

## Proteome-Derived Peptide Probes for Biomedical Research & Imaging

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Peptide-based chemical probes are powerful tools to decipher protein function in healthy and diseased cells and instrumental in the validation of therapeutic strategies. The advent of novel readouts for target engagement, along with advancements in synthetic and biosynthetic screening technologies, has resulted in the discovery of a multitude of protein-selective probes. However, despite these advances, achieving proteome-wide specificity in ligand development remains a major challenge.

In our research, we have tackled this challenge by first systematically mapping entire proteomes of intrinsically disordered protein regions and then leveraging naturally occurring endogenous proteome-wide target selectivity of linear binders. The integration of microarray-based screening [1] and quantification in solution [2] enabled us to further improve affinity and achieve proteome-wide specificity. Recently demonstrated by antibody-superior target visualization in brain tissue [3] as well as live primary neurons.

With additional examples, including the combined synthesis and screening of pathogen-specific mRNA-targeting antisense antibiotics, I will highlight opportunities and challenges of our approach for advancing biomedical research and drug discovery.

[1] Schulte et al. *Meth Mol Biol* **2023**, 2578; 143-159; Schulte et al. *iScience* **2020**, 24, 101898.

[2] Schulte et al. *Commun Biol* **2022**, 5, 1070; Schulte et al. *STAR Protoc* **2021**, 2, 100605.

[3] Khayenko et al. *Angew Chem* **2022**, 61, e202202078.