

The cell cycle is a series of processes that cells go through to grow and divide. Key players in this cycle are proteins known as cell cycle kinases, which drive the progression of cell division by modifying other proteins through a process called phosphorylation. These kinases are crucial for responding to signals that can lead to cancer. Interestingly, some of these proteins are not needed in normal, healthy cells but are essential for the development and maintenance of various cancers.

One such protein complex, DDK, which includes the CDC7 kinase and its partner DBF4, is known to control DNA replication. We believe targeting DDK could be a powerful strategy for treating cancers, especially those with certain genetic defects like p53 mutations (which are among the most frequently identified mutations in cancers).

Evaluation of the effectiveness of targeted therapy aimed at a specific protein, as well as the potential toxicity of such therapy, involves the need for conducting studies on laboratory animals. However, studying DDK has been challenging because deleting the *CDC7* gene causes early death in mice, making it difficult to test DDK's role in cancer in animal models. The innovative approach we propose, allows for selective and reversible degradation of the targeted protein in adult animals. We can thus investigate the role of DDK in tumor formation.

In our studies, we will be using special mouse models of aggressive cancers like triple-negative breast cancer and lung adenocarcinoma, along with mice that have a degradable form of CDC7. We want to find out if depleting CDC7 (thus *de facto* blocking DDK entirely) affects the health of these mice and impacts their tumors. Specifically, we are investigating whether shutting down CDC7 will kill cancer cells with p53 mutations while leaving healthy cells unharmed.

Additionally, we discovered an unexpected function of DDK in cell movement, which is important during cancer metastasis. When we disrupt CDC7, cancer cells move less and show reduced markers of movement, suggesting that DDK helps cancer cells become more invasive. This is because DDK seems to influence the activity of ZEB1 and possibly ZEB2, which are key in a process called epithelial-mesenchymal transition (EMT). EMT allows cancer cells to spread and form new tumors.

Understanding how DDK affects cancer progression and metastasis could lead to new treatments that have a significant impact on patients worldwide.