

Comments to the Editor

The Lipidic Cubic Phase as a Membrane Mimetic

Separovic et al. (1), in commenting on our recent Letter (2), state that "...the main point of this Biophysical Letter...that the 'in meso' approach is a physiologically relevant environment, is misleading...".

The thrust of the work described in the Letter was to test the hypothesis that the inherent flexibility of the hosting mesophase under trial conditions would enable the in meso crystallization of a small membrane protein. By "small", we were referring to integral proteins or peptides with four or fewer transmembrane crossings. Linear gramicidin was chosen as the model small protein with which to perform the test. The fact that gramicidin was reported to assume different conformations made it an appealing model system. One of the objectives of the study therefore was to determine whether it would crystallize in any form by the in meso method. And it did. This result was considered significant because it meant that the method might now be brought to bear on other integral membrane peptides that abound in Nature. We fail to see how this result is misleading.

The work described in the Letter led to hypotheses since investigated (3). This and the obvious issues that the results raise, which could not be addressed in the Letter for lack of space, are discussed in detail in the article by Höfer et al. (3). There, mechanisms are presented for how crystallization of the double-stranded form of gramicidin might come about under in meso conditions. Tracking the peptide's conformation through sample preparation on to crystal growth is

needed to establish exactly how a particular form ends up in the final crystal.

We remain convinced that the bicontinuous lipidic mesophase, with which in meso crystallogenesis is done, is a reliable membrane mimetic (4,5). As always, solved structures must be evaluated for biological relevance by whatever means possible.

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