1.1.10 DNA-Encoded Library Technology

An alternative approach to access new drug-like chemical space for hit exploration is to use DNA-encoded library technology (DELT). Owing to the "split-and-pool" nature of DELT synthesis, it becomes possible to make huge numbers of compounds in a cost- and time-efficient manner (millions to billions of compounds).

Despite its uncertainty of the mechanism of action, the interest in RNA targeting remains high. DNA stores the information for protein synthesis, and RNA carries out the instructions encoded in DNA, leading to protein synthesis in ribosomes. While a majority of drugs is directed at targeting proteins responsible for a disease, sometimes it is not enough to suppress the pathogenic processes. It seems like a smart strategy to start earlier in the process and influence RNA before proteins are even synthesized, therefore substantially influencing the translation process of genotype to unwanted phenotype (disease manifestation).

1.1.11 Phenotype

Many drugs are discovered using phenotypic screening than target-based approaches. Beyond just comparing phenotypic and target-based approaches, there is a clear trend toward more complex cellular assays, for example, going from immortal cell lines to primary cells, patient cells, co-cultures, and three-dimensional (3D) cultures. The experimental setup is also becoming increasingly sophisticated, going far beyond univariate readouts toward observing changes in subcellular compartments, single-cell analysis, and even cell imaging.

The simplest phenotypic screens employ cell lines and monitor a single parameter such as the cellular death or the production of a particular protein. High-content screening where changes in the expression of several proteins can be monitored simultaneously is also often used.

1.1.12 Biologics

Modern molecular biology techniques have also expanded the drug space beyond traditional synthetic small-molecular-weight compounds and have enabled the design, production, and development of biologic molecules such as drugs. Of the 624 drugs approved by the FDA over the past 20 years, 84 were biologics. However, their impact for the pharmaceutical industry has been even bigger than these numbers suggest, as most of the top-selling drugs are biologics. So far, these drugs were dominated by antibodies, soluble receptor constructs, immunoglobulin fusion proteins, and secreted naturally occurring proteins. The most prominent examples are tumor necrosis factor (TNF) alpha-blocking antibodies (infliximab and adalimumab) and the soluble TNF receptor fusion protein (etanercept) for the treatment of rheumatoid arthritis, the anti-CD20 antibody rituximab for non-Hodgkin's lymphoma, the antivascular endothelial growth factor A (VEGF-A) antibody bevacizumab for colorectal and other cancers, and the antihuman epidermal growth factor receptor 2 (HER2) antibody trastuzumab for the treatment of breast cancer. Beyond these "classical" drugs, the biologics space has grown over recent years, for example, by the introduction of antibody–small-molecular-weight-drug conjugates and bispecific antibodies, and is likely to continue