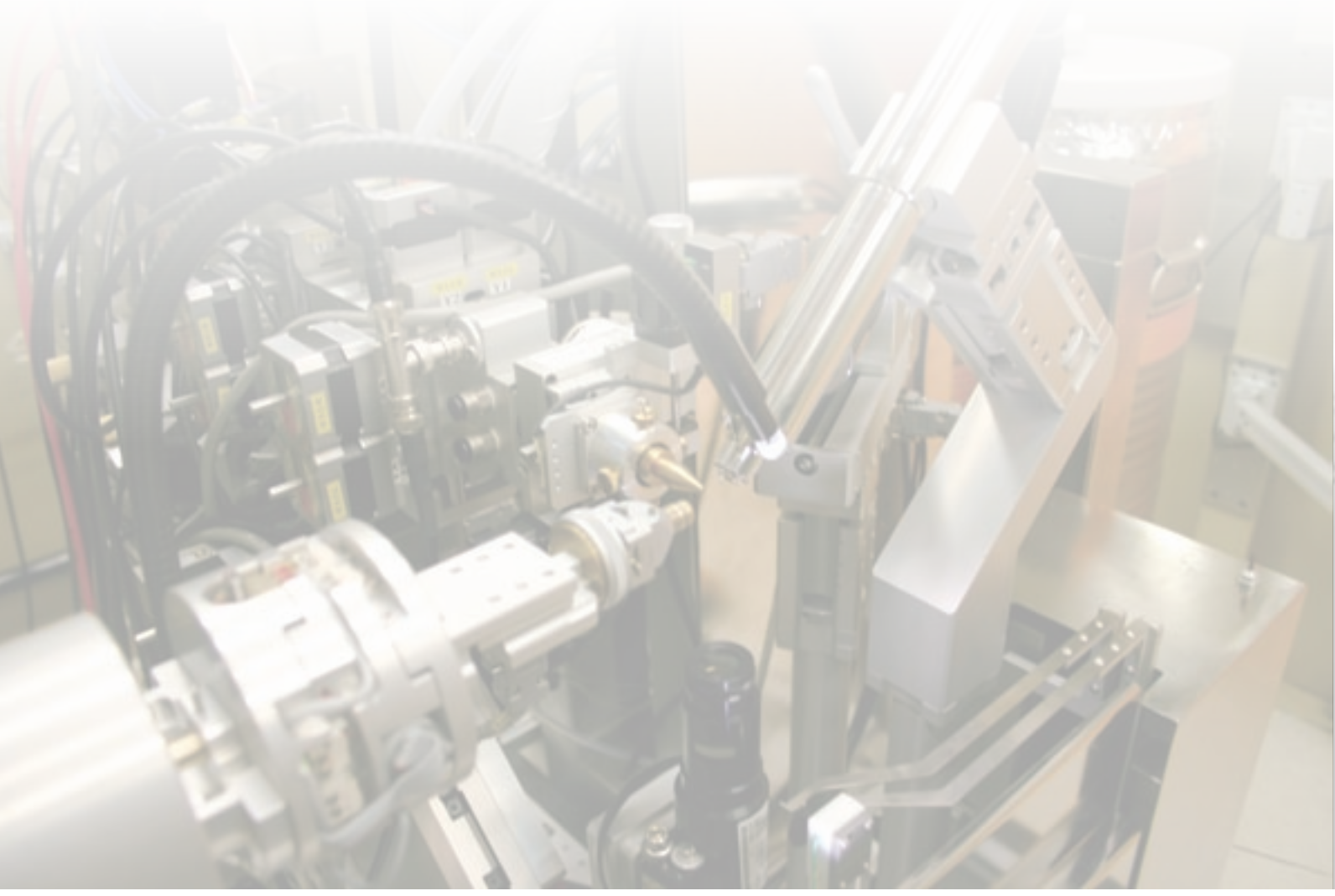
GET Topology to Target Tail-Anchored Proteins

This report features the work of Chwan-Deng Hsiao and his co-workers published in J. Biol. Chem. ***287****, 4783 (2012).*

Tail-anchored (TA) proteins, comprising a cytosolic N-terminal region followed with a transmembrane domain and partially inserting into the organelle membranes in a living cell, have many and diverse important functions, such as regulating apoptosis, operating vesicular transport via intracellular membrane fusion, translocating proteins into mitochondria or across the endoplasmic reticulum (ER) membrane, and assisting in folding or degradation of membrane proteins. TA proteins are found in the mostly major organelles of a cell such as the nuclear envelope, peroxisomes, mitochondria, ER, and Golgi. For a living cell to target the TA proteins for correct localization and membrane insertion is crucial.

The system of guided entry of a tail-anchored protein (GET), which consists of proteins Get1, Get2, Get3, Get4 and Get5, is responsible for the targeting of tail-anchored proteins to the ER. It is of interest to understand how the GET-sgt2 system recognizes, delivers and targets TA proteins into the membrane of specific cellular organelles. Although many researchers are attracted to elucidate the structural information and the individual roles of most components of a GET system, the interactions and interplay of GET proteins are still open questions.

C.-D. Hsiao and co-workers investigated the interaction surface and topology of the Get3-Get4-Get5 protein complex from *Saccharomyces cerevisiae*. This task was daunting because its complicated nature makes



difficult its handling in aqueous solution for crystallization. Extending their previous crystallographic work,[1] these authors eventually sought four complementary techniques -- size-exclusion chromatography, computational docking, isothermal titration calorimetry (ITC), and small-angle X-ray scattering (SAXS). According to the summary shown in Fig. 1, they discovered a promising structural model of protein complex Get3-Get4-Get5, and proposed a working framework of the cycle of TA protein insertion into an ER membrane by the GET system. This TA protein is first recognized and delivered from Get4-Get5-Sgt2 to the open form of Get3. The TA protein is then carried by the closed form of Get3 and separates from other soluble GET members. Get2 in the membrane portion of the GET system tethers the Get3-TA protein onto the ER membrane. Get1 subsequently disrupts the closed form of Get3 to facilitate the membrane insertion of the TA protein dependent on ATPase. Afterward, Get3 is released from the membrane portion of the GET system and rejoins the soluble portion of the GET system for another cycle of targeting a TA protein.

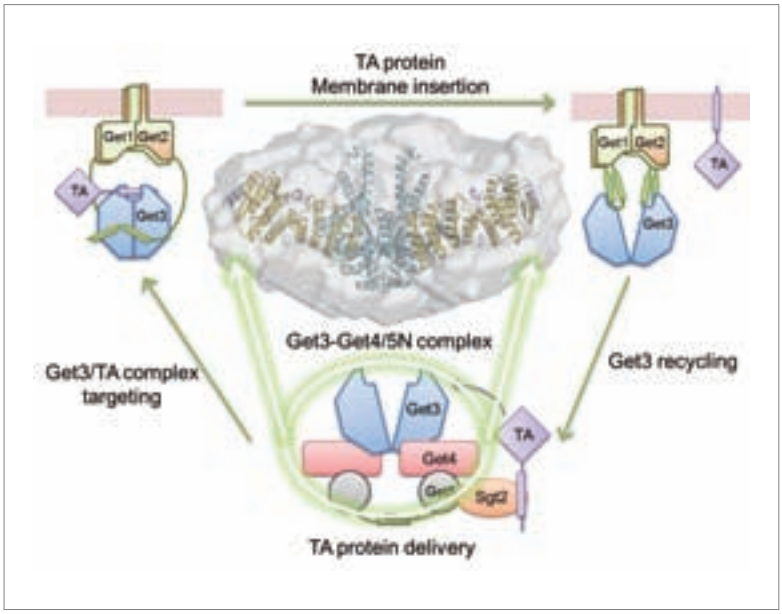


Fig. 1: Schematic framework of TA protein delivery, targeting and insertion into a member. This drawing is a concept adapted from Ref. 1.

The SAXS and protein crystallography (PX) data of this work were collected at beamlines **BL23A/13B/13C/SP12B2** of NSRRC. Detailed information is available in their publications.[1, 2]

References

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2. Y.-W. Chang, T.-W. Lin, Y.-C. Li, Y.-S. Huang, Y.-J. Sun, and C.-D. Hsiao, J. Biol. Chem. **287**, 4783 (2012).