Cancer drug development in the post-genomic age

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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 have yielded several exciting platforms on which to develop novel therapies. The dramatic increase in the pace of discovery of new molecules for clinical trial will require innovative approaches for their clinical development.

To enhance the speed of assessment, it will be essential to identify surrogate endpoints to validate the effectiveness of a potential drug. 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 endpoints will replace the current phase I dose escalation schedules by which the maximum tolerated dose of a cancer drug is determined.

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 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 will soon be available to monitor patterns of gene expression before and after therapy. Such techniques will 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 specialized techniques will by necessity concentrate the early phase of drug development in a few centres of excellence rather than the current diffuse pattern.

Leveraging the clinical–scientific interface in cancer research is the key component in accelerating the development of novel therapies. Creating innovative partnerships between an increasingly consolidated and globalized industry and major cancer treatment centres is now essential to enhance the speed of drug development. Currently 370 compounds are undergoing clinical trial for cancer, and this number can confidently be expected to reach over 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.

Background

Cancer drug development is entering a remarkable new phase. Technical developments in molecular biology have led to a plethora of new screening targets. Chemotherapy for cancer was first used in 1944 – an indirect consequence of the bombing of a US battleship, the John E. Harvey in Bari harbour in Italy during the previous year. Naval physicians noted leucopaenia in many survivors and made the connection with the release of nitrogen mustard carried as a chemical warfare agent. Mustine is an alkylating agent, although its DNA-binding properties were unknown at the time of its first clinical use in leukaemia. Sixty-seven patients were treated and a 25% response rate reported1 in 1946, marking the dawn of chemotherapy. Although a plethora of anti-cancer drugs were discovered by serendipity, the effectiveness of chemotherapy in treating cancer has been relatively disappointing, with little change in overall outcome seen over the last 25 years.

Several cancers can be effectively cured by chemotherapy but these are relatively rare. The common solid tumours such as breast, lung, prostate and colorectal cancer are only partially responsive to drug therapy. Drug resistance is either present at the start or is rapidly acquired through multiple molecular mechanisms. Figure 1 summarizes 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. It is estimated that 60% of cancer drugs are used in the US, which contains

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only 4% of the world’s population. Although the majority of people with cancer live outside Europe, Japan and the US, these patients only receive 6% of the supply of chemotherapy. The high cost of available drugs and the absence of expertise in dealing with their side effects are the main reasons for this. The marketing strategies of the pharmaceutical industry are developed around the newer high cost drugs leading to distortion of prioritization, especially in poorer parts of the world. Attempts to introduce essential generic drug lists are countered by aggressive marketing techniques.

Global pipeline reconstruction

Using published sources of information including the internet we have reconstructed the global pipeline of drugs currently in clinical development. We estimate that there are about 370 drugs currently in clinical trial. Increasing consolidation through mergers and acquisition in the pharmaceutical industry has led to fewer major players. There are currently only six companies with eight or more compounds under development (Figure 2). There are many biotechnology companies with single compounds in early phase studies but if successful these will be absorbed into larger organizations with the financial muscle to take a drug to full development and regulatory approval – a process which now costs at least US $ 500 million.

Exploratory compound flow

Over the last five years there has been an increasing shift to the discovery of drugs acting through defined molecular mechanisms. This has been driven by the explosion in sequencing and bioinformatics, the availability of effective expression vectors for target The Human Genome Project has created a dictionary of the genome. But we can now also interrogate it through sophisticated bioinformatic systems. Not only do we have the library but we have the search tools. We can now 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 synthesized 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 c g 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. 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 (Figure 3). By 2015 successful molecular targeted approaches will overtake cytotoxics and transform cancer medicine (Figure 4). These new drugs will be individualized, 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 discovery

The classical way in which we develop cancer drugs is split into three phases. In phase I, maximally tolerable doses determined by gradually escalating the dose in patients with cancer. 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 then carry out phase II studies in which a series of patients with cancers that can be easily measured by X-rays or photographs 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 last and longest phase. Here patients are randomized to receive either the new drug or the best available treatment and their long-term survival determined.

This traditional approach may not be 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. 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 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. Such techniques promise to revolutionize 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.

Determination of effective dose

Classical anti-cancer drug development has traditionally been carried out in three phases. In phase I, the maximally tolerable dose was determined in patients with tumour that were not necessarily assessable for response. One tenth of the lowest preclinical LD_{10} was used as the starting dose and gradually escalated using decreasing increments. The pattern followed that of the population expansion of breeding rabbits first described in the 14th century by the Italian mathematician Fibonacci. The Fibonacci scale has now been replaced by accelerated titration designs. This reduces the total number of patients required to achieve the maximally tolerable dose (MTD) whilst maintaining safety. Ethically it is justifiable as without a significant increase in risk it reduces the number of patients treated below the therapeutic threshold and therefore could not benefit from being part of a trial.

Once the MTD has been determined, phase II studies are designed to assess the efficacy of a new compound. Commercial sense favours carrying out such studies in patients with common tumours where the potential market is large. Ideally, response data can be obtained for several cancers. Clearly, patients entered into phase II studies must have assessable disease by clinical, radiological or biochemical measurement. The decision to go to pivotal phase III studies is a major financial commitment. Here a large multicentre study compares the new agent against best available therapy for patients. This classical development process is now changing rapidly.

New paradigm of drug development

Novel cancer drugs interact with specific molecular targets. They have been identified either by screening libraries of chemicals against a specific target using a biochemical assay or by designing structures in silico using a range of sophisticated computer programs and then carrying out the appropriate organic synthesis. Because their target is known and an assay available for identifying drug–target interaction it should be possible to determine a pharmacodynamic (PD) endpoint in a patient. 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. It provides good information of the likely dose required for the pivotal studies. The maximally tolerable dose identified for the cytotoxics may be well above the maximally effective dose. If this is not recognized 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 (Figure 5).

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 are being developed (Figure 6).

Development of cdk2 inhibitors

Cyclin-dependent kinases are core enzymes of the cell cycle machinery and govern progression between the different phases of the cell cycle. They are novel targets for selective inhibition by small molecules. Cdk2 is a protein kinase that facilitates the G1/S transition checkpoint. Here several molecules interact in a complex manner to initiate DNA synthesis. PRb is phosphorylated on threonine at the 821 position, resulting in the release of the E2F-1 transcription factor. This is brief and if persistent will send cells down the apoptosis pathway. An effective cdk2 inhibitor should arrest cells in G1 causing cytostatic inhibition of tumour growth and trigger cell death. There are multiple biochemical changes amenable to assay provided serial samples of tumour are available before and after drug administration. Acute myeloid leukaemia, although relatively rare, provides the opportunity to easily access tumour cells through venesection and bone marrow aspiration. Figure 7 shows the biomarkers to be examined in one early development protocol. The aim is to find out as much as possible about the drugs effect on cellular biochemistry before designing more complex efficacy studies.

A further layer of difficulty is the time dependency of any selective tumour destruction. This may be determined by the kinetics of tumour growth as well as the patho-
genetic molecular abnormality. Rather than work out all

![Figure 5. Novel cancer drug dose response.](image)

![Figure 6. Novel methods of clinical development.](image)
the possible timing permutations in a classical phase II setting, it makes sense to invest heavily in a detailed understanding of the biochemical perturbations induced in normal and tumour cells to maximize selectivity. Such an approach should speed up the development process enormously.

Cancer prevention

Cancer has many causes. We can identify the cause of three quarters of the world’s cancers. It has been estimated that tobacco products cause approximately 3 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. This is an extremely complex area as it is entwined in politics, taxation, corruption and big business. Even the media have been manipulated by the tobacco industry through their advertising power with good evidence of suppression of the true risks of smoking. Although there have been considerable inroads into tobacco use in Europe, the developing world is now suffering the brunt with a dramatic increase in teenage smoking and the likelihood of an epidemic of lung cancer over the next 20 years. Manufacturers have bought up local factories and are now producing globally branded cigarettes with their image of success, wealth and sexual prowess.

The second major cause of cancer is diet. This is estimated to cause another 3 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. The perception that organic, vegetarian-based diets reduce cancer incidence has simply not been validated. There is no mechanistic reason why organic food should be less cancer-causing than normal farm produce. Plants contain far more potent natural cancer-causing agents than any traces of pesticides.

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 immunization has been shown to reduce the incidence of hepatoma by 90%. Yet politicians avoid tackling 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 centers and bone marrow transplantation units for breast cancer.

The public perception of cancer risk is heavily swayed by interesting but negligible or non-existent risk factors. These are fanned by good media stories and the desire to find scapegoats in our unhealthy lifestyle. Cellphones, radiation from power lines, plastic films, and even stress figure large in public surveys on causes of cancer even though the risk, if any, is nearly impossible to measure. Education is clearly the key to the future.

Over the next twenty years novel programmes of cancer risk assessment will be established. 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 be available. New screening technology coupled with drugs and vaccines that prevent cancer will come into routine use. Gene chips will be implanted under the skin and send radio signals to a home computer when abnormal fragments of DNA are detected prompting further investigations.

Cancer-preventive drugs and hormones are already available for certain high risk situations: tamoxifen for

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**Figure 7.** Developing cdk2 inhibitors.

**Figure 8.** Cancer prevention studies.
breast cancer and the cox 2 inhibitors for familial polyposis – a condition that if untreated will inevitably lead to colon cancer. Over the next few years this area is likely to 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 (Figure 8). The ability to prevent cancer will dramatically increase the number of people who will need to regularly attend clinics. Few countries have anticipated this potential tripling of patients with a cancer label and most have no contingency plans in place for such developments.

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. 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.