Chapter 10

TARGETING NF-κB IN ANTICANCER ADJUNCTIVE CHEMOTHERAPY

Dedicated to the memory of Valerie Fincham.

Everything in the laboratory she touched turned into gold.

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Abstract: After more than three decades of its declaration, the war against cancer still appears far from being won. Although there have been decisive victories in a few battles, such as the one against testicular cancer, the overall result is sobering. Hopes for an imminent cure had been raised among the public by the promises of molecular biology, combinatorial chemistry and high-throughput screening. These promises have manifested themselves in the widely proclaimed strategy of rationally targeted anticancer drug discovery, which may be summarized as the ‘one-gene-one target-one drug’ approach. Over the years, however, it has gradually become clear that, in most cases, treatment of cancer with a single drug may at best delay progression of the disease but is unlikely to lead to a cure. Thus, it appears that rationally targeted monotherapy will have to be replaced by rationally targeted combination therapy. Inhibitors of NF-κB look likely to become an important weapon in the anticancer combination therapy arsenal.

Key words: NF-κB; combination therapy; kinase inhibitor; proteasome inhibitor; Gleevec; Velcade
1. INTRODUCTION

A commentary in the July 2003 issue of the Cleveland Clinic Journal of Medicine by Maurie Markman, chairman of the Department of Hematology/Medical Oncology and The Cleveland Clinic Taussig Cancer Center, raised the question if we are winning or losing the war against cancer (Markman, 2003). An answer to this question was given eight months later by Clifton Leaf, Executive Editor of Fortune Magazine and cancer survivor, who, in a provocative article (Leaf, 2004), spelled out why we may be far from winning this war. While there may not be the cancer epidemic proclaimed by some (Fisher et al., 1995; Regenstein, 2002; Eaton 2002; Chambon and Beuzard, 2004), it is a sad and undeniable fact that, despite the billions spent on cancer research around the world since President Nixon declared war on this dreadful disease in 1971, long-term survival of advanced forms of cancer has hardly increased and the percentage of people dying of cancer in the developed world has hardly changed, even when adjusted for age, in the 33 years which have since elapsed (Leaf, 2004; Stewart and Kleihues, 2003; Cancer Facts and Figures 2004).

Clearly, a new strategy for the treatment of cancer is urgently needed, as Michael Baum, professor emeritus of surgery at University College London, already pointed out in a 2002 article in Prospect (Baum, 2002). But what could this new strategy be? Most likely, a single strategy will not be enough to win the war against cancer. As the great British immunologist Sir Peter Medawar once correctly remarked: 'Cancer is not one disease and there will not be one cure for it!'. Indeed, although it has been possible to identify common features shared by practically all types of cancer, such as genetic instability and unchecked proliferation, different sets of genetic lesions may give rise to individual tumours outwardly appearing as belonging to the same type of cancer. This tremendous complexity inherent to cancer is amplified by the characteristic genetic instability of cancer cells, a hallmark of the disease (Hanahan and Weinberg, 2000). The consequent evolution in multiple directions towards ever increasing malignancy manifests itself in markedly different responses to standard anticancer therapy shown by different patients suffering from a particular type of cancer (Watters and McLeod, 2003). This complicating fact indicates that what is required are therapeutic regimens tailored to the individual tumour and the specific set of molecular defects which gave rise to it (Carr et al., 2004). However, personalized therapy is unlikely to be sufficient to win this war because of the considerable robustness and ability to develop resistance, which is another characteristic feature of tumours. This results from their composition of heterogenous and continuously evolving populations of cells. Because the only way to cure a cancer is to destroy every last one of these cells, a single