TARGET SELECTION IN DRUG DISCOVERY

Protein structure and function

❖ **Structural proteins**

Structural proteins do not normally act as drug targets. However, the structural protein **tubulin** is an exception.

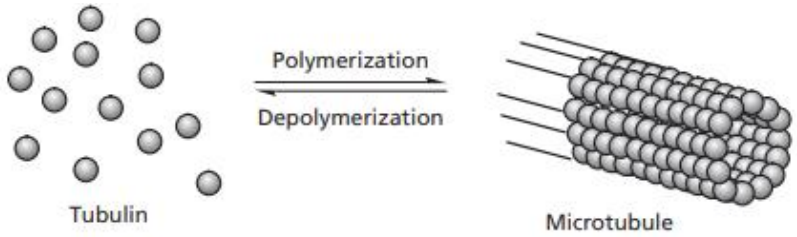


FIGURE 2.19 Polymerization of tubulin.

Drugs that target tubulin and inhibit this process are useful anticancer agents

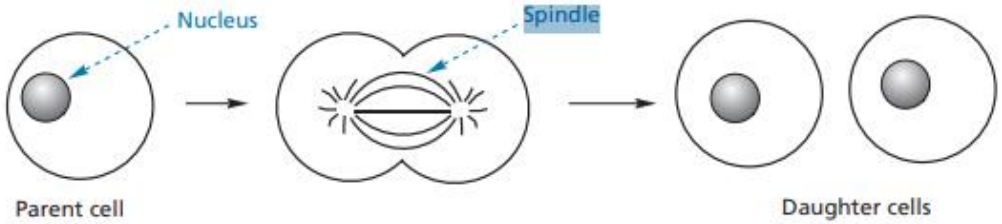
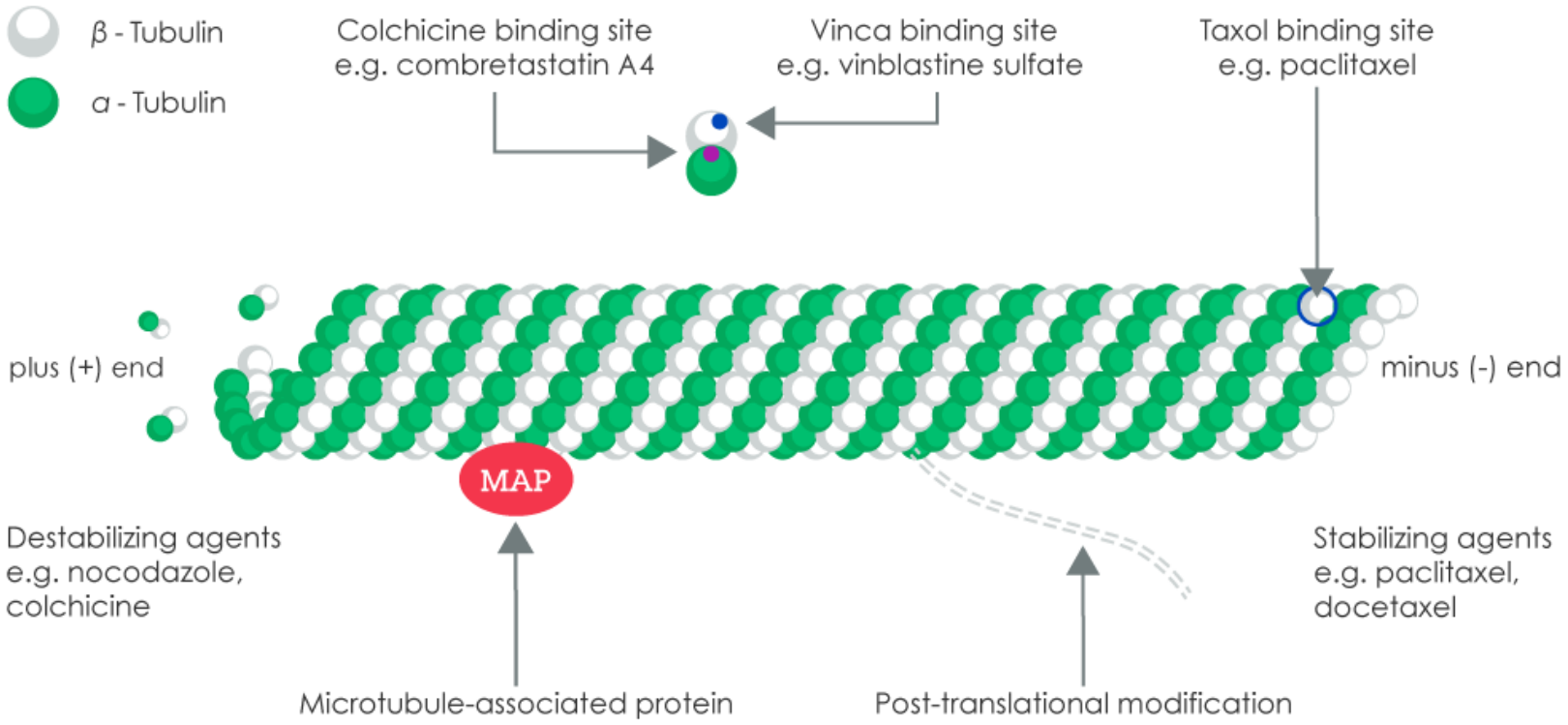


FIGURE 2.20 Cell division.

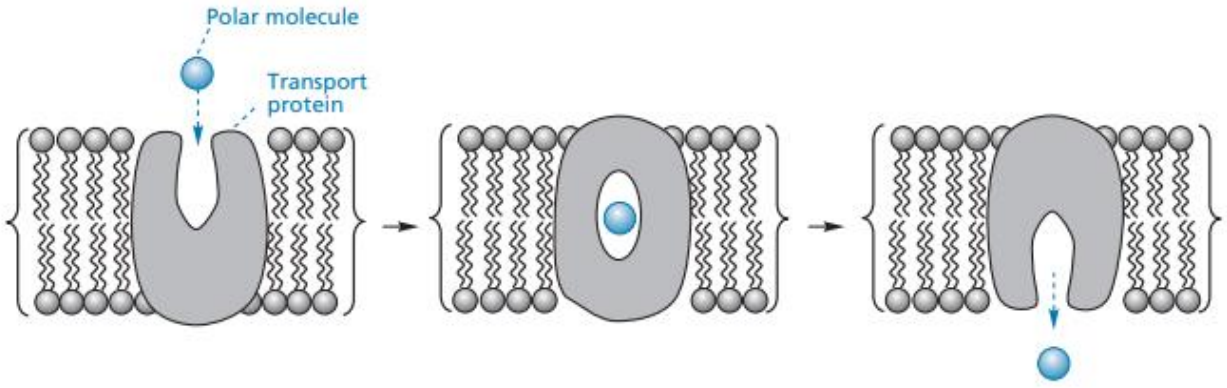
Protein structure and function



Protein structure and function

❖ **Transport proteins**

Are present in the cell membrane and act as the cell's 'smugglers" smuggling the important chemical building blocks of amino acids, sugars, and nucleic acid bases across the cell membrane such that the cell can synthesize its proteins, carbohydrates, and nucleic acids. They are also important in transporting important neurotransmitters.



Why is this smuggling operation necessary?

The transport proteins can float freely within the cell membrane because they have hydrophobic residues on their outer surface which interact favourably with the hydrophobic centre of the cell membrane.

Transport proteins are not all identical; there are specific transport proteins for the different molecules.

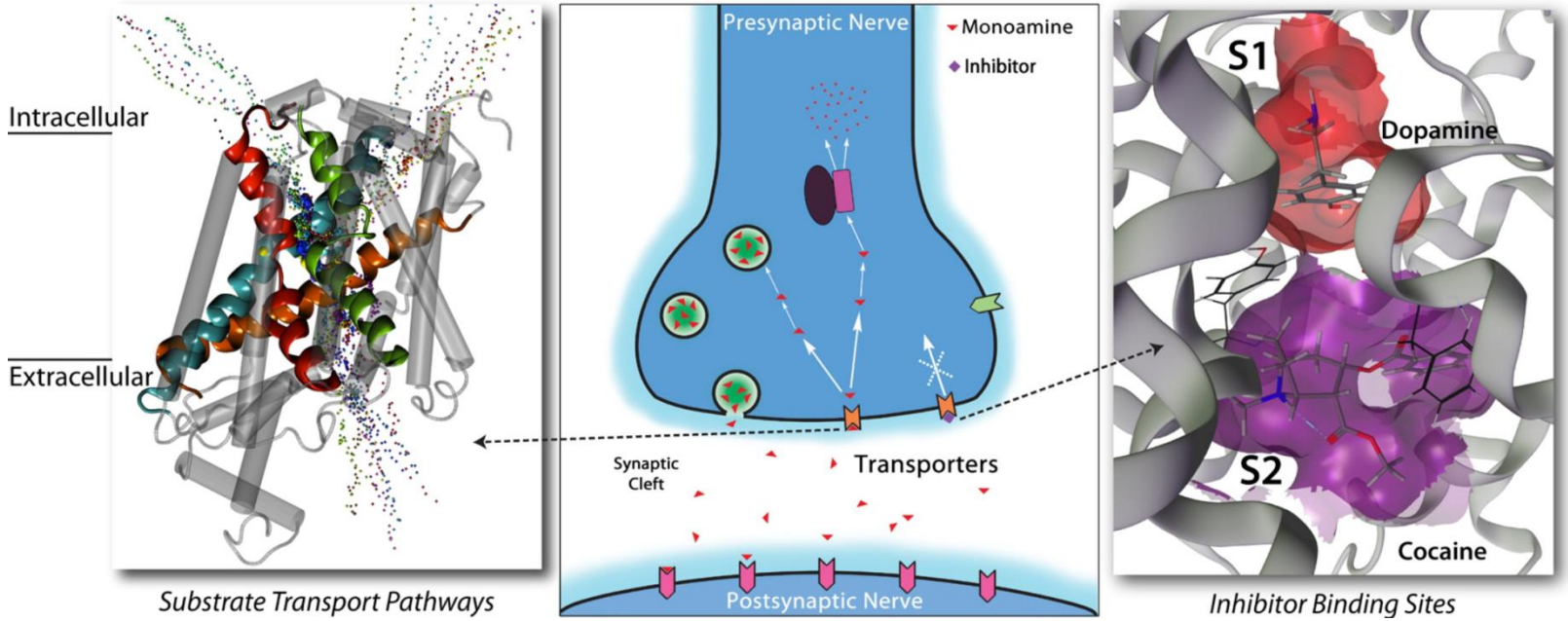
Protein structure and function

❖ **Transport proteins**

There are several important drugs which target transport proteins.

They have a binding site which ‘recognizes’ and binds a specific guest molecule, but it is sometimes possible to fool a transport protein into accepting a drug that resembles the usual guest. If that drug remains strongly bound to the transport protein, it will prevent the protein from carrying out its normal role.

Cocaine and the tricyclic antidepressants bind to transport proteins, and prevent neurotransmitters, such as noradrenaline or dopamine , from re-entering nerve cells

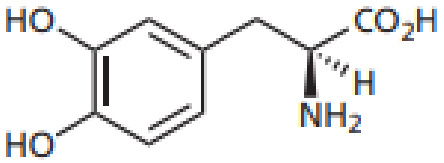


Protein structure and function

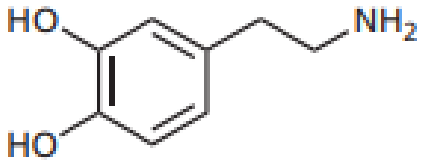
❖ **Transport proteins**

Trojan horse approach for transport proteins

Another way round the problem of membrane permeability is to design a prodrug which can take advantage of transport proteins in the cell membrane, such as the ones responsible for carrying amino acids into a cell. A well-known example of such a prodrug is levodopa



Levodopa



Dopamine

Levodopa is a prodrug of dopamine and has been used in the treatment of Parkinson's disease.

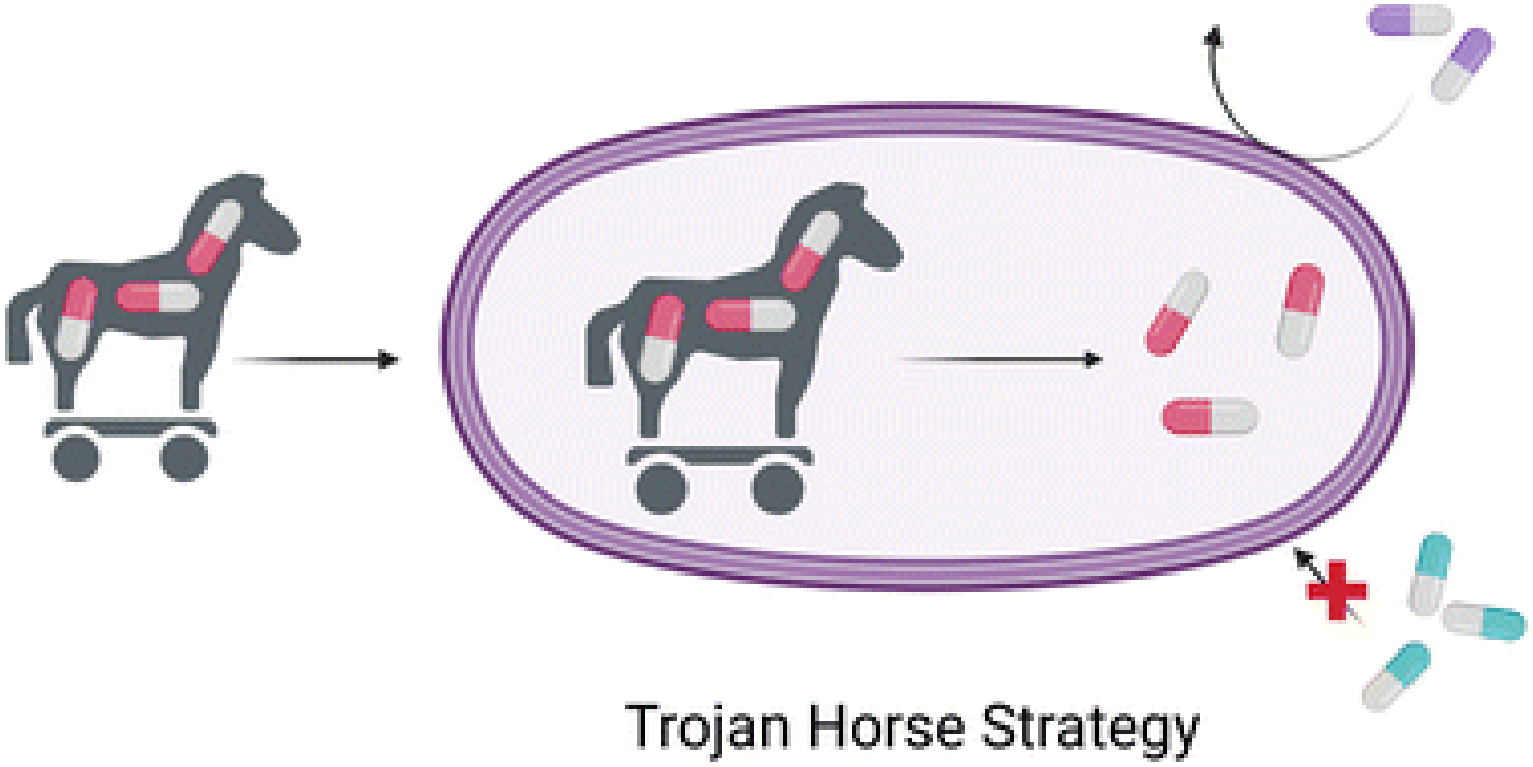
Dopamine itself cannot be used as it is too polar to cross the blood–brain barrier. Levodopa is even more polar and seems an unlikely prodrug, but it is also an amino acid, and so it is recognized by the transport proteins for amino acids which carry it across the cell membrane. Once in the brain, a decarboxylase enzyme removes the acid group and generates dopamine.

Protein structure and function

❖ **Transport proteins**

Trojan horse approach for transport proteins

Siderophore conjugates to combat antibiotic-resistant bacteria

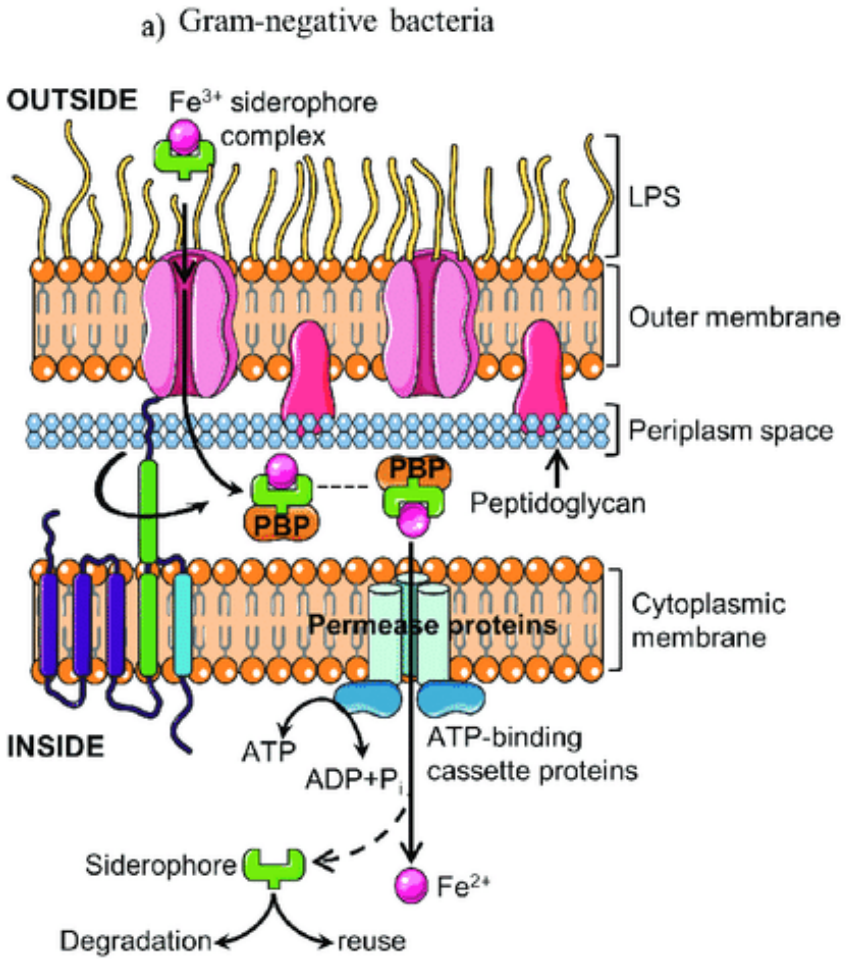


Protein structure and function

❖ **Transport proteins**

Trojan horse approach for transport proteins

Siderophore conjugates to combat antibiotic-resistant bacteria



- Iron is an essential nutrient for bacterial growth, replication, and metabolism.
- bacteria have developed various mechanisms to sequester or scavenge iron from the host environment
- active transport systems that consist of bacterial small molecule siderophores

Siderophore-conjugated antibiotics that exploit such iron-transport systems are under development for the treatment of infections caused by gram-negative bacteria.

Protein structure and function

- **Transport proteins**

Trojan horse approach for transport proteins

Siderophore conjugates to combat antibiotic-resistant bacteria