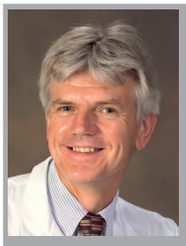
Identifying new targets for cancer therapy: the dawn of personalized cancer treatment?

"This issue of Therapy *includes articles and reviews providing an insight into the current 'state-of-the-art' for targeted therapy in several diseases."*



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The concept of personalized cancer treatment has developed rapidly towards an achievable goal in the last 10 years, driven partly by the identification of multiple new 'druggable' intracellular targets, and partly by the expanding use of techniques such as gene-expression profiling to uncover genes and gene products central to the pathogenesis of individual tumors. This issue of *Therapy* includes articles and reviews providing an insight into the current 'state-of-the-art' for targeted therapy in several diseases.

Probably the first truly targeted therapy to have a major clinical impact has been rituximab, directed at the CD20 antigen in B-cell lymphomas. This and other monoclonal antibody-based therapies with activity in lymphoma are described in a thorough review by Drs Khubchandani and Czuczman [1], which also describes multiple intracellular targets, including spleen tyrosine kinase (syk) histone deacetylases and the PI3/Akt/mTOR pathway. This latter pathway is also known to be important in many other tumors, where it may also be a potential therapeutic target. Dr Djedid *et al.* describe the potential of this, and other targets in glioblastoma multiforme, a chemoresistant tumor for which targeted therapies hold new promise [2]. They also describe a potential role for inhibitors of the EGF receptor (EGFR) and angiogenesis, both of which are also important treatment modalities in renal cell carcinoma. Drs Kim and Rini provide insight into the role of these agents in renal cell carcinoma, as well as the role of tyrosine kinase inhibitors such as sunitinib and sorafenib [3]. These latter two agents appear to have effects on multiple signaling pathways, including those related to VEGF and PDGF receptors.

In their review of targeted therapy for metastatic colon cancer Dr Perez-Garcia *et al.* highlight the importance of membrane receptors as targets, particularly the VEGF receptor (VEGFR) and EGFR [4]. Agents directed against these targets have now been shown to improve outcome when combined with chemotherapy. The concept of combining these monoclonal antibodies is expanded in the Research Highlights by Dr Kamrava *et al.* [5]. They conclude that further randomized studies are required to determine whether combined antibody approaches, when given alongside standard chemotherapy, are superior to single antibody therapy, and suggest that combinations should not yet be used outside clinical trials.

Targeting EGFR and VEGF is a recurrent theme which is expanded upon in the article by Drs Metro and Capuzzo, who describe therapeutic targets in non-small-cell lung cancer [6]. They underline the importance of ongoing studies to select appropriate patients for targeted approaches. For example, they describe the data regarding mutation analysis or fluorescence *in situ* hybridization studies of EGFR copy number as predictors of response to EGFR-directed strategies.

In their respective contributions, Drs Mahller and Cripe [7] and Dr Peer [8] describe preclinical data supporting the potential for cancer stem cells as therapeutic targets, and the possible role of interfering RNAs to inhibit otherwise 'undruggable' intracellular targets. These articles explore the potential for the next generation of molecularly targeted therapies.

The potential for targeted agents is clear. The fact that so many of the targets described in these articles are common to many different types of cancer emphasizes their importance for treatment of common malignancies. Many of these agents have already proven to be highly active in various diseases, and rational combinations are now being assessed in early phase clinical trials. Careful clinical and correlative biologic studies in certain diseases such as lung and colorectal cancer have helped to identify patients likely to benefit from specific targeted agents. Combinations of these targeted agents

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with 'conventional' chemotherapy regimens have also proved beneficial in certain diseases, including malignant lymphomas.

As these new agents have entered into clinical trials and clinical practice, new challenges emerge. Agents initially developed as highly disease-specific agents, such as imatinib in chronic myeloid leukemia, have subsequently been shown to have activity in other diseases, due in part to their ability to block more than one tyrosine kinase. The concept of 'multitargeted' tyrosine kinase inhibitors has emerged, in truth underlying the lack of specificity and overlapping activity of some of these agents. These compounds are uncovering the complexity of intracellular signaling pathways, and resistance to individual drugs is being observed. The need for the use of multiple agents in combination directed at several targets is now apparent. Optimal end points in clinical trials of many of these agents need to be defined. These need to include correlative studies confirming the successful interference with the target, as well as standard clinical response and toxicity end points. Further gene-expression profiles and tissue microarray studies will be needed in each disease to try to uncover the relevance of individual molecular pathways to pathogenesis of disease. Further individualization of therapy will depend on studies of polymorphisms that may directly affect responses to targeted therapy in individual patients – responses to rituximab according to individual CD16 polymorphisms are one example of this.

In summary, the articles contained in this issue highlight the explosion of knowledge and excitement in this area of cancer research. Thank you to all of those who contributed.

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