Malfunction of the chloride channel CFTR causes the lethal genetic disease, cystic fibrosis. Since the discovery of the CFTR gene in 1989, tremendous efforts have been made to uncover the functional mechanism of CFTR and how different mutations are associated to the disease phenotypes. CFTR consists of five domains, namely two transmembrane domains (TMDs), two nucleotide binding domains (NBDs) and a regulatory (R) domain. After phosphorylated by protein kinase A (PKA) to its R domain, CFTR becomes an ATP gated channel. NBDs are considered the engine of CFTR. Fueled by ATP hydrolysis, conformational changes in the NBDs drive the gating process in the TMDs. Nonetheless, the exact role of ATP-hydrolysis in the gating cycle is still unclear. This study focuses on unraveling the coupling mechanism between the ATP hydrolysis cycle and the gating cycle. The clinical applications of these new findings will be discussed as well.