As the site of peptide bond formation, peptidyl transferase center (PTC) is essential for protein synthesis. This site is targeted by a number of clinically used antibiotic classes, including oxazolidinones, which inhibit bacterial protein synthesis. Pathogenic microbes have evolved defense mechanisms to prevent inhibition of translation. Among the most concerning is a single-methylation of the peptidyl transferase center of the ribosome, by methylating enzyme Cfr. This enzyme confers resistance to seven classes on ribosome-targeting antibiotics, and is wide-spread in both clinical and veterinary isolates of antibiotic resistant microbes across the globe. Cfr has been linked to several clinical outbreaks of antibiotic resistance world-wide, including those in the US. Using directed evolution of Cfr as a platform to generate enzyme variants, we have developed tools to investigate the mechanistic link between ribosome methylation and antibiotic resistance. Using a variant that achieves stoichiometric ribosome methylation, we have obtained a 2.2-Å cryoEM structure of Cfr-methylated ribosomes. A complex of a Cfr-modified ribosome with radezolid, an oxazolidinone antibiotic that overcomes Cfr-mediated resistance, the nascent peptide and a tRNA suggests strategies for development of improved oxazolidinone variants.