LDM® platform (Patented)

The first-ever platform establishes simultaneous regulation of reactivity, chemoselectivity, site-selectivity, site-modularity, and residue modularity. Besides meeting the technological demands of biochemistry and biophysics, this comprehensive technology for precision engineering of proteins renders homogeneous antibody-drug conjugates (ADCs) for directed cancer chemotherapeutics and antibody-fluorophore conjugates (AFCs) for image-guided surgery. Currently, our team is working towards the translation of selected candidates towards pre-clinical investigations. Also, the recent developments demonstrate that the platform enables protein and organelle specificity within the cells and living organisms.

[1] Traceless cysteine-linchpin enables precision engineering of lysine in native proteins, Reddy, N. C.; Molla, R.; Joshi, P. N.; Sajeev, T. K.; Basu, I.; Kawadkar, J.; Kalra, N.; Mishra, R. K.; Chakrabarty, S.; Shukla, S.; Rai, V. *Nat. Commun.* **2022**, *13*, 6038.

[2] Linchpin empowers promiscuous electrophile to render site-selective modification of histidine and aspartic acid in proteins, Rawale, D. G.; Thakur, K.; Pranav, S.; Sajeev, T. K.; Ramesh, A.; Adusumalli, S. R.; Mishra, R. K.; **Rai, V.** *Chem. Sci.* **2021**, *12*, 6732-6736.

[3] Chemoselective and site-selective lysine-directed lysine modification enables single-site labeling of native proteins, Adusumalli, S. R.; Rawale, D. G.; Thakur, K.; Purushottam, L.; Reddy, N. C.; Kalra, N.; Shukla, S.; **Rai, V.** *Angew. Chem. Int. Ed.* **2020**, *59*, 10332-10336.

[4] Single-site labeling of native proteins enabled by a chemoselective and site-selective chemical technology, Adusumalli, S. R.; Rawale, D. G.; Singh, U.; Tripathi, P.; Paul, R.; Kalra, N.; Mishra, R. K.; Shukla, S.; **Rai, V.** *J. Am. Chem. Soc.* **2018**, *140*, 15114-15123.

Gly-tag® technology (Patented)

It provides the first-ever chemical technology for N-Gly specific modification. Recently, a segment of biologists has been developing engineered enzymes to meet the related technological demands. However, our already established Gly-tag technology provides a remarkable advantage in specificity, efficiency, and cost factors. With this breakthrough, our group is investigating the immense possibilities in the field of cell-surface engineering and precision therapeutics.

[5] Single amino acid Gly-tag enables metal free protein purification, Purushottam, L.; Unnikrishnan, V. B.; Rawale, D. G.; Gujrati, M.; Mishra, S. D.; Sajeev, T. K.; Reddy, N. C.; Adusumalli, S. R.; Mishra, R. K.; **Rai, V.** *Chem. Sci.* **2020**, *11*, 13137-13142.

[6] Single-site glycine-specific labeling of proteins, Purushottam, L.; Adusumalli, S. R.; Singh, U.; Unnikrishnan, V. B.; Rawale, D. G.; Gujrati, M.; Mishra, R. K.; **Rai, V.** *Nat. Commun.* **2019**, *10*, 2539.

Maspecter® toolkit (Patented)

The confidence in the precision of bioconjugation required us to address a few limitations of the proteomics-based analysis. In this perspective, we developed Maspecter series products that allow us to detect peptides at attomolar concentrations. Moreover, it provides one of the most efficient toolkits for conjugation site analysis in antibody-conjugates.

[7] Sensitivity booster for mass detection enables unambiguous analysis of peptides, proteins, antibodies, and protein conjugates, Singudas, R.; Reddy, N. C.; **Rai, V.** *Chem. Commun.* **2019**, *55*, 9979-9982.

Dis**IN**tegrate (D**IN**) theory

The chemical toolbox for the selective modification of proteins has witnessed immense interest in the past few years. The rapid growth of biopharma and the need for precision therapeutics have fuelled this growth further. However, the broad spectrum of selectivity parameters creates a roadblock to the field's growth. Additionally, bond formation and dissociation are significantly redefined during the translation from small molecules to proteins. Understanding these principles and developing theories to deconvolute the multidimensional attributes could accelerate the area.

We have established a disintegrate (D**IN**) theory for systematically disintegrating the selectivity challenges through reversible chemical reactions. It empowers hypothesis-driven research in the field similar to how retrosynthetic analysis has facilitated total synthesis.

[8] DisINtegrate (DIN) theory enabling precision engineering of proteins, Chauhan, P.; Ragendu, V.; Mohan, K.; Molla, R.; Unnikrishnan, V. B.; **Rai, V.** *ACS Cent. Sci.* **2023**, *9*, 137-150.

[9] Protein-protein interaction in multicomponent reaction enables chemoselective, site-selective, and modular labeling of native proteins, Molla, R.; Joshi, P. N.; Reddy, N. C.; Biswas, D.; **Rai, V.** *Org. Lett.* **2023**, *25*, 6385-6390.

Additional ADC contribution

[10] Computationally designed antibody-drug conjugates self-assembled via affinity ligands, Gupta, N.; Ansari, A.; Dhoke, G. V.; Chilamari, M.; Sivaccumar, J.; Kumari, S.; Chatterjee, S.; Goyal, R.; Mukherjee, M.; Sarkar, A.; Mandal, S. K. **Rai, V.**; Biswas, G.; Sengupta, A.; Roy, M.; Roy, S.; Sengupta, S. *Nat. Biomed. Eng.* **2019**, *3*, 917-929.