for every patient. New methodologies are needed to optimize the design of combinatorial therapies to achieve the best response rates with minimal toxicity because this decision requires a transition from the one-drug/one-biomarker approach to global strategies that simultaneously assign markers to a catalog of drugs.

Classically, the drug mechanism of action refers to the description of a specific biochemical event, although in recent years, a series of drug-induced molecular/phenotypic measurements in an experimental system afford "signature"-based predictions. When these measurements arise from many drugs, the corresponding data provide multivariate signatures that fingerprint the drugs according to their relative signature similarity, but these molecular/phenotypic signatures have not been adapted to the examination of multidrug combinations. For instance, by examining the response to a diverse selection of chemotherapeutics of cells expressing short hairpin RNAs (shRNAs), which are sequences of RNA used to silence target gene expression via RNA interference (RNAi),[50] it is possible to generate a functional shRNA signature that permits the accurate grouping of these drugs into established biochemical modes of action and the prediction of mechanisms of action for molecules that are poorly characterized.[51] However, when two drugs are combined, one agent may simply reinforce the action of another or, alternatively, their combined effects may be distinct from either individual compound. Correspondingly, the shRNA signature of a combination drug would either resemble that of an individual drug or exhibit distinct genetic dependencies. In the latter case, the combined signature may be an average of individual drugs to mimic a compound not present in the combination or to adopt a novel signature. Some strategies to optimize the design of combinatorial therapies in order to achieve the best response rates with minimal toxicity have been proposed.[52]

Personalized treatments with targeted therapies designed to treat cancers carrying specific molecular alterations have been proposed as the next battle in the war against cancer. The use of clinical biomarkers to identify patients who are more likely to benefit from a given target therapy makes it possible to match a given treatment with specific patient characteristics.[53] At this point, problems associated with rapidly mutating targets and the development of drug resistances appear. For instance, in the context of breast cancer, the level of the receptor tyrosine kinase HER2/*neu* is used to select the monoclonal antibody trastuzumab (Herceptin®) as an adjuvant therapy,[54] but some patients who initially respond to the targeted therapy regress subsequently due to the occurrence of secondary molecular alterations such as the expression of the protein p95HER-2, a truncated form of the HER2 receptor lacking the extracellular domain to bind the antibody. In the context of melanoma, vemurafenib (Zelboraf®) is useful in patients with the b-Raf (V600E) mutation, where the valine-600 residue of this protein is replaced by glutamic acid.[55] However, most effectively treated patients regress after approximately 1 year due to compensatory pathways, such as receptor tyrosine kinases or N-Ras upregulation or dimerization of aberrantly spliced b-Raf (V600E).[56] In contrast to melanoma patients, colon cancer patients harboring the same b-Raf (V600E) mutation show a very limited response to this drug—a difference that can be understood by considering that treatment with vemurafenib induces feedback activation of EGFR, leading to stimulated cell growth. This adverse effect counteracts the advantages of b-Raf inhibition, especially in colon cancer, in which EGFR levels are higher than those in melamoma.[57]

The development of monoclonal antibodies as anticancer agents has been remarkable in the past few years, but many antibody-based approaches have serious limitations because they are ineffective on target antigen-negative tumor cells, which may be preexistent in the lesion or raised through antigen shedding, masking, or therapy-induced downregulation. Other advanced strategies, such as the use of