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Topics in Medicinal Chemistry

Cancer

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Drug research requires interdisciplinary team-work at the interface between chemistry, biology and medicine. Therefore, the new topic-related series should cover all relevant aspects of drug research, e.g. pathobiochemistry of diseases, identification and validation of (emerging) drug targets, structural biology, drugability of targets, drug design approaches, chemogenomics, synthetic chemistry including combinatorial methods, bioorganic chemistry, natural compounds, high-throughput screening, pharmacological in vitro and in vivo investigations, drug-receptor interactions on the molecular level, structure-activity relationships, drug absorption, distribution, metabolism, elimination, toxicology and pharmacogenomics.
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Preface to the Series

Medicinal chemistry is both science and art. The science of medicinal chemistry offers mankind one of its best hopes for improving the quality of life. The art of medicinal chemistry continues to challenge its practitioners with the need for both intuition and experience to discover new drugs. Hence sharing the experience of drug discovery is uniquely beneficial to the field of medicinal chemistry.

The series *Topics in Medicinal Chemistry* is designed to help both novice and experienced medicinal chemists share insights from the drug discovery process. For the novice, the introductory chapter to each volume provides background and valuable perspective on a field of medicinal chemistry not available elsewhere. Succeeding chapters then provide examples of successful drug discovery efforts that describe the most up-to-date work from this field.

The editors have chosen topics from both important therapeutic areas and from work that advances the discipline of medicinal chemistry. For example, cancer, metabolic syndrome and Alzheimer's disease are fields in which academia and industry are heavily invested to discover new drugs because of their considerable unmet medical need. The editors have therefore prioritized covering new developments in medicinal chemistry in these fields. In addition, important advances in the discipline, such as fragment-based drug design and other aspects of new lead-seeking approaches, are also planned for early volumes in this series. Each volume thus offers a unique opportunity to capture the most up-to-date perspective in an area of medicinal chemistry.

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Preface to Volume 1

With supreme irony, the beginnings of modern cancer chemotherapy originated in chemical warfare. Autopsy findings from soldiers killed in the First World War by exposure to sulphur mustard gas led to the proposal in the 1940s that low doses of nitrogen mustard might cause regression of human lymphatic tumors. The pioneering success of this idea, albeit only equating to brief remission of disease, established the principle that rapidly growing tumors could be more susceptible to cytotoxic agents than normal tissues.

During the next half-century, through the endeavours of government institutions, academia and the pharmaceutical industry, a variety of potent cytotoxic drugs were discovered, such as antifolates, anthracyclins and platins. Although there have been successes, most notably in treatment of testicular cancer by platinum-based drugs, chemotherapy can currently still offer only a modest increase in survival time in the majority of advanced disease cases. An optimistic view, however, is that in the coming decades advances in prevention, detection and treatment will finally see cancer become considered not a fatal but chronic disease.

During the 1970s, recognition that tumors in the breast and prostate are subject to hormonal regulation had provided the first opportunity for a more targeted approach to cancer chemotherapy. The pioneering antiestrogenic agent tamoxifen originated from fertility research in the 1960s and later became the first anticancer drug approved for preventative use by the US Federal Drug Administration. Progress in the treatment of hormone-dependent prostate cancer followed advances in breast cancer, with the introduction of nonsteroidal androgen antagonist drugs like flutamide. The first chapter in this volume summarises more recent developments in the area of antihormonal chemotherapy.

Since the effects of cytotoxic agents on normal cells are responsible for many of the well-known side effects of these drugs, the emphasis has now moved predominantly to drug targets essential to tumor function but not to vital organs and tissues, an approach which should in principle give a better selectivity margin than seen for historical cytotoxic drugs. By the late 1980s, advances in molecular biology had begun to provide greatly increased understanding of regulatory and signaling networks in normal cells that control fundamental cellular processes such as vascularisation, growth and proliferation. The role

of many of these networks was found to be greatly enhanced in tumor cells, in response to factors such as genetic make up, age and exposure to environmental carcinogens. Interference with these key regulatory and signaling networks forms the content of much of this volume.

During the late 1990s humanised monoclonal antibodies, such as trastuzumab for treatment of breast cancer, provided the first clinical success using molecular targeted treatment. Advances in understanding of tumor biology also coincided with developments in chemical synthesis and in vitro screening technology, which increased the feasibility of finding small molecule leads with activity against the new targets, and for some targets structural knowledge also played an increasing role in optimisation of these leads.

In the opening years of the 21st century, regulatory approval followed for imatinib, gefitinib and erlotinib, the first small molecule signal transduction inhibitors. Like monoclonal antibodies, clinical studies with these drugs are providing tumor profiling data from which better understanding of the role of genetic factors in determining patient response is starting to emerge. Clinical experience is also beginning to fulfil the anticipation that these targeted agents could offer a more manageable side effect profile than cytotoxic therapy.

The last decade has thus seen clinical trials for a range of drugs that exploit fundamentally different cellular mechanisms from historical cytotoxic chemotherapy, and a number of these agents have now been granted regulatory approval, a landmark recently highlighted as the journal Nature's 24th Milestone in Cancer. Experience from these trials is providing growing insight into the role of factors such as patient selection, clinical trial design and drug resistance mechanisms. An estimated 500 chemotherapeutic agents were undergoing clinical trials in 2004, and this volume reviews the medicinal chemistry behind some key classes of anticancer agent encompassed within these numbers that have the potential to follow drugs like imatinib into clinical practice. The coming decades will reveal if the shift to personalised medicine widely envisaged through introduction of these agents becomes reality against the full diversity of human tumors, and provides a real breakthrough towards fulfilment of a therapeutic vision which began over half a century ago.

September 2006, Alderley Park, UK Robert H. Bradbury

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