Tata Institute of Fundamental Research
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Colloquium

Efficacious strategies for cysteine-mediated protein bioconjugation

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The development of chemoselective organic reactions that proceed rapidly under physiological conditions to form stable covalent linkages have revolutionized modern biological and clinical research. One such reaction, Michael addition between the thiol functional groups of cysteine residues of proteins and maleimides to form thio-maleimide linkages, is extensively used for labelling proteins with fluorophores, affinity tags, polyethylene glycol moieties and drug molecules for a diverse range of applications. In particular, the tremendous success of antibody-drug conjugates (ADCs) generated by appending drug molecules to antibodies by employing this chemistry has had a transformative impact on cancer therapy. Consequently, recent reports on the susceptibility of these linkages to undergo thiol exchange-mediated breakdown in the physiological milieu are extremely alarming. In my talk, I shall describe two approaches that my research group has developed to overcome this problem. One of these approaches is based on our discovery that unlike conventional maleimides, exocyclic olefinic maleimides form thiol exchange-resistant conjugates and hence are preferable for thiol bioconjugation. In another approach, we have rationally designed a photoactivable maleimide derivative that after bioconjugation can be irradiated with UV light to trigger rapid thio-maleimide ring hydrolysis to form stable conjugates. I shall also discuss how we plan to use these new scaffolds for generating stable ADCs.

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04:00 PM (Tea/Coffee at 03:30 PM)

Auditorium, TIFR-H