

~~39~~. Ken Mok (TBSI) A New and Beneficial Biological Function Resulting From Partial Unfolding of Proteins

## **Abstract**

### **HAMLET and related alternatively-folded proteins with tumoricidal functions**

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HAMLET/BAMLET (Human/Bovine  $\alpha$ -lactalbumin Made Lethal to Tumour cells) and its related partially unfolded protein–fatty acid complexes are novel biomolecular nanoparticles that possess relatively selective cytotoxic activities towards tumour cells [1,2]. Pioneered by C. Svanborg (Lund Univ, Sweden), significant progress has been made to deduce the underlying mechanism(s) of cell death brought about by HAMLET and other related complexes such as BAMLET [3]. From a protein biophysical chemists' / structural biologists' point of view, we have chosen to ask what would be the 'minimal cytotoxic unit' to give rise to this remarkable property. It is now well known that one of the key characteristics is the that the protein is partially unfolded - also resulting in endowing native proteins with additional functions in the alternatively folded states – but how important is this property in terms of the cytotoxic activity?

In relation to this, significant results have confirmed previous suggestions that the fatty acid moiety may be the ultimate cytotoxic agent, and that the protein moiety simply serves as carrier (or 'mule') by increasing its effective critical micelle concentration [4]. Through the examples of other cases, we show that the partially unfolded property of the protein as well as the nature of fatty acid binding is as much as important in determining the cytotoxicity – in other words, there is a delicate balance of structural malleability and related changes in binding affinities that determine the tumoricidal properties. Any efforts to design small-molecule mimics appear to require a better understanding of these structural aspects.

#### References:

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