Advances in biotechnology have led to the increased use of proteins as therapeutics. However, the structural complexity of human therapeutic proteins limits their recombinant expression in convenient and well-characterized bacterial systems. Although different proteins in cells have different folding requirements to be functional, they are all synthesized by the same machinery: ribosomes. The mapping of the ribosomal crystal structure has revealed that newly-synthesized proteins exit the ribosome machinery through a long and narrow tunnel, the polypeptide exit tunnel. How then might protein translocation through this tunnel contribute to the early stages of protein folding and to the fate of different proteins in bacteria? The notion that the confining and interactive nature of this biological tunnel plays a key role in protein folding is highly intriguing. However, the physics of what drives protein translocation through the ribosome exit tunnel remains largely obscure. This talk will focus on our use of molecular simulations and experimental molecular biology techniques to: (1) gain mechanistic insights into how the passage of proteins through a tunnel can induce conformational changes that impact the early stages of the folding process, and (2) engineer the natural interactions that take place during the translocation of target proteins through the tunnel as a platform for new biotechnology applications. In the latter instance, we have successfully applied our strategy to engineer functional antibody fragments directly in the bacterial cytoplasm. Such intracellular antibodies that fold well and function in the cytoplasm are known as "intrabodies" and have great potential in functional genomics/proteomics efforts and in molecular medicine.