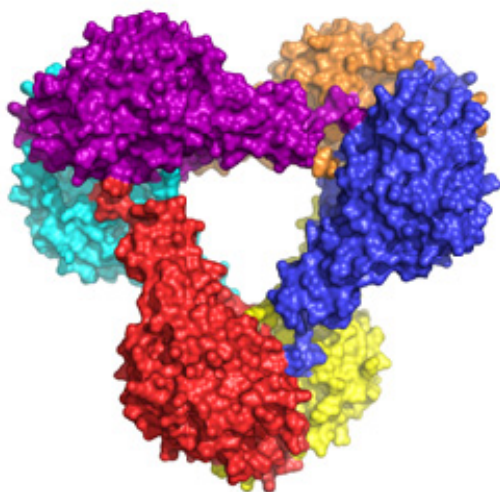


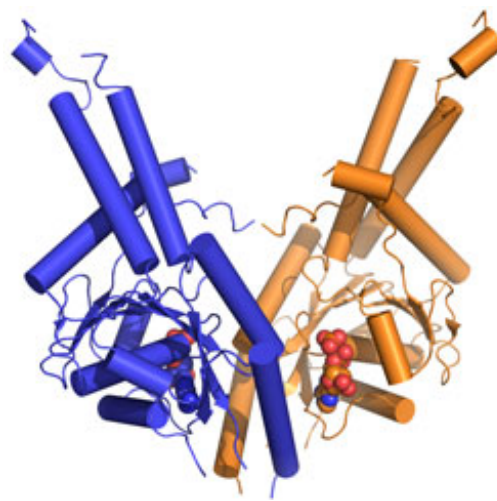
## Model for Eukaryotic Tail-anchored Protein Binding Based on the Structure of Get3

Targeting of newly synthesized membrane proteins to the endoplasmic reticulum (ER) is an important cellular process. Most membrane proteins are recognized and targeted co-translationally by the signal recognition particle (SRP). A number of membrane proteins (eg. SNAREs, apoptosis factors, and protein translocation components) are 'tail-anchored' by a single carboxy-terminal transmembrane domain. Due to this topological constraint, these proteins are not able to follow the SRP-dependent co-translational pathway that typifies most integral membrane proteins. Instead, these proteins must find their correct membrane for insertion post-translationally (1). The ATPase Get3 was the first protein identified directly involved in TA targeting and is part of the Get pathway (Guided Entry of Tail-anchored proteins) that also contains the ER membrane proteins Get1/2 and the putative ribosome receptor proteins Get4/5 (2). Multiple studies have shown that Get3 binds directly to the hydrophobic tail-anchors and, in conjunction with ribosome and ER factors, utilizes an ATP cycle to bind and then release TA proteins at the ER membrane.

To get a detailed mechanistic view of how Get3 performs its important targeting function a team at Caltech led by Bil Clemons used data collected at SSRL Beam Line 12-2 to determine the three-dimensional structure of Get3/TRC40 (Fig. 1). The structure of Get3 in the ADP form was a hexamer (Fig. 1a). It is expected that Get3 functions as a dimer (Fig. 1b). Based on homology to other proteins, the structure allowed for the prediction that binding of ATP would lead to a dramatic conformational change bringing two hydrophobic grooves together to form a TA-binding pocket. The team probed functional interfaces and essential residues using phenotypic rescue allowing them to define a model of how Get3 couples ATP hydrolysis to the binding and release of TA-proteins.



**Figure 1a**



**Figure 1b**

This work represents the first structural study in this novel pathway. Future work will allow for a refining of this model including the details of the binding of substrate and activation for ATP hydrolysis.

## Primary Citation

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2. Schuldiner M, et al. (2005) Exploration of the function and organization of the yeast early secretory pathway through an epistatic miniarray profile. *Cell* 123:507-519.

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