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Harnessing Protein Electrostatics to Enable Fast and Precise Protein Modification at Nanomolar Concentrations

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Résumé :

Chemical and biochemical methods that enable site-selective protein modification are central to the study of protein function and to their integration into diagnostic and therapeutic applications. While achieving high selectivity is essential to obtain homogeneous, well-defined products, the rate at which reactions occur on the protein surface is equally critical. Fast reactions help minimize by-product formation as well as protein aggregation or precipitation.

To meet these requirements, protein chemists rely on a limited set of intrinsically fast and selective reactions that are effective at the protein level. However, under the dilute conditions commonly used for handling protein reagents, the rate of protein modification can fall well below expectations based solely on the intrinsic rate constant of the underlying chemical transformation. In such regimes, additional factors become limiting, including the low frequency of productive encounters between reactants.

In this presentation, I will describe the strategies we are developing to accelerate protein modification under dilute conditions by exploiting protein electrostatics.[1-5]

Keywords: Selective protein modification; electrostatics; native chemical ligation, thioester

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