Abnormal protein aggregation is associated with a growing number of inherited and sporadic genetic diseases. However, little is known about the relationship between the sequence of aggregating peptides and the process of intracellular accumulation. To test the specificity of protein aggregation, we examined the cellular localization and composition of aggregates formed by different aggregation-prone proteins. We found that CFTR- and huntington-derived peptides accumulate in separate aggregates when co-expressed in the same cell, indicating that aggregation of misfolded proteins is a selective process. We also demonstrated that fusion to a reporter protein considerably alters the distribution of the aggregating peptide. When fused to green fluorescent protein (GFP), the peptide containing amino acids 1370-1480 of CFTR accumulates in large perinuclear or nuclear aggregates. The same CFTR fragment devoid of GFP localizes predominantly to discrete accumulations associated with mitochondria. Importantly, both types of accumulation are dependent on the presence of the same two amino acids within the CFTR sequence. The inability of different misfolded proteins to co-aggregate or form a specific type of aggregate is accompanied by differences in association with molecular chaperones, which suggests a possible role for chaperones in regulating the pattern of protein accumulation. Together, our results contradict the common view that protein aggregates are non-specific associations of misfolded molecules. Instead, we propose that sequence- and structure-specific interactions are critical for protein aggregation, thus suggesting potential avenues for preventing aggregate formation in disease states.