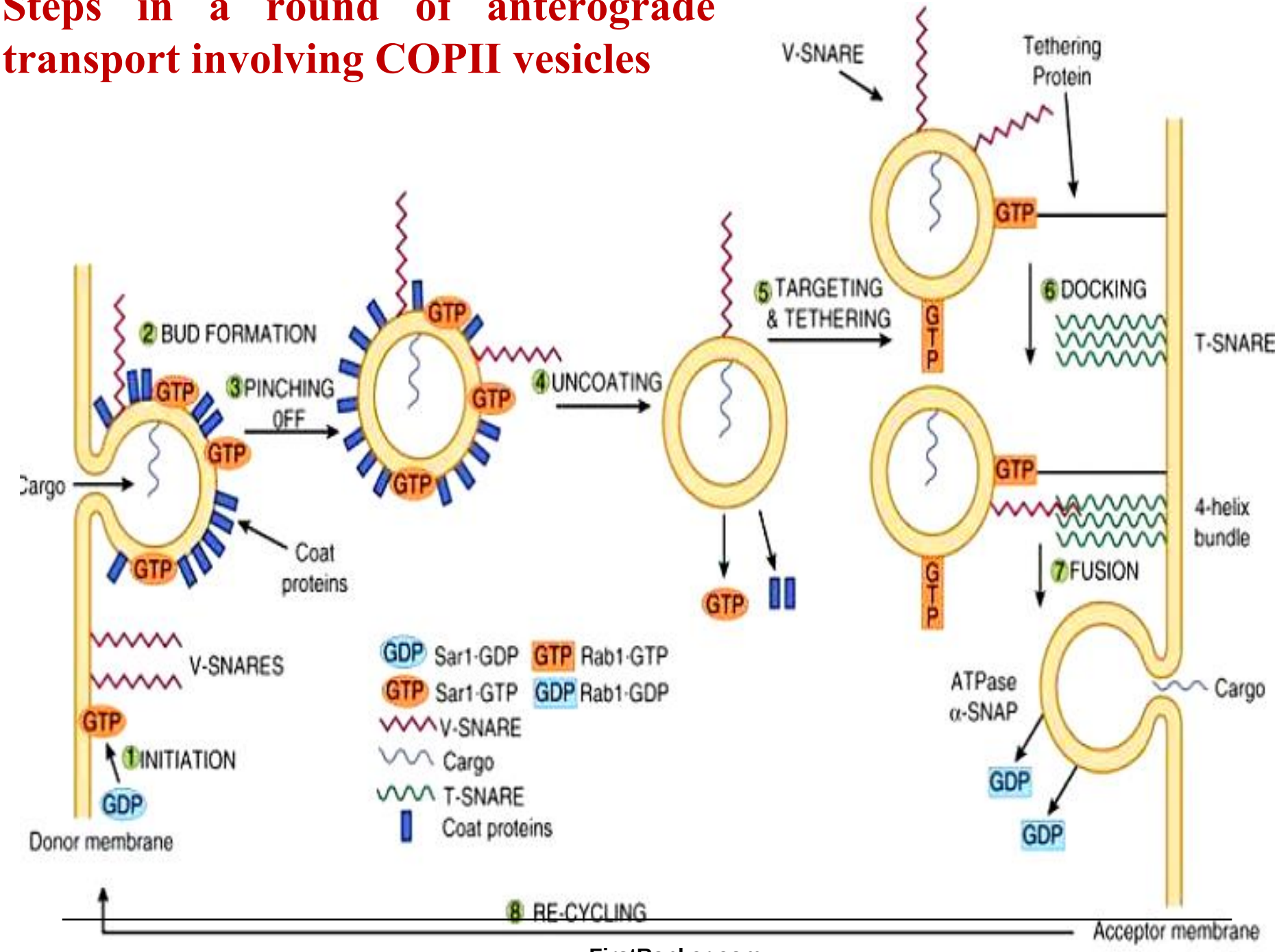
Receptor Mediated Endocytosis

- The major mechanism of vesicular transport between ER and Golgi.
- Takes place in the regions of the membranes known as coated pits
- The coated pits has high concentration of protein clarthrin and this mechanism of receptor mediated endocytosis is the clarthin coated vesicle method
- However there is another method in which the receptor mediated endocytosis takes place without the clarthin coated vesicles
- The SNARE proteins helps in the later type of the receptor

Some Types of Vesicles and Their Functions

Vesicle	Function
COPI	Involved in intra-GA transport and retrograde transport from the GA to the ER
COPII	Involved in export from the ER to either ERGIC or the GA
Clathrin	Involved in transport in post-GA locations including the PM, TGN and endosomes
Secretory vesicles	Involved in regulated secretion from organs such as the pancreas (eg, secretion of insulin)
Vesicles from the TGN to the PM	They carry proteins to the PM and are also involved in constitutive secretion

Steps in a round of anterograde transport involving COPII vesicles



Steps in a round of anterograde transport involving COPII vesicles

- Step 1: Sar1 is activated when GDP exchanged for GTP and it becomes embedded in the ER membrane to form a focal point for bud formation.

- Step 2: Coat proteins bind to Sar1·GTP and cargo proteins become enclosed inside the vesicles.

- Step 3: The bud pinches off, formatting a complete coated vesicle. Vesicles move through cells along microtubules or actin filaments.

- Step 4: The vesicle is uncoated when bound GTP is hydrolyzed to GDP by Sar1.

- Step 5: Rab molecules are attached to vesicles after switching of Rab.GDP to Rab.GTP, a specific GEF .Rab effector proteins on target membranes bind to Rab·GTP, tethering the vesicles to the target membrane.

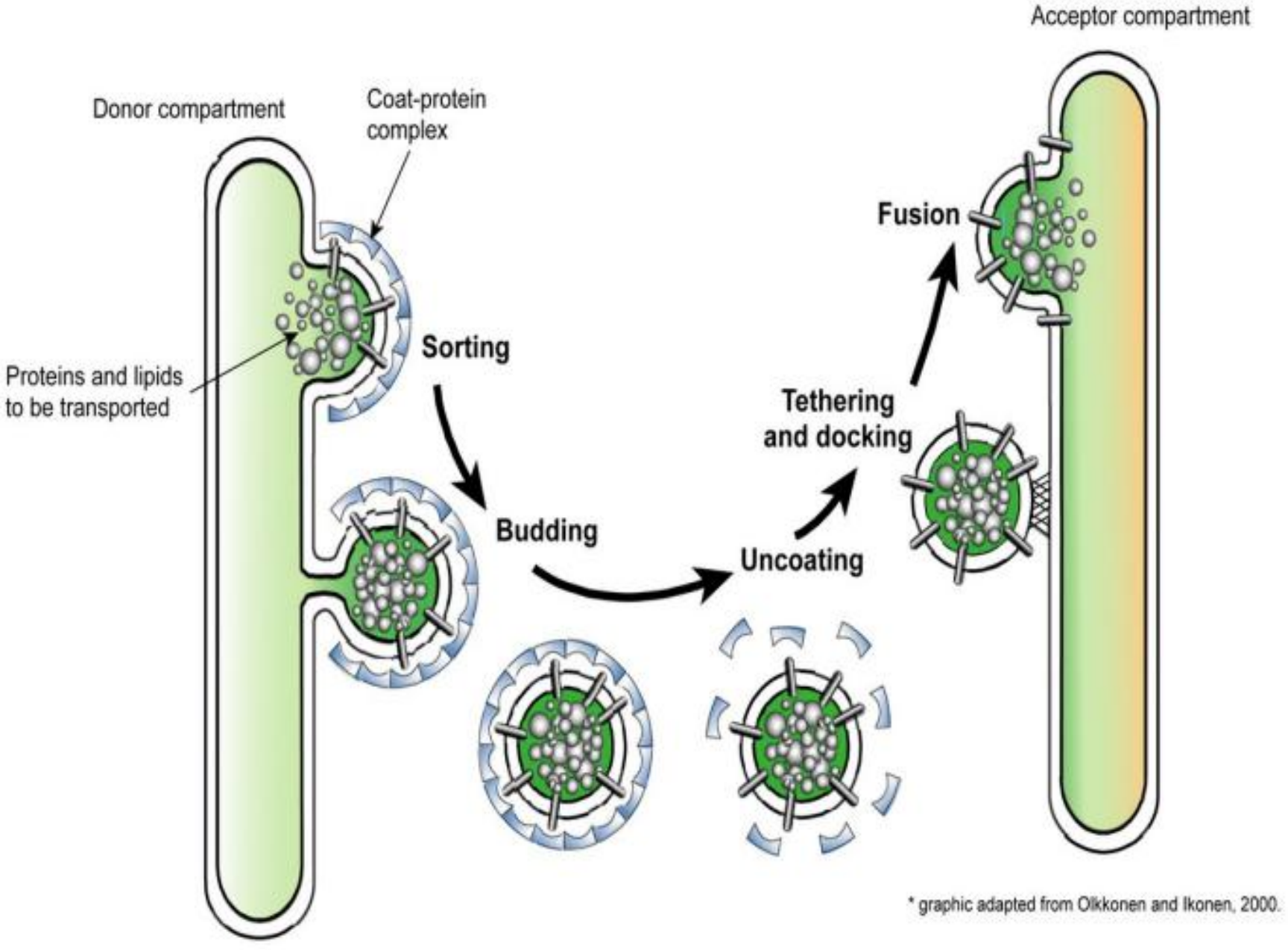
- Step 6: v-SNAREs pair with cognate t-SNAREs in the target membrane to form a four helix bundle which docks the vesicles and initiates fusion.

- Step 7: When the v- and t-SNARES are closely aligned, the vesicle fuses with the membrane and the contents are released.

  GTP is then hydrolyzed to GDP, and the Rab·GDP molecules are released into the cytosol.

  An ATPase (NSF) and α-SNAP dissociate the four-helix bundle between the v- and t-SNARES so that they can be reused.

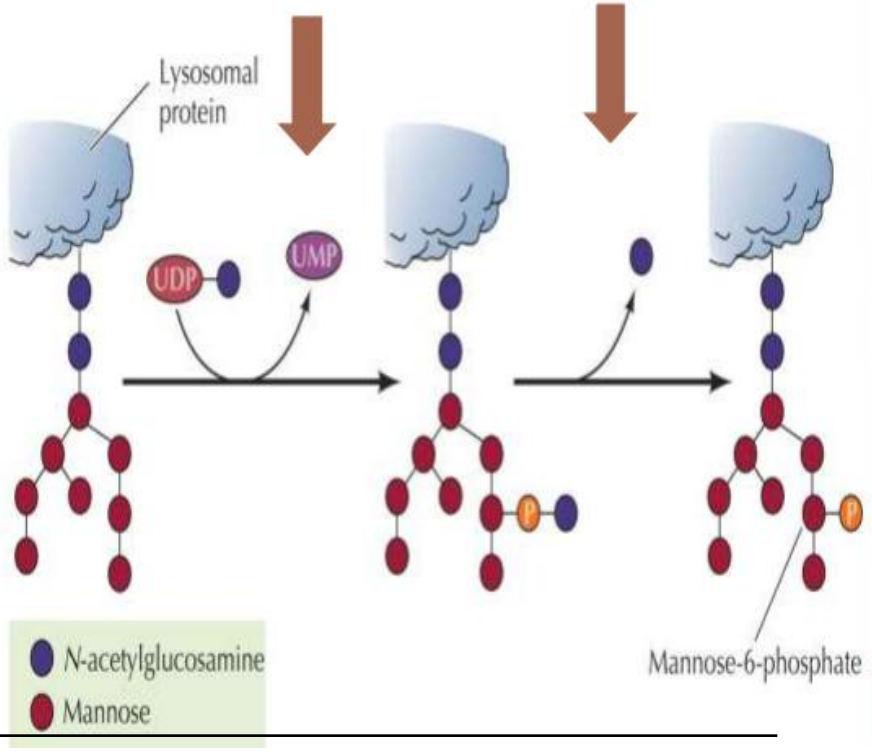
- Step 8: Rab and SNARE proteins are recycled for further rounds of vesicle fusion



Selective transport of proteins to lysosomes

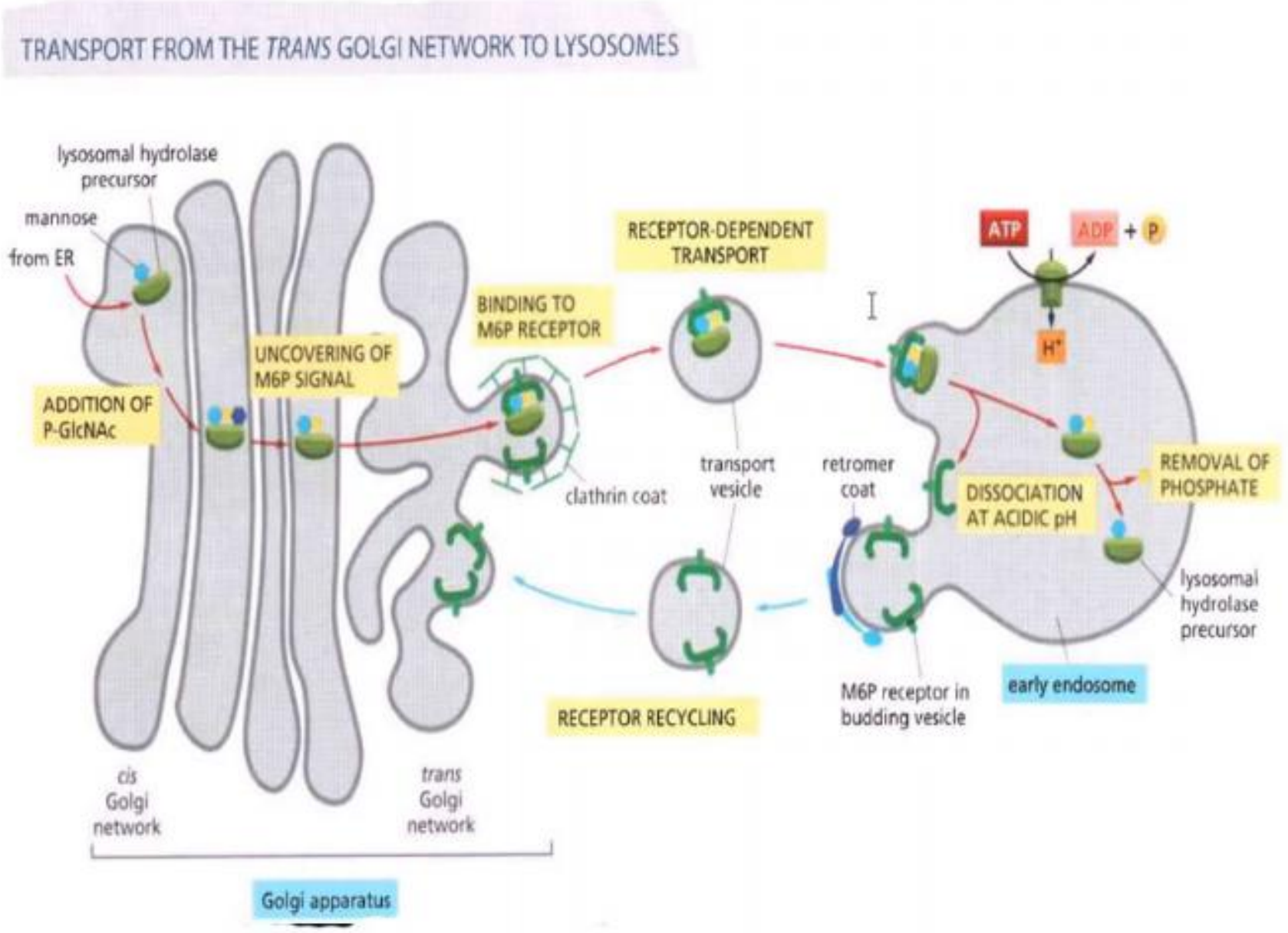
- The best-characterized pathway of protein sorting in the Golgi is the selective transport of proteins to lysosomes.
- Protein destined for incorporation into lysosomes are modified by mannose phosphorylation.
- This occurs while the protein is still in the cis Golgi network.

•These phosphorylated mannose residues are specifically recognized by a mannose-6-phosphate receptor in the trans Goligi network

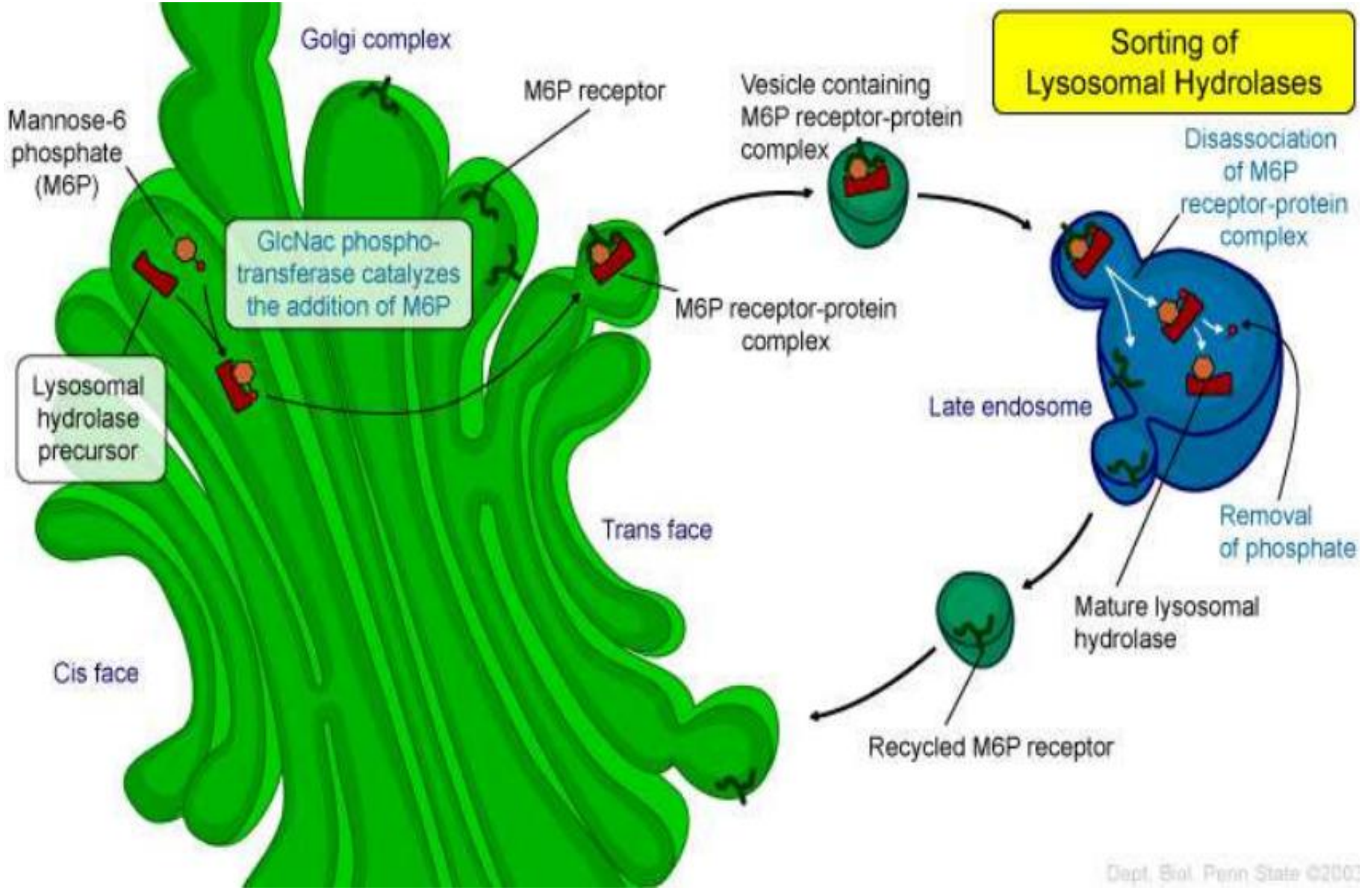


The M-6-P pathway

- In the trans-Golgi network, the phosphorylated enzymes bind to M6-P receptors .
- Which direct the enzymes into vesicles coated with the fibrous protein clathrin.
- The clathrin lattices is rapidly depolymerized to its subunits, and the uncoated transport vesicles fuse with late endosomes.
- Within this low pH compartment, the phosphorylated enzymes dissociate from the M6P receptors and then are de-phosphorylated.

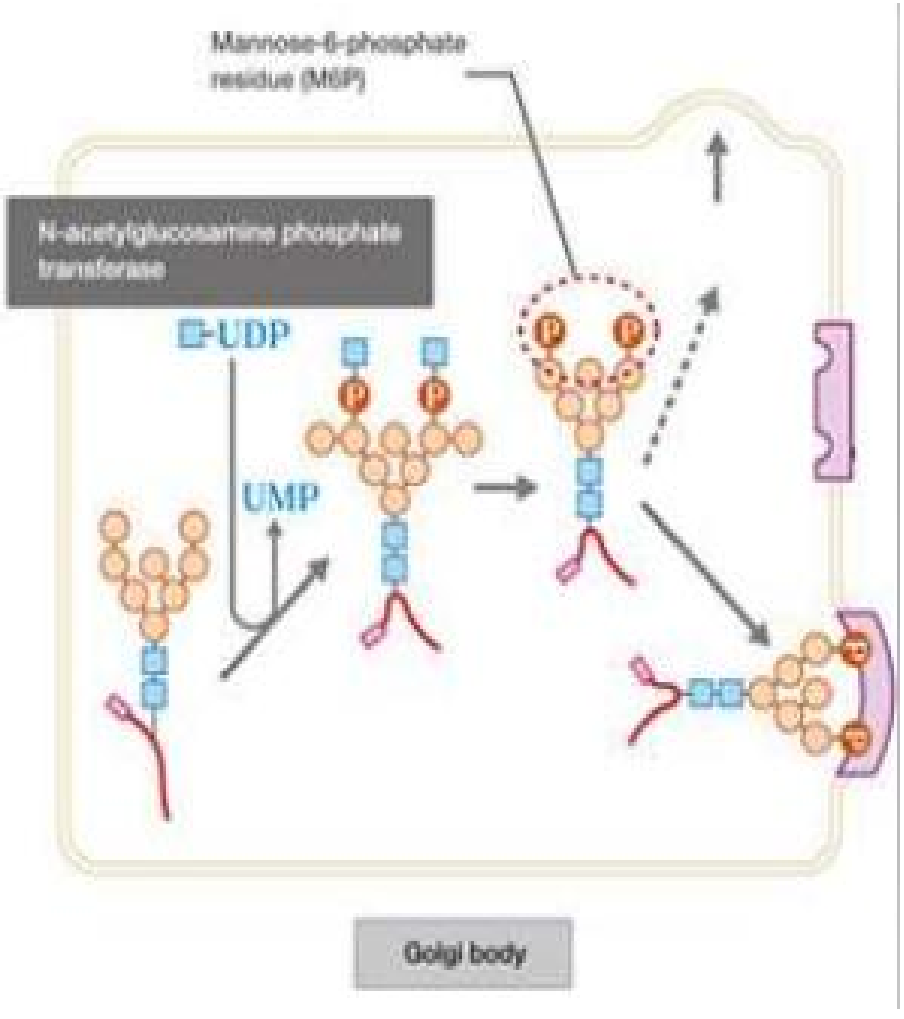


Targeting to lysosomes



I-cell disease

- Mucolipidosis II
- UDP-N -acetyl glucosamine phosphotransferase
- Cultured fibroblasts-deficient in numerous lysosomal enzymes
- Inclusions in lysosome
- These enzymes were found to be present in excess in tissue culture media and in extracellular fluids
- Psychomotor and skeletal defects



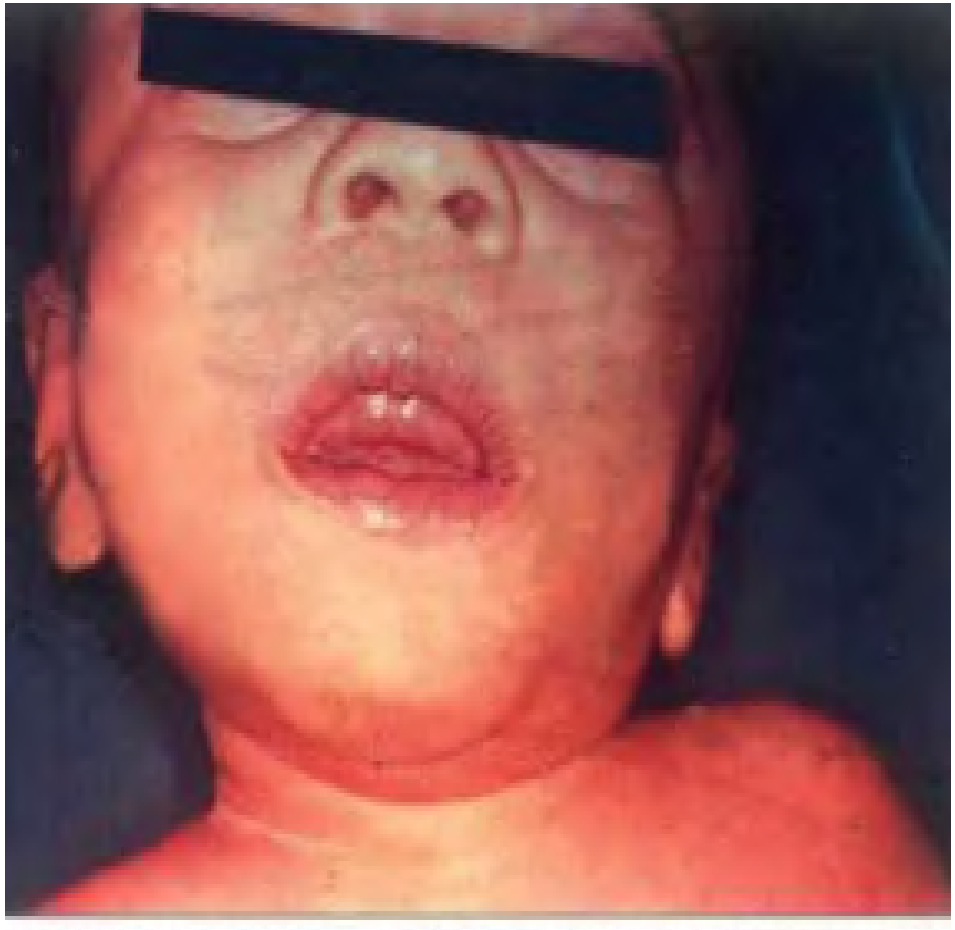


Figure 1: Clinical photograph of a two-year old girl with coarse facial features, gum hypertrophy and thick alveolar ridges

Botulinum Toxin

- Most lethal toxin known
- Most serious cause of food poisoning
- One component of the toxin is a protease specific only to the synaptobrevin
- Thus by inhibiting the v-SNARE the release of acetylcholine into the NMJ is halted

Brefeldin –A

- An anti viral produced by fungus Penicillium brefeldianum
- Prevents GTP from binding to ARF in the step 1 of the anterograde pathway that Is the step of Coat assembly
- So in the presence of this fungal metabolite the golgi apparatus appears to disintegrate and fragments are lost

Disorders Related to Intracellular Transport

Familial Hypercholesteremia

- Familial hypercholesterolemia, FH (type II hyperlipoproteinemia) is an autosomal dominant disorder
- Results from mutations affecting the structure and function of the cell-surface receptor that binds plasma LDLs (low density lipoproteins) removing them from the circulation
- The defects in LDL-receptor (LDLR) interaction result in lifelong elevation of LDL-cholesterol in the blood

1. Receptor null mutation (lack of receptor synthesis in the ER
2. Defective intracellular transport to golgi apparatus
3. Defective extracellular ligand binding
4. Defective endocytosis
5. Failure to release LDL molecules inside the endosome