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Editorial

New drug design and development in cancer: present status and future perspectives

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Cancer pharmacology and new drug development are at an exciting stage. Our understanding of the molecular basis of drug action has never been greater. Advances in recombinant DNA technology have benefited us in many ways. For example, they have provided us with new techniques with which to study the adducts formed by conventional DNA-interactive drugs and the processes involved in the repair of the genetic material. Cloning of genes that affect drug resistance can now be carried out, and the transfection of these genes into deficient cells provides a means to determine their precise role in bringing about the particular resistance phenotype. This also applies to genes involved in cancer causation. The elucidation of the molecular basis of oncogenesis is proceeding at an exhilarating pace. The overexpression or mutation of dominantly active oncogenes has been shown to drive the proliferation of malignant cells, whereas the mutation or deletion of tumour-suppressor genes removes a brake from cancer-cell growth. The cloning and expression of the various cancer genes has allowed their function to be assigned to particular points in the signal-transduction cascade – from growth factors and their receptors through intracellular signaling proteins to nuclear oncoproteins and transcription factors. At the same time as explaining the molecular basis of oncogenesis, these discoveries continue to uncover new targets for innovative drug development.

Interesting drug candidates are emerging, such as growth-factor antagonists and inhibitors of protein kinases and other signaling enzymes. Clinical trials have begun – for example, with ether lipids and suramin, which inhibit multiple signaling processes, and bryostatin 1, which is a specific protein kinase C agonist. Cancer genes are turning out to be important not only for controlling cell proliferation but also for processes such as angiogenesis, metastasis, differentiation, drug resistance and programmed cell death or apoptosis. These too are attractive targets for anticancer drug design. Apoptosis is an especially promising new area of current interest, since to be effective, anticancer drugs not only should arrest cancer-cell growth but should ideally kill the tumour cells through the apparent involvement of a specific suicide program. Understanding this program may be crucial for the identification of new pharmacological targets and may lead to a better understanding of primary resistance.

New targets for some of the older drugs are also revealed by modern techniques – topoisomerase II for epipodophyllotoxins and anthracyclines, and topoisomerase I for camptothecins are good examples. Derivatives of these parental drugs, such as irinotecan (CPT11) and topotecan (SKF-104 864) for camptothecins, may lead to new clinical insights, since early trials have revealed that these drugs may be active in cancers resistant to conventional treatments. Although there is considerable excitement about the potential for signal-transduction inhibitors and for apoptosis inducers to have a major impact on the discovery of more specific drugs, a number of agents identified by more conventional screening approaches are showing promise in early clinical trials. These include the anthrapyrazole DuP 941, the antitubulin agents taxol, taxotere and rhizoxin, and also temozolomide, which shows striking activity in brain tumours.

Regardless of the source of a given new anticancer drug – from a complex natural product produced by a marine organism to a fully synthetic agent designed on the basis of X-ray crystallography and computational chemistry – the preclinical and clinical development must be done in a rational way. The approach must not only be adapted to the pharmacology and mechanism of action of each individual drug, it must also be flexible enough to allow a suitable response to any unexpected clinical finding. Considerable progress has been made in more fully integrating pharmacokinetics and metabolism studies into rational drug development, and an important goal is now to integrate pharmacokinetic observations more fully with indicators of pharmacodynamic response – that is, effects on tumour and normal tissues. Prospective evaluation of pharmacokinetically guided dose escalation is ongoing. The hope

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is that this will significantly reduce the time and cost involved in phase I studies. At the same time, developments in the theory and practice of therapeutic drug monitoring should markedly improve the optimisation of drug dosage to individual patients in clinical oncology.

European investigators have played an important part in many of the discoveries mentioned above. Certainly the number and quality of innovative early clinical studies is extremely impressive. An important part of this work is carried out under the auspices of the European Organization for Research and Treatment of Cancer (EORTC) and the United Kingdom Cancer Research Campaign Phase I/II Clinical Trials Committee, but increasing numbers of studies are supported by national research groups such as the Association for Research on Treatments Against Cancer (ARTAC) in France and the Deutsche Krebsgesellschaft in Germany. EORTC drug development is overseen by the New Drug Development and Coordinating Committee (NDDCC), with day-to-day running by the New Drug Development Office (NDDO) in Amsterdam. Participating groups include the Pharmacokinetics and Molecular Mechanisms (PAMM) Group, the Screening and Pharmacology Group (SPG) and the Early Clinical Trials Group (ECTG), together with the Preclinical Therapeutic Models Group (PTMG), the Clinical Screening Group (CSG) and a number of other clinical groups.

New anticancer drug development is a truly international effort and all national or international groups should work closely together in Europe and with other countries. The coordination of the activities of the EORTC and CRC groups with those of the United States National Cancer Institute is facilitated by the EORTC/NCI/CRC Steering Committee. Resources and expertise are increasingly shared so as to avoid bottlenecks and duplication of effort. Agreements have been reached such that clinical trials data collected in recognised European centres can be accepted for submission to regulatory authorities in the United States. There is also close cooperation in screening, formulation and toxicology, and also in the sharing of compounds for clinical development. In addition to the EORTC, CRC and NCI, the other emerging national groups should be associated with this collaborative effort. More than ever before we are also appreciating the value of working closely with our colleagues in the pharmaceutical industry. This type of collaboration is helped by the creation of cooperative groups such as ARTAC in France. ARTAC is a non-profit association for therapeutic research in cancer that exists under the auspices of the French Ministry of Research. It was founded in 1984 by oncologists, industrialists and patients to promote and support the early development and the clinical applications of new molecules in cancer treatment. Its members are basic scientists, clinical oncologists and pharmacologists from many pharmaceutical companies and academic institutes, all of whom collaborate in the organisation of phase I, II and III clinical trials through an extensive network of clinical investigators.

As in other areas of oncology, new drug development is so fast-moving and wide-ranging that dissemination of information by means of meetings and publications is extremely important. The papers that follow are based on some of the presentations made at the Fourth International ARTAC Workshop on Therapeutic Trials in Cancer and AIDS, held in Paris in September 1991.