valuable ideas for the design of new chemotypes and, perhaps even more importantly, for the further optimization of lead structures. In this way, lead finding today may no longer be seen as a one-off activity at the beginning of a drug discovery project but rather as a continuing activity which accompanies compound optimization. Both, lead finding and lead optimization, can cross-fertilize each other, and the former may be run in iterative cycles with knowledge gained from previous cycles as well as lead optimization efforts feeding forward into the next cycle.

2.7 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 as drugs. Of the 624 drugs approved by the FDA over the past 20 years, 84 were biologics (Mullard 2014). However, their impact for the pharmaceutical industry has been even bigger than these numbers suggest as seven of the ten biggest selling drugs in 2013 were 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, 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 anti-vascular 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 introduction of antibody-small molecular weight drug conjugates or bispecific antibodies, and is likely to continue to grow at a rapid pace over the coming years. The advantages of biologics are their high affinity for and specificity to their targets, but so far they are mostly limited to secreted or cell surface targets.

3 Where Do Targets Come from?

A minority of drug discovery projects prior to the mid-1980s were target based. One such case is the discovery of statins as HMG-CoA reductase inhibitors to lower cholesterol levels (Tobert 2003). Details of the cholesterol biosynthesis pathway were worked out in the 1950s and 1960s and HMG-CoA reductase established as the rate-limiting enzyme. The first potent inhibitor was found in the mid-1970s using an assay that involved radioactively labeled substrates in cell extracts. Today the establishment of targets for drug discovery is in many cases still based on advances in basic science over many decades and constituted by a series of important discoveries. For example, the capacity of tumor cells to stimulate angiogenesis was discovered in 1945 (Algire and Chalkley 1945) and the presence of soluble tumor-derived factors demonstrated in 1968 (Greenblatt and Shubi 1968).