2.2.2 Genomes and Genome Mining Approaches

The sequencing and publication of the human genome is often considered one of mankind's greatest scientific achievements of modern history. Scientists have also managed to sequence the genomes of a large number of fungal and bacterial strains. At first, scientists primarily used the information from these sequenced genomes for an understanding of the model organism of interest (Li et al. 2004) or to find new potential targets for the development of drugs (Miesel et al. 2003).

However, it was recently discovered that bacterial and fungal genomes contain many "silent" (cryptic) gene clusters, i.e., clusters that are not expressed, that have the potential of translating into natural products or natural product-synthesizing enzymes, provided the right activation conditions are found. Due to our increased understanding of the biosynthesis of various natural products by the enzyme groups of polyketide synthases and nonribosomal peptide synthetases (Fischbach and Walsh 2006), it is now possible to scan the genome of lesser known species for genes (Hornung et al. 2007) or gene clusters that share some homology to gene clusters from species that are known to be translated into specific natural products and/or natural product-synthesizing enzymes. Subsequently, the gene clusters of interest can then be "activated" by expression in other, better controlled systems to see if new natural products will be formed. This technique is known as genome mining.

Although genome mining is still a relatively new technique, it has already led to the discovery of a large number of new natural products. Examples of natural products discovered through genome mining include the ribosomally synthesized lantipeptides curvopeptin from bacterial species *Thermomonospora curvata*, erythreapeptin from bacterial species *Saccharopolyspora erythraea* (Völler et al. 2012) and haloduracin from bacterial species *Bacillus halodurans* (McClerren et al. 2006), nonribosomally synthesized peptide coelichelin from bacterial species *Streptomyces coelicolor* (Lautru et al. 2005), ribosomally synthesized peptides plantazolicin A and B from bacterial species *Bacillus amyloliquefaciens* FZB42 (Kalyon et al. 2011), and small molecules terrequinone A and aspyridone A from fungal species *Aspergillus nidulans* (Bok et al. 2006; Bergmann et al. 2007). By combining genome mining with metabolic engineering, a high amount of structurally diverse natural products could be obtained in the near future, possibly leading to many new drug leads.

2.2.3 Metabolic Engineering

Metabolic engineering approaches are directed towards either the overproduction of desired natural products, production of natural products in other, better producers (heterologous production), or generate entirely new natural products which would normally not be produced at all. Because overproduction and heterologous production have both more or less been established for several examples, this paragraph will focus on the generation of new natural products through metabolic engineering. A considerable number of natural products are produced by polyketide synthetases (PKS) and nonribosomal peptide synthases (NRPS) (Richard Hutchinson 2003). While this makes understanding the biosynthesis of newly discovered natural