Abstract for IAS Focused Program on Membrane Trafficking: Molecular Mechanisms and Physiological Relevance (July 6-7, 2023)

Rethinking the Secretory Pathway

Benjamin Glick

Department of Molecular Genetics and Cell Biology, The University of Chicago, US

Email: bsglick@uchicago.edu

The Golgi apparatus is a polarized organelle in which various resident proteins are concentrated in different cisternae. Golgi polarity has been thought to reflect division of this organelle into compartments termed *cis*, medial, *trans*, and *trans*-Golgi network. But the compartments model has serious limitations: (1) Resident Golgi proteins show overlapping rather than separate distributions. (2) Golgi compartments have never been precisely defined in molecular terms. (3) The compartments model lacks a mechanistic explanation for Golgi polarity. (4) Golgi cisternae are not stable structures, but instead are transient intermediates that undergo biochemical maturation. For these reasons, an understanding of Golgi organization requires a new perspective.

The cisternal maturation model offers a natural framework for studying Golgi polarity. This model proposes that Golgi cisternae form *de novo*, then mature, then ultimately disintegrate into secretory vesicles. Each cisterna undergoes the same series of transformations. Thus, by characterizing the life cycle of an individual cisterna, we gain mechanistic insight into the entire organelle. Our focus is on resident Golgi transmembrane proteins. During cisternal maturation, transmembrane proteins recycle in transport vesicles, progressively altering the biochemical compositions of the cisternae. The goal is to identify which vesicular recycling pathways operate at the Golgi, and to determine how and when each recycling pathway is switched on and off.

We are tackling this problem through a kinetic analysis of Golgi maturation in *Saccharomyces cerevisiae*. This yeast has a non-stacked Golgi, so individual cisternae can be tracked by fluorescence microscopy. The temporal changes in composition of a single yeast Golgi cisterna are equivalent to the spatial changes in composition of cisternae across a stacked Golgi. Because different vesicular recycling pathways have distinct kinetic signatures, the polarized distribution of resident Golgi proteins results from the existence of multiple sequential recycling pathways. Recently, we have devised intracellular vesicle capture assays that enable us to assign both vesicle tethers and resident Golgi transmembrane proteins to specific recycling pathways. This work is revealing functional connections between the recycling pathways, thereby illuminating the molecular logic circuit that drives cisternal maturation and establishes Golgi polarity.