development. For this reason, it is necessary to select those patients for whom TGF-β inhibition is therapeutically useful.

Progress in the development of potential drug molecules is often problematic because it is difficult to convert hits into "druggable" compounds—that is, into molecules with adequate pharmaceutical properties. To this end, it is necessary to know the chemical properties of a lead compound, especially solubility and reactivity, because these properties are relevant for cellular uptake and metabolism in order to transform a lead compound into a real drug. The "druggability" of a drug candidate describes its adequate absorption, distribution, metabolism, and excretion (ADME) properties. In this task, the individualized knowledge of important metabolic enzymes, such as cytochrome P450 CYP3A4, permits improvement of the effectiveness and patient tolerance for antitumor compounds. A preliminary knowledge of ADME properties may be gained by using *in silico* techniques, although an experienced chemist can provide accurate insights into this picture by simple inspection of a given structure. The chemical properties of a drug candidate also govern its proposed formulation. In connection with ADME properties, the nonspecific biodistribution of anticancer drugs throughout the body,[37] requiring the administration of a large total dose to achieve high local concentrations in a tumor, is a major problem in cancer chemotherapy. Drug targeting aims at preferent drug accumulation in the target cells, independently of the method and route of drug administration.[38] One approach to improve the selectivity of cytotoxic compounds is the use of prodrugs that are selectively activated in tumor tissues, taking advantage of some unique aspects of tumor physiology such as selective enzyme expression, hypoxia, and low extracellular pH. More sophisticated tumor-specific delivery techniques allow the selective activation of prodrugs by exogenous enzymes (gene-directed and antibody-directed enzyme prodrug therapy) and the increased permeability of vascular endothelium in tumors (enhanced permeability and retention effect, EPR) permits that nanoparticles loaded with an antitumor drug can extravasate and accumulate inside the interstitial space, where the drug can be released as a result of normal carrier degradation.[39] In this discussion of contributions to the development of antitumor agents, it has to be mentioned that chemistry has also made possible important advances in prodrug development and in related targeted approaches, such as antibody-coupled drugs or photoactive agents.

Another major issue in cancer chemotherapy is acquired drug resistance, which is often developed by cancer cells after an initially effective treatment. Furthermore, following the development of a resistance mechanism in response to a single drug, cells can display cross-resistance to other structural and mechanistically unrelated drugs, a phenomenon known as multidrug resistance (MDR), in which ATP-dependent transporters have a significant role.[40] Resistance problems were observed during the early stages of cancer chemotherapy in the very first patient treated with a nitrogen mustard in 1942.

An additional problem in the development of anticancer drugs is the large gap from promising findings in preclinical *in vitro* and *in vivo* models to the results of clinical trials. Conventional anticancer drug screening is typically performed in the absence of accessory cells of the tumor microenvironment, and this preclinical drug testing may overestimate potential clinical activity, explaining at least in part the gap between preclinical and clinical efficacy in cancers.[41] Although a large number of clinical trials are in progress and new results are continuously being published, a statistically significant benefit is observed for very few of them.[42] In this regard, it has been claimed that to increase the efficacy of anticancer clinical trials, it is necessary to develop and use more clinically relevant cancer models. With the help of advanced engineering techniques, the development of complex 3D *in vitro* cancer