Developing methylotrophic bacteria into cell factories that meet the chemical demand of the future could be both economical and environmentally friendly. Methane is not only an abundant, low-cost resource but also a potent greenhouse gas, the capture of which could help to reduce greenhouse gas emissions. Rational strain design workflows rely on the availability of carefully combined knowledge often in the form of genome-scale metabolic models to construct high-producer organisms. In this review, the authors present the most recent genome-scale metabolic models in aerobic methylotrophy and their applications. Further, the authors present models for the study of anaerobic methanotrophy through reverse methanogenesis and suggest organisms that may be of interest for expanding one-carbon industrial biotechnology. Metabolic models of methylotrophs are scarce, yet they are important first steps toward rational strain-design in these organisms.