Schekman's laboratory developed genetic and biochemical approaches to dissect the process of protein secretion in the baker's yeast, *S. cerevisiae*. The genes and proteins his lab discovered in yeast were found to organize the secretory pathway in all eukaryotes. Part of the pathway has been dissected using biochemical reconstitution of the formation and fusion of transport vesicles that mediate protein traffic from the endoplasmic reticulum to the Golgi apparatus. Schekman's lab has probed the molecular mechanism of defects in protein sorting that lead to human diseases of development such as spina bifida and a disease of craniofacial morphology that results in a tissue-selective defect in the secretion of collagen. Recent results suggest a role for ubiquitin conjugation of a coat protein complex in the envelopment of vesicles that covey collagen from the endoplasmic reticulum. Later in the secretory pathway, membrane proteins are sorted for traffic to distinct regions of the cell surface such as the apical and basolateral surfaces in polarized epithelial cells. New results suggest that the proximal and distal surfaces may also receive membrane cargo by a sorting process originating in the trans membrane of the Golgi complex. Sorting at his station may involve cargo signal motifs that are recognized by one of several different GTP-binding proteins and cytosolic coat protein complexes.