In collaboration with Peter Walter’s lab at UCSF, we used our functional genomics approach to uncover the target of the drug-like molecule ISRIB. ISRIB was discovered in the Walter lab as an inhibitor of the integrated stress response, a central pathway in the mammalian proteostasis network. In mice, ISRIB enhances memory and learning. However, the molecular target of ISRIB was previously unknown.

In an unbiased genetic screen, we found that ISRIB’s action depends on eIF2B, the nucleotide exchange factor for translation initiation factor eIF2. In biochemical follow-up studies, the delta subunit of eIF2B was confirmed as the direct target of ISRIB. This molecular understanding of ISRIB’s mechanism of action will be the basis for developing it into a drug for the treatment of human neurological diseases.

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