which may then lock the resistance mechanism. The search for antibiotics through random screening seems to have been abandoned in view of the poor performance in finding leads in favor of rational, target-based approaches. Molecular biology, robotics, miniaturization, massively parallel preparation and detection systems, and automatic data analysis now dominate the search for drug discovery leads.

Natural product extracts and bacterial culture collections do not necessarily work well together on drug discovery platforms. The separation, identification, characterization, scale-up, and purification of natural products for large-scale libraries suitable for these HTS are daunting, and rational arguments for the selection of organisms and/or natural product molecules are often absent, especially given the poor taxonomic characterization of strains in natural product bacterial strain collections.

Many of these screening systems are not sufficiently robust to handle complex mixtures of natural products from ill-defined biological systems and may be inhibited by interactions with uncontrolled physicochemical conditions, simple toxic chemicals, and known bioactive compounds. This has led to significant efforts in rational drug design, combinatorial chemistry, peptide libraries, antibody libraries, combinatorial biosynthesis, and other synthetic and semisynthetic methods to provide clean inputs to screens. However, natural products are still unsurpassed in their ability to provide novelty and complexity. In the chemical screening of natural products, complex mixtures of metabolites from growth and fermentation are separated, purified, and identified using high-pressure liquid chromatography, diode array ultraviolet (UV)/visible spectra, and MS. Novel chemical structures are passed on for screening, now uncontaminated, with background interference from the original complex mixture, and built up into high-quality, characterized natural product libraries. This strategy suffers from poorly characterized culture collections, which makes the choice of organisms for screening difficult, and from the inability to control the expression of metabolic potential.

1.5 Recombinant Drugs

Recombinant DNA techniques coupled with the typing of human genes now allow the development of a new class of drugs, ranging from the expression of proteins to individualized drugs that would show specific response in patients. Once a biotechnological target has been identified, decisions must be made regarding the choice of the expression organism and the screening procedures to evaluate efficiency. Rules of thumb include relying on proven organisms such as actinomycetes, using taxon-chemistry and taxon-property databases to predict antibiotic potential, and focusing on novel and overlooked taxa. An example of the last consideration is the study of cyanobacteria to isolate the HIV-inactivating protein cyanovirin-N. There is a strong view that biopharmaceutical leads are more likely to be detected in cell function assays than in the in vitro assays. In this context, the construction of surrogate host cells for in vivo drug screening is an interesting development. For example, the ability of *Saccharomyces cerevisiae* to express heterologous proteins makes it an attractive option; it is used in screens based on substitution assays, differential expression assays, and transactivation assays, which are proved to be an effective route for drug discovery.