3 Tumor Models in the Lead Identification and Optimization (LO) Process

The lead identification and optimization is more or less identical with the classical drug development process. Depending on the nature of the target, this will include in vitro assay development, followed by a screening phase of selected compound, peptide, antibody, or RNAi libraries to identify a lead structure. Once a lead structure has been identified, optimization processes are started, frequently in parallel for several leads (Fig. 3).

As the most difficult part of the targeted drug development, this part has to address the molecular mechanism of action in correlation to optimal pharmacodynamic activity (physiological mechanism of action), optimal pharmacokinetics (absorption-distribution-metabolism-excretion (ADME)), toxicity, as well as resistance development.

A large number of functions are getting involved in this integrated preclinical drug development to address:

- The extent of target inhibition in correlation to pharmacological effects (i.e., inhibition of tumor growth, blood flow, metabolism)
- Identification of main indications (primary tumors, metastases)
- Sensitivity on combination with other drugs (drug modifier screen, i.e., high-throughput (HTS) proliferation assays or siRNA technology)
- Sensitivity to drug transporters (ABC transporters), cellular uptake, and intracellular distribution

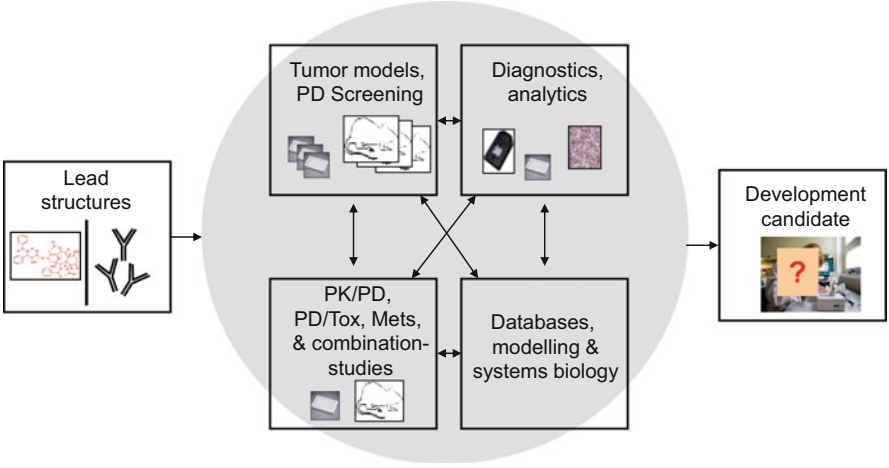

Fig. 3 Integrated research for novel drug candidates. Medicinal chemistry and experimental biology, supported by main preclinical functions, are interactively involved in the preclinical oncology drug development processes