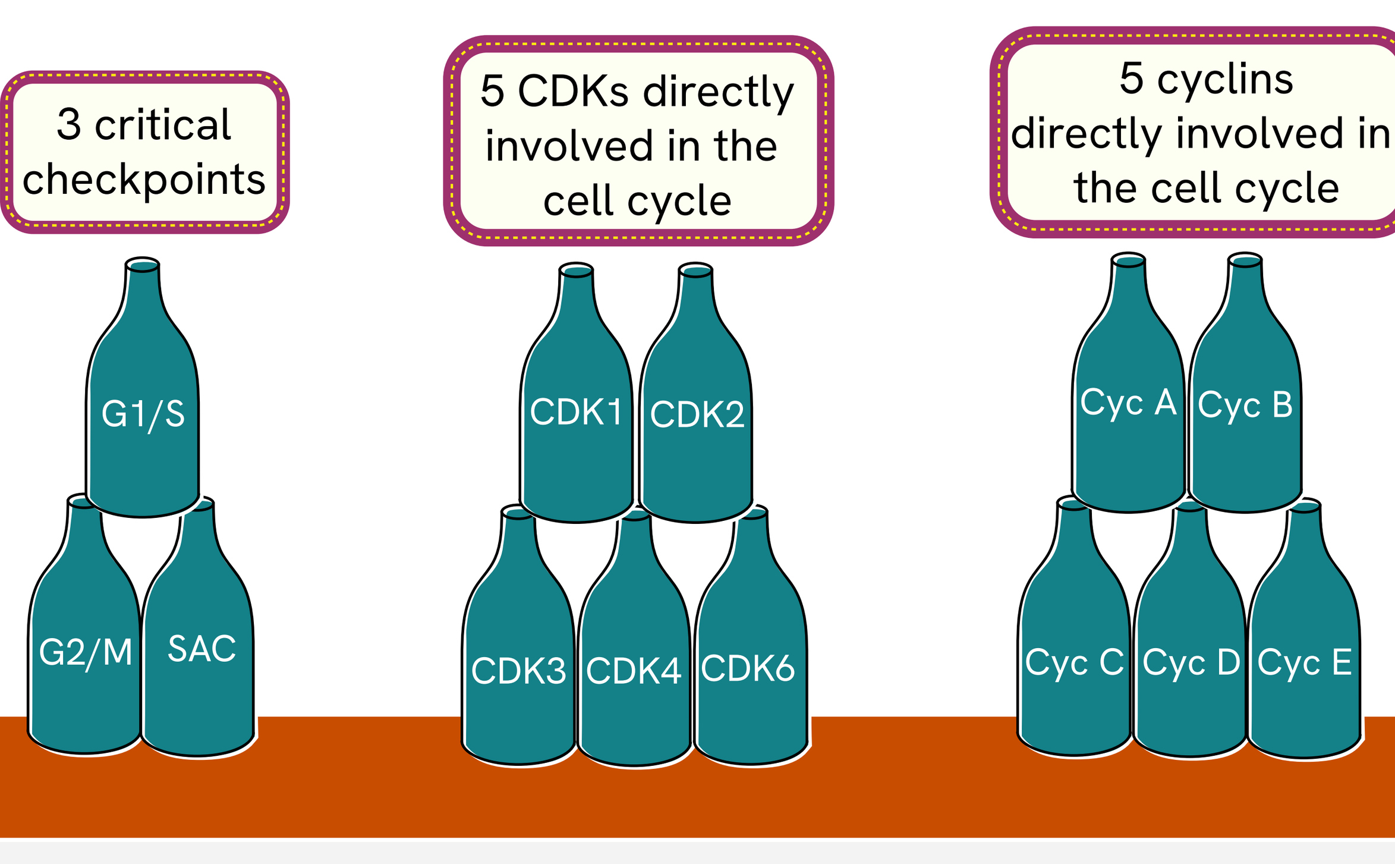
STEP RIGHT UP! IT'S THE CELL CYCLE!

CELL CYCLE KEY FACTS

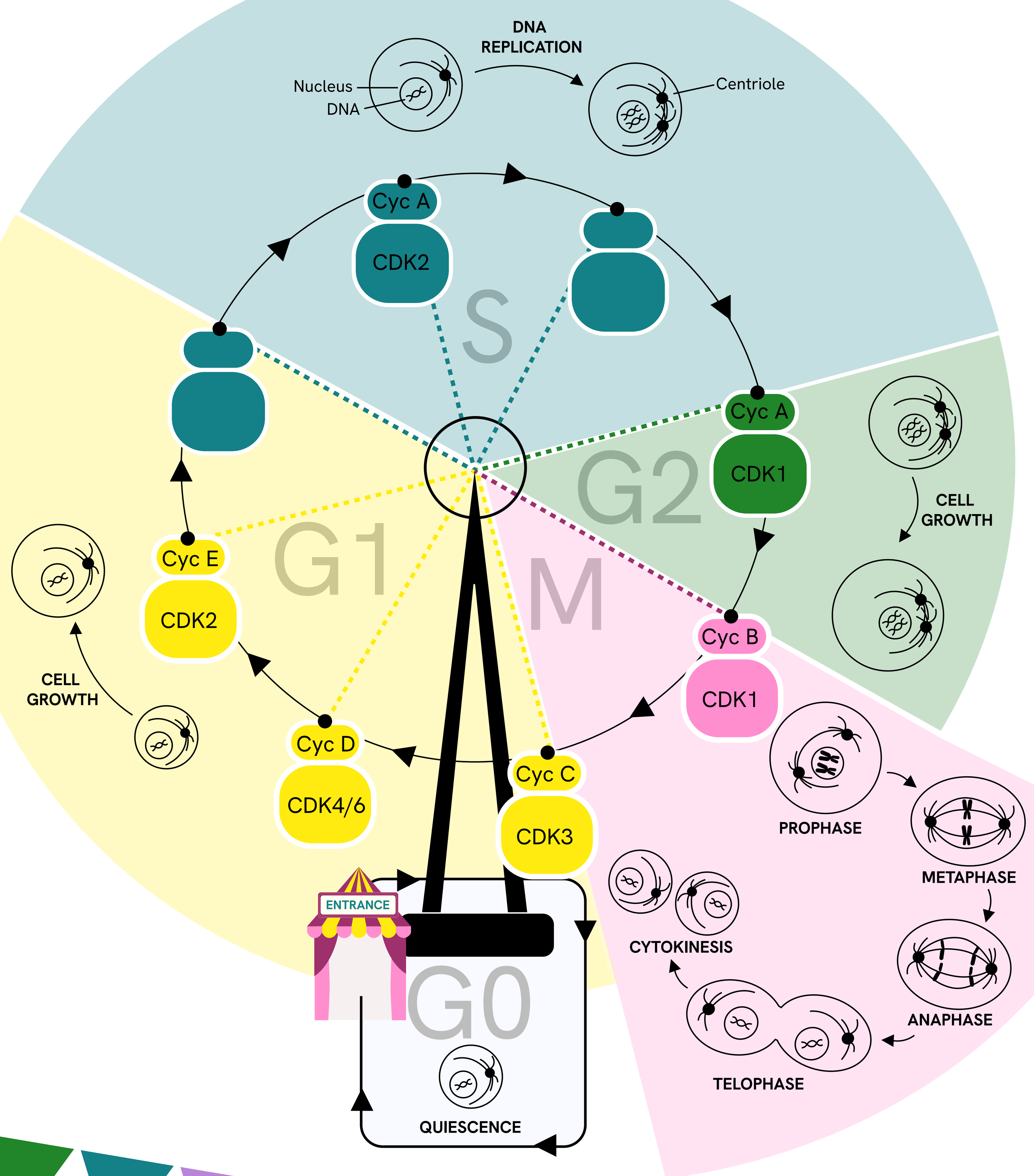


The cell cycle is a series of events that a cell passes through to grow and divide. The cycle is split into distinct phases and depends on checkpoints to replicate and divide correctly.

Checkpoints rely on cyclin-dependent kinases (CDKs) and cyclins (Cycs) to slow or stop progression through the cell cycle if defects are detected. Critical checkpoints occur at different phases of the cell cycle: before DNA replication (G1/S), after DNA replication (G2/M), and during mitosis (spindle assembly checkpoint or 'SAC').

Dysregulation of the cell cycle and checkpoints can lead to diseases, such as cancer—where cells have sustained proliferation.

THE CELL CYCLE FERRIS WHEEL

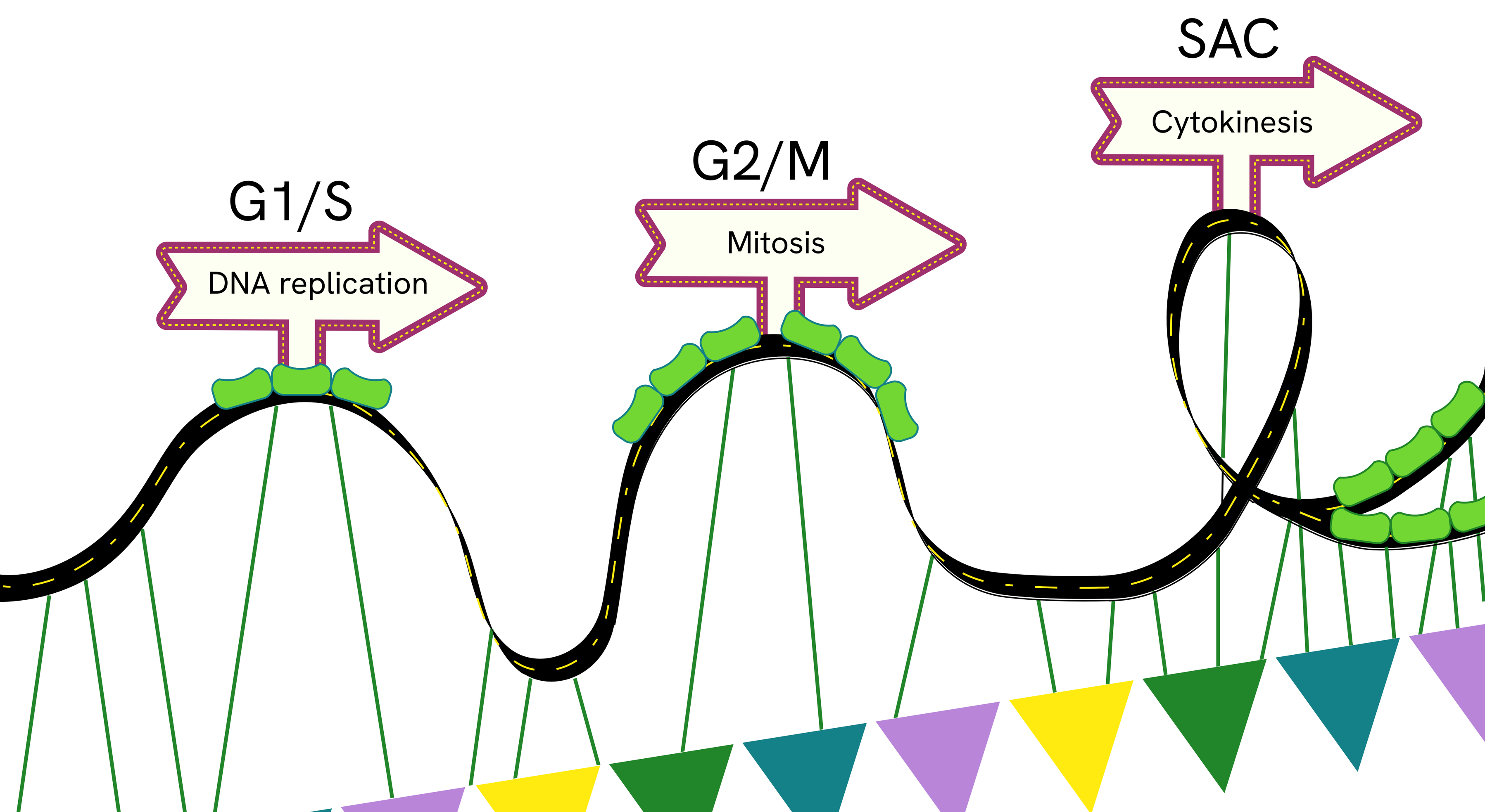


CRITICAL CHECKPOINTS

Critical checkpoints act as surveillance systems that check for defects during the cell cycle, such as DNA damage and faulty DNA segregation. These checkpoints prevent genetic errors passing onto daughter cells and ensure cells progress through the cell cycle correctly.

If defects are detected, critical checkpoints slow down or stop the cell cycle from progressing through to the next phase of the cell cycle. Critical checkpoints rely on CDK activity and include:

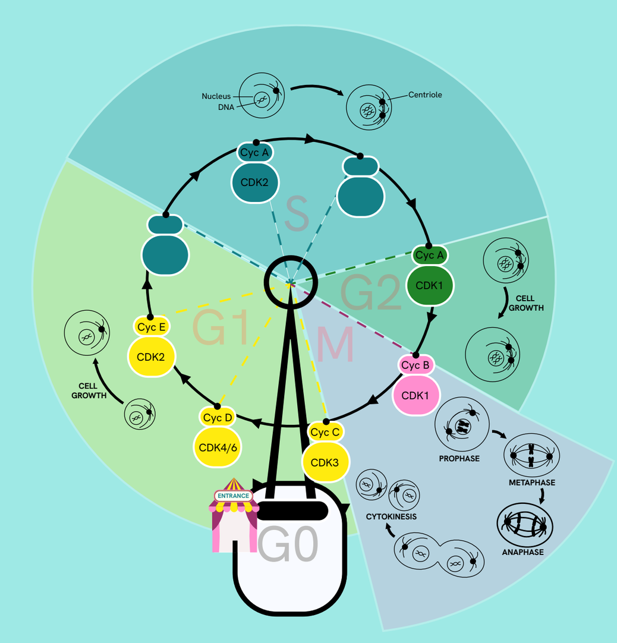
- **G1/S checkpoint** – which checks for DNA damage, controlling entry from G1 phase into S phase (where DNA is replicated)
- **G2/M checkpoint** – which checks for DNA damage, controlling entry into M phase (where chromosomes are segregated)
- **Spindle assembly checkpoint (SAC)** – which checks chromosomes are correctly attached to the spindle, controlling entry into anaphase and commitment to cell division (cytokinesis).



CHECKPOINTS IN CANCER

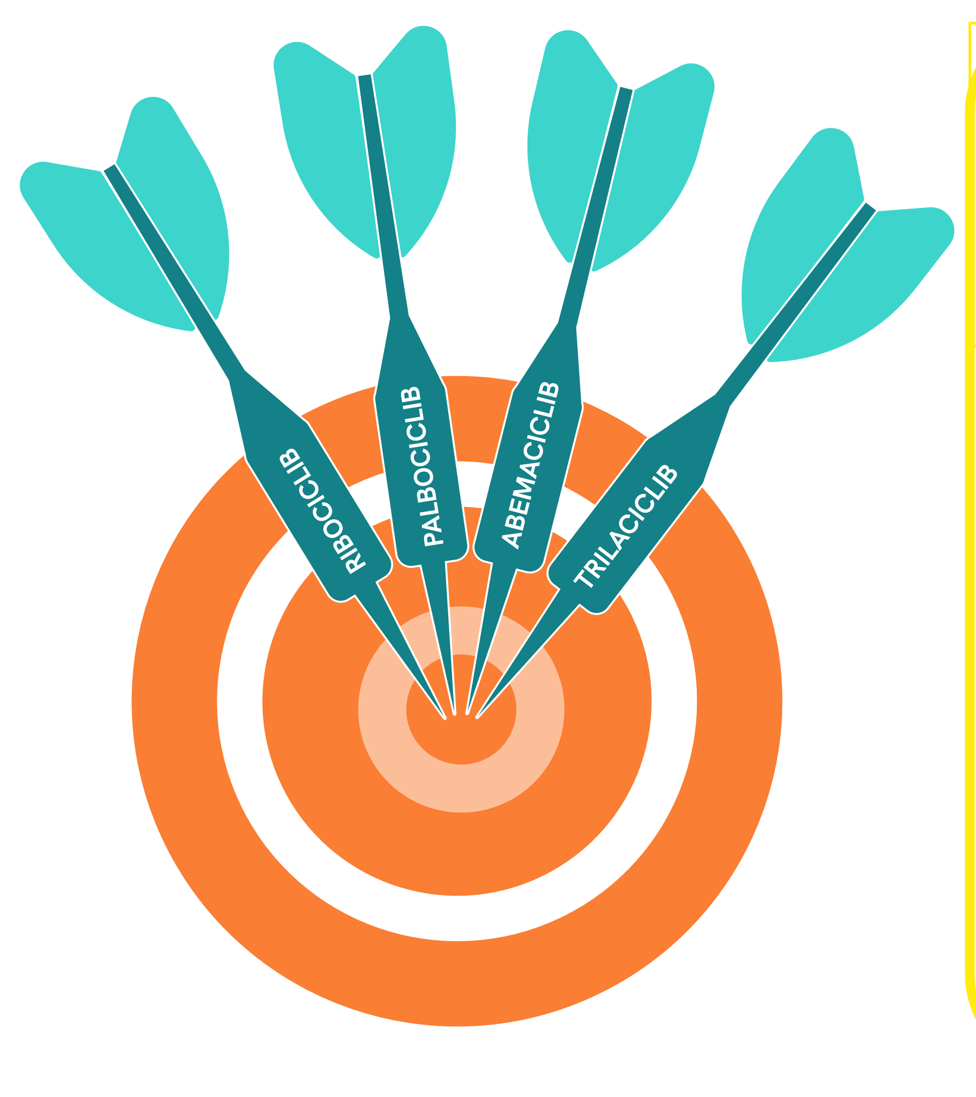
Dysregulated cell cycle can cause uncontrolled growth, leading to diseases such as cancer.

Most cancer mutations occur before the S phase and can prevent cell cycle exit.

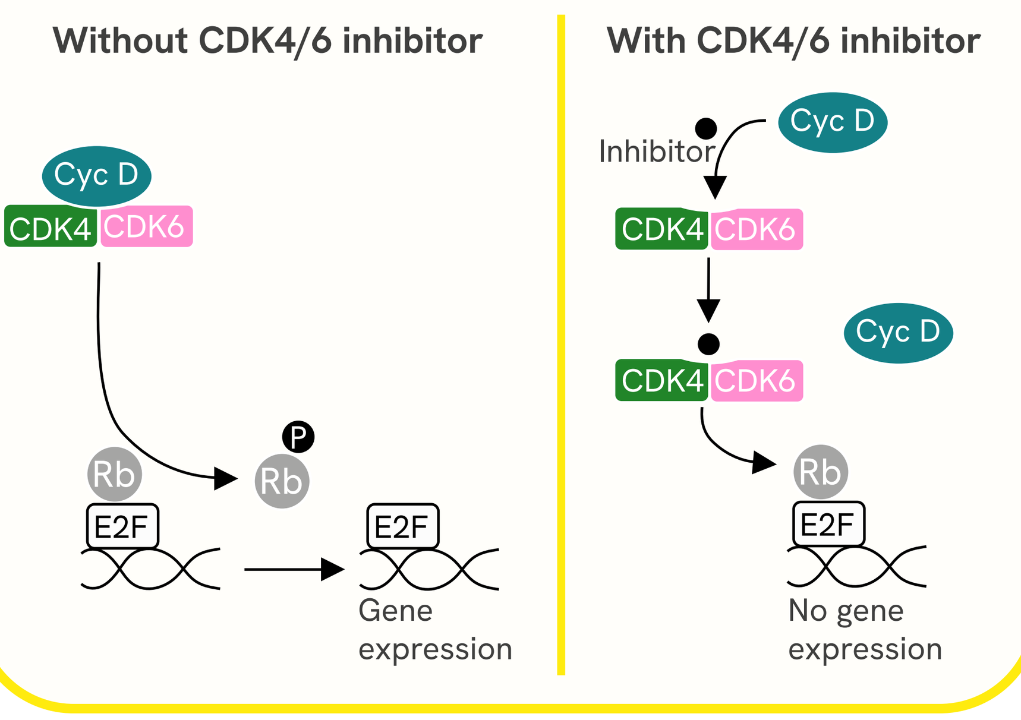


50–70% of breast cancers have Cyc D1 overexpression, promoting cell cycle progression.

CDK INHIBITOR CANCER THERAPIES



Four CDK inhibitors have FDA approval for use as cancer treatments. All four CDK inhibitors target CDK4/6, blocking Cyc D binding which prevents E2F gene expression and progression through the cell cycle.



References

Helen K. Matthews et al. Cell cycle control in cancer. Nature Reviews Molecular Cell Biology. September 2021.
Andreas Panagopoulos et al. The hammer and the dance of cell cycle control. Trends in Biochemical Sciences. April 2021.
Lucy H. Swift et al. The relationship between checkpoint adaptation and mitotic catastrophe in genomic changes in cancer cells. Genome Stability
Danî Kalsbeek et al. G2/M-phase checkpoint adaptation and micronuclei formation as mechanisms that contribute to genomic instability in human cells. International Journal of Molecular Sciences. 2017
Douglas Hanahan et al. Hallmarks of cancer: The next generation. Cell. March 2011.
Søs Grønbæk Mathiassen et al. Autophagy and the cell cycle: A complex landscape. Frontiers in Oncology. March 2017.
Oana-Maria Thoma et al. Cyclin-dependent kinase inhibitors and their therapeutic potential in colorectal cancer treatment. Frontiers in Pharmacology. December 2021.
Nicholas Willis et al. Regulation of DNA replication by the S-phase DNA damage checkpoint. Cell Division. July 2009.
Yingmei Wang et al. Centrosome-associated regulators of the G2/M checkpoint as targets for cancer therapy. Molecular Cancer. February 2009.
Adele L. Marston et al. Multiple duties for spindle assembly checkpoint kinases in meiosis. Frontiers in Cell and Developmental Biology. December 2017.
Arian Lundberg et al. The long-term prognostic and predictive capacity of cyclin D1 gene amplification in 2305 breast tumours. Breast Cancer Research. February 2019.
Robert Roskoski Jr. Properties of FDA-approved small molecule protein kinase inhibitors: A 2023 update. Pharmacological Research. January 2023.
Mridula A. George et al. Clinical and pharmacologic differences of CDK4/6 inhibitors in breast cancer. Frontiers in Oncology. July 2021.