- Gene regulation by the drug in sensitive and resistant models
- Mechanisms of apoptosis and effects on the immune system
- Potential adverse effects and their modulation
- PK/pharmacodynamics (PD) correlations and optimal treatment schedules
- Imaging of response

Similar to the drug development, the biomarker optimization might use or require some of the models in parallel.

In analogy to the TIV process, increased demands on the lead optimization have changed the requests on the disease models. The target-driven approaches now require models with defined levels of target expression which will be mainly generated by genetic modifications and cloning:

- Homogeneous, standardized in vitro tumor models, naturally or genetically engineered with target over- or underexpression for screening (isogenic models), models for classical drug resistance
- Homogeneous, standardized in vivo tumor models, natural or genetically engineered with target over- or underexpression for pharmacodynamic optimization (transgenic mice)
- Models for pharmacokinetic/pharmacodynamic correlation studies in different species (mouse, rat, and/or non-rodent species), models for evaluation of side effects (toxicology) in correspondence to pharmacodynamic effects

4 Translational Research (TR) Process

Translational research in oncology from the perspective of the drug developer should provide the simple answer: "who is the right patient for my new drug," whereas the oncologist is interested in: "which is the right drug for my patient." This means that in the later stages of cancer drug development and in the management of patients with cancer, "predictive biomarkers" are urgently needed which can be used to identify optimal target populations of patients; predict the efficacy of the drug and patient's response, resistance, and toxicity; and rapidly distinguish between nonresponders and patients who respond to therapeutic intervention (Kelloff and Sigman 2012). The major challenge for translational cancer research is the development of patient-specific models conserving the histology and genome of the donor tumors and providing the basis for experimental target validation, individual drug testing, and response prediction. Several cancer system biology consortia are currently developing new patient-derived xenograft (PDX) models. The PDX cultures maintained complex tissue architectures, intra-tumor heterogeneity, driver mutations, and marker expression. Screening of 57 PDX models with 12 compounds revealed pathway-specific drug responses (Rivera et al. 2014). These newly developed PDX models are providing efficient tools for personalized drug development under the given time constraints of clinical settings.