried out in healthy volunteers in future using a molecular endpoint to evaluate dose.

Drug metabolism variances resulting from enzyme polymorphisms can create huge differences in how a drug is handled in different individuals. These pharmacogenetic differences have been studied intensively for commonly used drugs for hypertension and CNS disorders. The same methods have been applied to cancer drugs with intriguing results. The best example is the determination of

dihydropyrimidine dehydrogenase activity and 5-fluorouracil (5FU) metabolism. 5FU is an old but still widely used drug for colorectal and other gastrointestinal malignancies. It is usually well tolerated but can produce severe diarrhoea, mouth ulceration and skin changes in ~5% of people. These effects can be predicted by examining for sensitivity polymorphisms before therapy [26]. Safety pharmacology increasingly relies on predictive testing in novel laboratory systems – cell lines, tissue simulators and preclinical models. It might eventually be possible to recognize the molecular correlates of toxicity *in silico*.

Cancer prevention

Perhaps the biggest revolution in oncology of this century will be our ability to predict cancer risk and prevent the disease pharmacologically. This requires the development of biomarkers to measure the level of risk and accurately monitor the efficacy of therapy [27]. There is a strong parallel to the use of statins to prevent cardiovascular disease. This class of drugs lowers serum cholesterol. This provides an effective biomarker as a surrogate for subsequent atherosclerotic disease. A fall in serum cholesterol is encouraging to both patient and physician resulting in long-term compliance. Currently no such markers exist for cancer. Without them it is impossible to institute a credible drug discovery effort as only large scale, randomized studies using cancer incidence as an endpoint can determine efficacy [28–30].

The risk of an individual developing cancer during their lifetime represents a complex interaction of environmental and lifestyle factors with their genetic background. Simply measuring exposure to potential carcinogens can be misleading as their downstream effects can vary in different individuals because of variation in uptake, metabolism, excretion and ability to cause mutations within crucial genes. Novel biomarkers of biologically effective dose are now being identified for specific agents through the measurement of DNA adducts.

Identifying genetic polymorphisms that carry increased cancer risk is another approach. Although mutations in genes such as *BRCA1*, *BRCA2* and *APC* (adenomatous polyposis coli), as well as microsatellite instability (MSI), are associated with high cancer incidence, it is likely that most cancer risk in a population results from low penetrance susceptibility genes whose function involves carcinogen metabolism, DNA adduct removal, DNA repair, cell cycle and apoptosis control as well as those involved in determining the immune response and the development of tolerance. Over the next decade, molecular epidemiology will use our new technology to clearly relate genetics and the environment, thus identifying more precise individual risks. This will catalyse the search for effective cancer preventive agents by the major pharmaceutical companies.

Conclusion

It currently takes an average of 10 years for a cancer drug to reach the market from the identification of the lead compound. The sheer number of potential cancer drugs now becoming available and the change of emphasis to targeted molecular mechanisms will require a rigorous selection process during the early phase of clinical development. Over the next decade, systematic programmes of cancer risk assessment will be established and cancer preventive agents will enter into the clinic. Novel surrogate endpoints will be essential to determine their benefit without waiting for a further generation of cancer patients.

One of the greatest challenges for an increasingly consolidated industry is to adapt to changing technology. The classical division of research departments into ‘discovery’ and ‘clinical’ is no longer optimal in this fast-paced area. Drugs entering the clinic need to come with validated biomarkers of their PD effect, surrogates for clinical efficacy and a plan to stratify patients for their probable response. Effective organization of translational science is the key to the future and yet a significant challenge. Scientists are judged by the number of drugs getting out of the laboratory and into the clinic rather than how many are eventually brought to market. They are managed separately from clinical and experimental groups. Clinical groups are concerned with operational excellence in the construction and execution of clinical trials. The drive to keep R&D costs down has resulted in the sharing of emerging laboratory technology across several therapeutic areas, which can adversely influence collaborative working. This problem has clearly been recognized by most in senior management, and can be seen by the willingness of the major oncology players to experiment with their organization.

Translational cancer research is now defined as the application of basic scientific research for the benefit of patients. In the context of drug discovery and development it defines the optimal clinical use of a drug and aids decision making by providing succinct indicators of success at crucial milestones. The creation of unique translational research networks, involving strategic partnerships with leading academic centres and innovative biotechnology companies as well as streamlining and focussing internal strengths is becoming essential for survival. Excellence in translational research will result in faster drug development, better risk-value assessment, clearer decision making, a reduction in attrition rate in late-stage development, increased regulatory confidence and outstanding life-cycle management.

References

1 Garrett, M. and Workman, P. (1999) Discovering novel chemotherapeutic drugs for the third millennium. *Eur. J. Cancer* 35, 2010–2030
2 Robinson, D. *et al.* (2000) The protein tyrosine kinase family of the human genome. *Oncogene* 19, 5548–5557
3 Biomarker Definitions Working Group (2001) Biomarkers and surrogate endpoints preferred definitions and conceptual framework. *Clin. Pharmacol. Ther.* 69, 89–95
4 Workman, P. and Clarke, P. (2001) Innovative cancer drug targets: genomics, transcriptomics and clinomics. *Expert Opin. Pharmacother.* 2, 911–915
5 Somberg, J.C. (1999) Biomarkers and surrogate endpoints. *Am. J. Ther.* 4, 179–180
6 Buyse, M. *et al.* (2000) Relation between tumour response to first-line chemotherapy and survival in advanced colorectal cancer: a meta-analysis. Meta-Analysis Group in Cancer. *Lancet* 356, 373–378
7 Kupelian, P. *et al.* (2002) bImpact of biochemical failure on overall survival after radiation therapy for localized prostate cancer in the PSA era. *Int. J. Radiat. Oncol. Biol. Phys.* 52, 704–711
8 Phelps, M. (2000) PET: the merging of biology and imaging into molecular imaging. *J. Nucl. Med.* 41, 661–681
9 Young, H. *et al.* (1999) Measurement of clinical and subclinical tumour response using ^{18}fluorodeoxyglucose and positron emission tomgraphy: review and 1999 EORTC recommendations. *Eur. J. Cancer* 35, 1773–1782
10 Levine, E. *et al.* (1995) Apoptosis, intrinsic radiosensitivity and prediction of radiotherapy response in cervical carcinoma. *Radiother. Oncol.* 37, 1–9
11 Wang, S. *et al.* (2001) Targeting HER2: recent developments and future directions for breast cancer patients. *Semin. Oncol.* 28(Suppl 18), 21–29
12 Druker, B. *et al.* (2001) Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukaemia. *N. Engl. J. Med.* 344, 1031–1037
13 Kipps, T.J. (2002) Advances in classification and therapy of indolent B-cell malignancies. *Semin. Oncol.* 29(Suppl 2), 98–104
14 Watanabe, T. *et al.* (2001) Molecular predictors of survival after adjuvant chemotherapy for colon cancer. *N. Engl. J. Med.* 344, 1196–1206
15 Evans, W. and Relling, M. (1999) Pharmacogenomics: translation functional genomics into rational therapeutics. *Science* 286, 487–491
16 Scherf, U. *et al.* (2000) A gene expression database for the molecular pharmacology of cancer. *Nat. Genet.* 24, 236–244
17 Bertucci, F. *et al.* (2001) Gene expression profiling of cancer by use of DNA arrays: how far from the clinic? *Lancet Oncol.* 2, 674–682
18 Simon, R. *et al.* (1997) Accelerated titration designs for Phase I trials in oncology. *J. Natl. Cancer Inst.* 89, 1138–1144
19 Pucci, B. *et al.* (2000) Cell cycle and apoptosis. *Neoplasia* 2, 291–299
20 Buolamwini, J. (2000) Cell cycle molecular targets in novel anticancer drug discovery. *Curr. Pharm. Res.* 6, 379–392
21 Kerbel, R. (2001) Clinical trials of antiangiogenic drugs: opportunities, problems and assessment of initial results. *J. Clin. Oncol.* 19, 45–51
22 Anderson, H. *et al.* (2001) Measuring changes in human tumour vasculature in response to therapy using functional imaging techniques. *Br. J. Cancer* 85, 1085–1093
23 Haverkamp, W. *et al.* (2000) The potential for QT prolongation and pro-arrythmia by non anti arrythmic drugs. *Cardiovasc. Res.* 47, 219–233
24 Hammond, T. *et al.* (2001) Methods of collecting and evaluating non clinical cardiac electrophysiological data in the pharmaceutical industry: results of an international survey. *Cardiovasc. Res.* 49, 741–750
25 Hessel, H. *et al.* (2001) The genotoxic risk of hospital, pharmacy and medical personnel occupationally exposed to cytostatic drugs–evaluation by the micronucleus assay. *Mutat. Res.* 497, 101–109
26 Saleem, A. *et al.* (2000) Modulation of fluorouracil tissue pharmacokinetics by eniluracil *in vivo* imaging of drug action. *Lancet* 355, 2125–2131
27 Furberg, A. and Ambrosome, C. (2001) Molecular epidemiology, biomarkers and cancer prevention. *Trends Mol. Med.* 7, 517–521
28 Srinivas, P. *et al.* (2001) Trends in biomarker research for cancer detection. *Lancet Oncol.* 2, 698–704
29 Lesko, L. and Atkinson, A. (2001) Use of biomarkers and surrogate endpoints in drug development and regulatory decision making: criteria, validation, strategies. *Annu. Rev. Pharmacol. Toxicol.* 41, 347–366
30 Kensler, T. *et al.* (2001) Biomarkers and surrogacy: relevance to chemoprevention. *IARC Sci. Publ.* 154, 27–47