



**Folding and Mis-folding of a 29kDa TIM Barrel Protein:  
Free Energy Landscape Perspective from NMR  
Spectroscopy**

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Viewed from the energy landscape perspective, which is essentially a theoretical formalism describing the progression of the unfolded polypeptide chain along a funnel-like energy surface to the native conformation, the presence of the partially folded intermediates add ruggedness to the folding free energy landscape. The partitioning into the folding and mis-folding pathways via the intermediates populated on the rough energy landscape can result in the formation of functionally active native state or disease causing amyloid structures. Site specific structural and thermodynamic insights derived from NMR spectroscopy and other biophysical methods have provided crucial information on the role of the partially-folded intermediates in guiding the folding and mis-folding reactions of a 29kDa TIM/(b/a)<sub>8</sub> barrel protein. The vital role of the Branched Aliphatic Side Chain (*BASiC*) amino acids in defining the hydrophobic clusters responsible for stabilizing mis-folded off-pathway and on-pathway intermediates populated on the energy landscape will be presented.