Such tools can be used for both dedicated reverse genetic experiments and broad, even genome-wide, screens.

Today, the existence of large and diverse compound libraries in combination with great advances in cell and organoid culture technologies makes phenotypic screening also an interesting approach for target and drug discovery. The recently approved hepatitis C virus NS5A inhibitor ledipasvir is based on the discovery of the target as well as the chemical lead structure in a phenotypic screen using a viral replicon system in a human hepatocyte cell line (Gao et al. 2010). Such screens can be extended to whole organisms. The first-in-class antimalarial drug KAE609 currently in phase 2 clinical trials was discovered employing a *Plasmodium* whole-cell proliferation assay with cultured intraerythrocytic parasites (Rottmann et al. 2010). KAE609 is a spiroindolone that targets the P-type cation-transporter ATPase4, a membrane transporter protein regulating sodium homeostasis and thus the osmoregularity of the parasite. Like artemisinin, KAE609 targets all stages of the life cycle of malaria parasites which is important for fast parasite clearance. Interestingly, phenotypic screening appears to be particularly successful for antiparasitic drugs, and around 80% of new antimalarial drugs in preclinical or early clinical phases at the moment have come from phenotypic screens (Cully 2014). In addition to these more complex phenotypic screens, also screens interrogating biological pathways have been used successfully for drug and target discovery. An example is the porcupine inhibitor LGK974 which targets an acyltransferase in the Wnt signaling pathway and is currently in phase 2 clinical trials for Wnt-dependent cancers (Liu et al. 2013). The inhibitor was found in a screen for inhibitors of Wnt secretion using a coculture system of a Wnt-secreting and a Wnt-reporter gene cell line.

4 Changing Landscape of Academic and Pharmaceutical Research

During the period covered by this chapter, there also have been major environmental changes for drug discovery.

4.1 Laboratory Size

At the beginning of the period, the traditional small laboratory illustrated in Fig. 4 was still prevailing where a master (primary investigator) was working with few apprentices (PhDs, postdocs) in relative isolation conducting experiments by hand and with relatively simple apparatus. Today laboratories are extensively computerized and automated (Fig. 5). With the advent of target-based drug discovery, testing of drugs in whole organism was replaced increasingly by in vitro methods with binding studies probably reaching the bottom of complexity. Today