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'As we move into a molecular target-based future, cancer diagnostics will assume far greater importance in healthcare delivery.'

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The effective use of diagnostics is a central component of optimal cancer patient management. Diagnostics can be divided into clinical imaging and sample analysis in the laboratory. The latter can be split into assays for specific molecules and more holistic measurements of RNA, protein or modified structures. Drug developers are increasingly turning to sophisticated diagnostic technologies to guide patient selection for trials of novel agents. Diagnostic tools such as biomarkers, surrogates, functional imaging and molecular signatures are becoming essential in guiding critical decisions in the development of novel anticancer agents.

Translational research

Imaginative clinical assays, often using repeat biopsies of tumor and normal tissue, pose significant technical, logistical and ethical challenges. This area of research will drive much closer interactions between discovery and clinical groups, the creation of imaginative partnerships between academic centers and industry and the formation of specialist, diagnostic contract research organizations (CROs). Multi-national, consolidated pharmaceutical companies are struggling to create new structures to encompass translational research and yet are under considerable time pressure to generate innovation forced by the genericization of the majority of high-revenue cytotoxics by 2008.

As we move into a molecular target-based future, cancer diagnostics will assume far greater importance in healthcare delivery (FIGURE 1). Initial treatment decisions are currently based on skilled histopathology and imaging studies to determine the type, grade and stage of the tumor. To this may be added

immunohistochemical assessment of hormonal receptor status and prognostic markers, such as c-erbB2 expression, yet histopathologists and their technical support staff are in short supply globally. This has driven increased laboratory automation at all stages, from tissue handling through to image capture. Diagnostic strategies based on sophisticated tissue analysis are now poised to radically change cancer management from the identification of people with a high risk of developing cancer through to the precise prediction of toxicity that a specific drug poses to an individual. Despite the hype, genomics, proteomics and other holistic strategies are too vague to be used to guide drug development decisions in practice today. The large number of variables creates a bioinformatic nightmare. Achieving the goal of personalized medicine for cancer will require a revolution in diagnostics and the dawn of a new era in tissue analysis through classic quantitative immunohistochemistry.

Tumor profiling

The traditional approach to cytotoxic drug development is not appropriate for many new agents for several reasons. Firstly, 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 [1]. This approach will replace the classic Phase I study that has previously been used to evaluate the maximal tolerated dose. Although PD end points have been used for DNA-binding drugs in the past, specific relevant assays were simply not available. Secondly, it may not

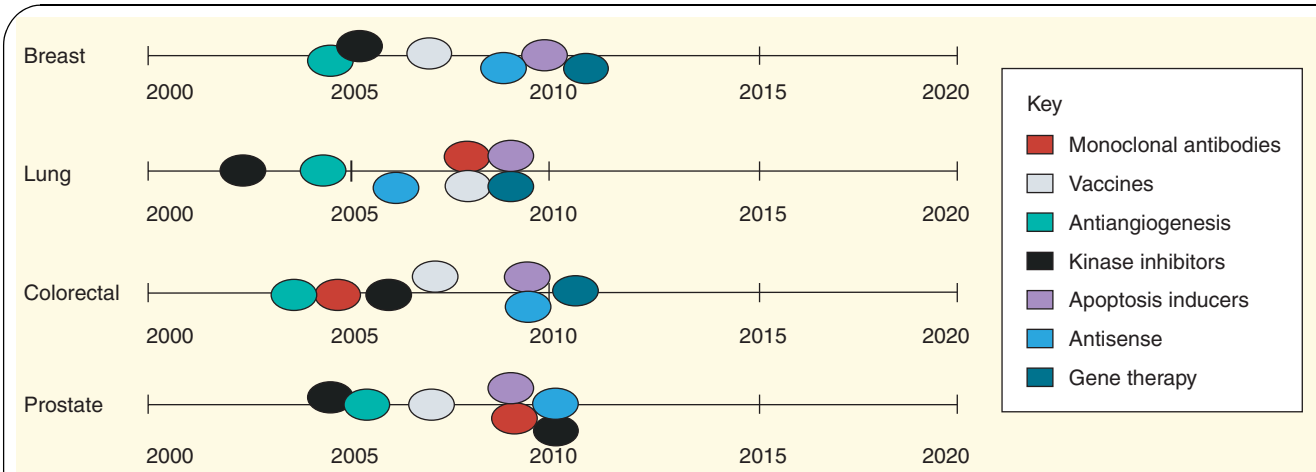


Figure 1. Predicted New Drug Application dates with the US Food and Drug Administration for novel cancer drugs. The period between 2005 and 2010 is forecast to be the critical period. The majority of high-value cytotoxic drugs will become generic by the end of 2008.

be possible to rely on tumor response in Phase II studies as a guide to survival benefit. Many of the new agents will cause disease stabilization and not shrinkage [2]. Thus, it will be necessary to commit to expensive randomized Phase III studies without having the confidence generated by a successful Phase II program. The key to success in this mechanistically based future will be the collection of far more data in the early phase of drug development by the use of surrogates of both molecular target effects and clinical efficacy. Increasing emphasis on linking diagnostics to therapy is now an essential component of cancer drug development (TABLE 1).

The holistic profiling of tumors using several technologies to determine the likely natural history and optimal therapy is possible. The beginnings of such correlations have been used in assays for the expression of specific gene products in an increased, reduced or mutated form. Examples include erbB1, erbB2, ras and p53 [3]. The emerging technologies of genomics, methylomics, proteomics and metabonomics can produce enormous data sets to correlate with tumor behavior patterns and response to different therapies [4]. 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. There is now a great need for ethically collected fresh tissue, both normal and malignant, to develop novel assays and determine variation. The new Human Tissue Authority in the UK is a welcome development, giving a well-defined legal framework for tissue donation after full consent.

Toolkit for early cancer drug development

The different components of an early development toolkit have different costs, risks and potential information yield (TABLE 2). The investment payback will depend on how critical 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 end points of clinical

benefit are particularly important for drugs whose long-term administration is necessary to achieve either tumor stabilization, such as antiangiogenic or anti-invasive agents, 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 resource by effectively reducing the risk of failure and late-stage attrition. Functional imaging studies are particularly helpful where optimizing the effect of a drug requires precise scheduling – cell cycle inhibitors and pro-apoptotic agents [5]. By obtaining real-time images of mitosis and apoptosis in patients, logical decisions to enhance selectivity can be made more easily. Some biomarkers may well be surrogates for clinical efficacy under certain defined conditions. Biomarkers have different levels of specificity. Some can be used for a range of drugs affecting a biological process, such as angiogenesis [6], others may be highly specific for the effects of a single agent. The toolkit therefore consists of a series of drawers containing generic assays for each category of a drug’s mechanism of action and a smaller compartment for the specific PD end point determination tools for an individual agent (FIGURE 2).

Table 1. Diagnostics in cancer drug development.

Diagnostic	Value
Predisposition screen	Identify patients for chemotherapy (prevention)
Screen for presence of cancer	Increase in patients (earlier disease)
Pharmacodynamic biomarker	Establish pharmacologic dose
Surrogate marker of clinical efficacy	Early indication of proof of concept
Predictive reclassification of disease	Target therapy to those likely to respond
Patient-specific toxicity prediction	Avoid adverse events, adjust dose

Table 2. A toolkit for cancer drug development.

Targets	Cell cycle	Apoptosis	Signal transduction	Inflammation	Invasion	Angiogenesis	Differentiation
Biomarker	+	+	+	+	+	+	+
Surrogate				+	+	+	
Imaging	+	+				+	
Predictive signatures	+	+	+	+	+	+	+

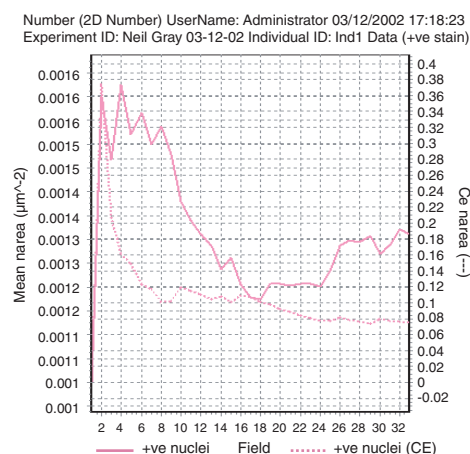
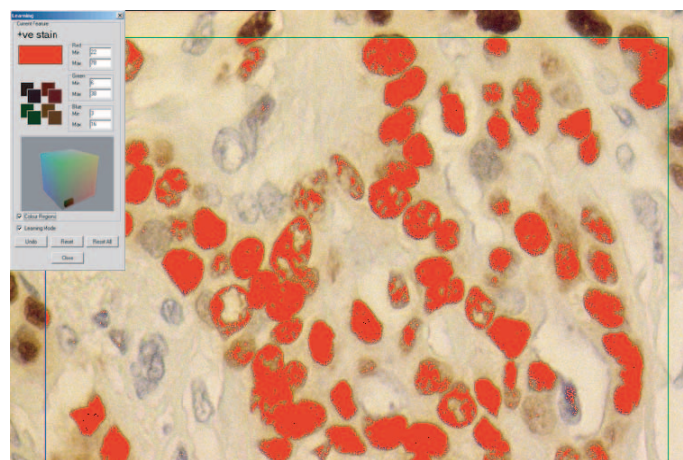


Figure 2. Software (Histometrix, Kinetic Imaging, Wirral, UK) to quantify protein levels by immunohistology objectively using preset criteria.

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. Timelines will get shorter. Over the next decade, systematic programs of cancer risk assessment will be established and cancer preventive agents will enter into the clinic. Novel surrogate end points 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 classic 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 likely 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 and their commercial success. They are managed separately from clinical and experimental medicine groups. Clinical departments are concerned with operational excellence in the construction and execution of clinical trials. The drive to keep research and development costs down has resulted in cross-therapeutic area sharing of emerging laboratory technology, which can adversely influence close collaborative working. The fact that a problem exists has clearly been recognized by most in senior management, as demonstrated by the willingness of major oncology companies to experiment with their organization.

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