models may provide a better opportunity to understand crucial cancer mechanisms and to develop new clinical therapies.[43]

Genome-based medicine has permitted the development of personalized treatments in which effective targeted therapies may be suitable only for small subgroups of patients.[44] DNA microarray technology permits the study of alterations in the transcriptional level of entire genomes, and it may become an important tool for predicting the chemosensitivity of tumors before treatment. Pharmacogenetics, which focuses on intersubject variation in therapeutic drug effects and toxicity depending on polymorphisms, is also particularly interesting in oncology because anticancer drugs usually have a narrow margin of safety, and the parameters generally used to adjust the dose of chemotherapeutic agents (weight or body surface area) are not sufficient to overcome differences in drug disposition.[45]

Cancer stem cells (CSCs) have similar characteristics to normal stem cells, specifically the ability to give rise to all cell types found in a particular cancer. They persist in tumors as a distinct population and cause relapse and metastasis, giving rise to new tumors. Conventional chemotherapies kill differentiated or differentiating cells that form the bulk of the tumor, but a population of CSCs can remain untouched, causing a relapse of the disease. Therefore, the development of specific therapies targeted at CSCs holds hope for improvement of survival and quality of life of cancer patients, especially for patients with metastatic disease. Cancer treatments targeting CSCs are discussed in Chapter 11, Section 7.

In parallel with these scientific developments, the cost of cancer drugs has increased exponentially. A controversial example is Provenge®, an autologous vaccine designed to stimulate the immune response to prostate cancer by targeting prostatic acid phosphatase and that costs $93,000 per treatment (2010 data). It is likely that we are witnessing a "bubble" based more on goodwill and hope than on results, and many researches think that there is an obvious need for a change of paradigm.[46]

6 COMBINATION THERAPY AND PERSONALIZED ANTICANCER TREATMENTS

Combination chemotherapies have been a mainstay in the treatment of disseminated malignancies for almost 60 years, but even the most successful regimens fail to cure many patients. Part of this failure is due to the absence of mechanistic information about how drugs interact to promote combination effects.[47]

It is now evident that the Ehrlich's magic bullet concept cannot be generally applied to cancer because it is a multifactorial disease and also a network problem. For this reason, the design of therapies should not focus on individual targets within a single pathway but, rather, on dysregulated cellular networks as a whole, giving place to combinatorial personalized therapies as the rational approach to overcome the failure of single drugs in complex diseases such as cancer, diabetes, and schizophrenia.[48] The strength of network biology lies in the multidimensional data that can be computationally integrated and used to identify specific and reliable therapeutic network targets to construct models of cellular decision-making processes. In this respect, in addition to protein networks, the cellular microenvironment is very important.[49]

The shift from single drug targeted therapy to combinatorial personalized therapies in cancer introduces a new challenge if we consider the whole arsenal of targeted therapies as a treatment option