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Discovering Novel Chemotherapeutic Drugs for the Third Millennium

M.D. Garrett and P. Workman

CRC Centre for Cancer Therapeutics at The Institute of Cancer Research, Block E, 15 Cotswold Road, Belmont, Sutton, Surrey SM2 5NG, U.K.

Michelle D. Garrett is a Team Leader at the CRC Centre for Cancer Therapeutics at the Institute of Cancer Research, Sutton, Surrey, U.K. She received her post-doctoral training in the Department of Cell Biology, Yale University School of Medicine, New Haven, Connecticut, U.S.A. (1991–1994). Michelle then moved to Onyx Pharmaceuticals, Richmond, California, U.S.A., where she joined the Cell Cycle Program, and went on to become Team Leader of Cell Based Assay Development for all programs at Onyx (1994–1999). The goals of her research at the Centre are to understand how cell cycle progression is regulated and to apply this knowledge to the development of drugs for cancer treatment.

Paul Workman is Director of the Cancer Research Campaign (CRC) Centre for Cancer Therapeutics at the Institute of Cancer Research, Sutton, Surrey, U.K. and is Harrap Professor of Pharmacology and Therapeutics at the University of London. He holds visiting chairs at the University of Manchester and Leeds and is a CRC Life Fellow. Senior positions were held previously at Zeneca Pharmaceuticals, Macclesfield, U.K. (1993–1997), the CRC Beatson Laboratories, Glasgow, U.K. (1991–1993) and the Medical Research Council Centre, Cambridge, U.K. (1976–1990). His research interests are in the discovery and development of novel mechanism-based anticancer drugs.

There is enormous potential for the discovery of innovative cancer drugs with improved efficacy and selectivity for the third millennium. In this review we show how novel mechanism-based agents are being discovered by focusing on the molecular targets and pathways that are causally involved in cancer formation, maintenance and progression. We also show how new technologies, from genomics through high throughput bioscience, combinatorial chemistry, rational drug design and molecular pharmacodynamic and imaging techniques, are accelerating the pace of cancer drug discovery. The process of contemporary small molecule drug discovery is described and progress and current issues are reviewed. New and potential targets and pathways for therapeutic intervention are illustrated. The first examples of a new generation of molecular therapeutics are now entering hypothesis-testing

Correspondence to P. Workman, e-mail: paulw@icr.ac.uk
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clinical trials and showing activity. The early years of the new millennium will see a range of exciting new agents moving from bench to bedside and beginning to impact on the management and cure of cancer.

Key words: contemporary drug discovery, novel molecular targets, small molecule mechanism-based drugs, high throughput bioscience assays, combinatorial chemistry, drug design and screening, molecular pharmacodynamics and imaging, hypothesis-testing clinical trials
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In its own microscopic way, becoming cancerous is about the most glamorous and successful thing a cell can do.
(John Diamond, 'C: Because cowards get cancer too', Vermillion, London, 1998.)

INTRODUCTION

DECADES OF modern treatment have taught us that cancer is a smart disease. Patients with many types of cancer may experience little or no significant response to even the best available combination of surgery, radiation and drug therapy. When responses are obtained, cancer cells most commonly develop resistance mechanisms that lead to the failure of subsequent treatments. Though glamorous may be an overstatement, our appreciation of the smartness of cancer cells has increased enormously with the progressive elucidation of the genetic basis for the initiation of malignant transformation and the stepwise progression to an increasingly malignant, locally invasive and metastatic phenotype. Our respect is further enhanced by our growing knowledge of the biochemical networks that cancer genes exploit during their natural history. To beat 'smart' cancer cells we will need even smarter therapies. This is a considerable challenge. The challenge is matched, however, by the real sense of excitement that has developed in the field of new anticancer drug discovery over the last couple of years [1]. That excitement is based on the premise that we can design much smarter and more effective therapies by aiming to counteract or exploit the very genetic and biochemical abnormalities that drive the disease itself [2].

A vast array of opportunities are now opening up for such mechanism-based cancer therapies. They include the use of small molecule drugs, antisense oligonucleotides, peptide and protein therapeutics including monoclonal antibodies (MAbs), gene therapy, vaccines and cell therapy. The list is too long to cover in the space constraints of this review. Given that other topics (such as gene therapy—see article by Ilyas and colleagues, pp. 1986–2002) are covered by other reviews in this series, we have chosen to focus on innovative small molecule approaches targeted to aspects of the malignant cell phenotype that are not dealt with elsewhere. Small molecules, generally defined by a molecular weight cut-off of < 500 Da, have pros and cons. On the one hand, small molecules are favoured by the pharmaceutical industry because of their attractive pharmacokinetic properties, especially tumour penetration, and their relative ease in terms of development and pharmaceutical production [3–5]. On the other hand, while small molecules have a tremendous track record in delivering effective drugs directed at targets such as enzymes (e.g. from dihydrofolate reductase to novel kinases), it is a formidable challenge to design small molecules that disrupt large domain protein–protein interactions (such as those involving SH2 domains) or that interfere with transcription factor-DNA complexes.

We will approach this review by first considering what exactly it is that we seek to attain from our new drugs for the Third Millennium. We will then review the two principal means by which our objectives can be met, namely by focusing on the novel molecular targets that are causally involved in the formation, maintenance and progression of the smart cancer cell and by the optimal utilisation of the most modern technologies. Progress and issues will be illustrated by selected examples. Finally we will address the prospects and challenges ahead as our new millennium drugs enter clinical practice.

THE 'FROM–TO ANALYSIS'

Cancer drug discovery is re-inventing itself, in order to exploit the latest intellectual technological developments. This re-engineering process is consuming large amounts of the considerable but inevitably finite resources that are available from industry, government and charitable sources. Before embarking on such re-engineering projects in industry, it is standard practice to start by hiring a team of management consultants who then carry out what is known as a 'From–To Analysis'. This can be an extremely valuable exercise, as it seeks to identify answers to two key questions: 'Where are we now?' and 'Where do we need to get to?' By defining the 'Gap' between the 'From' and the 'To' positions, it enables a rational strategy to be developed in order to achieve the desired goal and provides a clear basis for the prioritisation and allocation of the resources that are needed to deliver the strategy. Of course science is a high-risk enterprise in which outcomes are difficult to predict, and this is particularly so in new drug discovery and development. But this uncertainty, coupled to the dissatisfaction with the current situation that is shared by scientists, clinicians and patients alike, makes it all the more important to move forward with a radical but rational strategy for improvement. Let us conduct our own 'From–To Analysis'.

First the 'From'. The current state of play in which roughly 1 in 4 people in the developed world will die from cancer is clearly unacceptable. The World Health Organisation [6] predicts a rise in worldwide incidence from 10 to 20 million per annum and an increase in deaths from 6 to 10 million by the year 2020. For society this represents a huge unmet medical need and immense personal and social cost; for the pharmaceutical and biotechnology industry it represents a major market opportunity; and for science and medicine it represents an enormous and daunting challenge. What about the current role of drug treatment [6–8]? Excellent results can be obtained with chemotherapy in a small range of cancers. For example, cures are now achievable in several