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The Isolated Nucleotide Binding Domains of CFTR Form Bipartate ATPase To Regulate ATP Consumption MARK PALMIER, SILVIA BOMPADRE, University of Missouri — The CFTR Cl- channel belongs to the ATP binding cassette (ABC) family. Contains 2 transmembrane domains that form the channel pore, 2 nucleotide-binding domains (NBDs) and a regulatory domain. Channel opening is primed by ATP binding to NBDs and their dimerization. The stable dimer forms a bipartite ATPase. With ATP at its center hydrolysis occurs, leading to dimer separation and channel closure. Progress has been achieved in the characterization of CFTR gating. But conformational changes behind the gating transitions can only be inferred on structural data from other ABC transporters. The structural dynamics governing CFTR mechanisms are still unknown. Advancements in purification technology make it possible to address the question of dynamics. Our goal is to investigate the dynamics of NBD dimer formation and separation using Single Molecule Fluorescence. Here we show our progress: that dimerization is a tight binding event ($Kd \sim 1\mu$M), hydrolysis competence only when dimerized and FRET demonstrating the association of the two isolated domains in presence of ATP. The goal of this project is to discern the molecular mechanisms governing the CFTR function. When completed, our findings will increase the overall understanding of the relationship between function and dynamics.

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