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Investigating Calmodulin-Long QT Syndrome Restorative Interactions through Combinatorial Approaches

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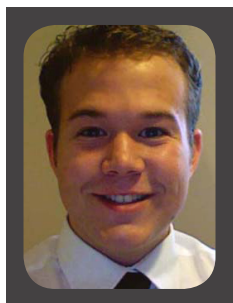
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Investigating Calmodulin-Long QT Syndrome Restorative Interactions through Combinatorial Approaches

A multitude of cellular processes, ranging from cell survival to neuronal excitability, are regulated by proteins with a pervasive binding specificity. To further our understanding of how these conserved sequences recognize and bind to a large number of diverse and physiologically vital binding partners in the healthy and diseased cell, it is necessary to understand and ultimately alter protein binding specificity. For nearly 30 years, calmodulin (CaM) has been a model system to study pervasive binding specificity. However, after numerous structural and biochemical studies, the molecular basis of this pervasive binding activity of the ubiquitous primary calcium signaling transducer remains unclear. Given that CaM binding affinity arises from a combination of hydrophobic contacts, sterics, hydrogen bonding and electrostatics, we are able to further explore the nature of the interactions conferring the enigmatic binding specificity in CaM through protein engineering. Protein combinatorial libraries offer an attractive approach towards identifying novel members with altered CaM binding specificity for downstream structure/function studies. To maximize this search, productive regions of protein sequence space (i.e. folded and soluble) must be sampled. Here we present the first application of the binary patterning approach of combinatorial protein library design to the CaM central linker region. This high-quality approach translates very well to the CaM protein scaffold: All library members over-express and are functionally diverse, having a range of conformations in the presence and absence of calcium as determined by circular dichroism spectroscopy. In addition, ANS-binding data show that each of these possesses significant diversity in binding specificity. Collectively, these data support that the binary patterning approach, when applied to the highly conserved CaM protein, can yield large collections of folded, soluble and highly-expressible proteins, which will facilitate the downstream investigation of selected proteins with altered CaM-binding specificity.