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# Targeting dysregulation of the cyclin d-cdk4/6-ink4-rb pathway

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## Introduction

The cyclin D-cyclin dependent kinase (CDK) 4/6-inhibitor of CDK4 (INK4)-retinoblastoma (Rb) pathway controls cell cycle progression by regulating the G1-S checkpoint. Dysregulation of the cyclin D-CDK4/6-INK4-Rb pathway results in increased proliferation, and is frequently observed in many types of cancer.[1,2] Thus, the development of selective CDK4/6 inhibitors offers a novel therapeutic approach for patients with advanced cancer.

### The rationale for inhibiting CDK4/6

To appreciate selective targeting in cancer, it is important to understand that the cell cycle exists in 4 phases: G0/G1, synthesis (S), G2, and mitosis (M). In G0, the cell is in an arrested state that can be either permanent (after senescence or terminal differentiation) or quiescent until mitogenic factors stimulate the cell to reenter the cell cycle. In the G1phase, these mitogenic factors activate intracellular signaling events that drive the cell cycle to progress into S phase. In the S phase, DNA is replicated. In the G2 phase, protein synthesis and cell growth occur, and in the M phase, the cell divides into 2 daughter cells.

Progression through these 4 phases is regulated by members of the CDK family, which includes CDKs 1, 2, 4, and 6. Each of these 4 CDKs is involved in regulating the transition from one phase of the cell cycle to the next. CDK4 and CDK6 are involved in the transition from G1 to S phase. These 4 CDKs are activated when a cyclin binds to them. A D-type cyclin (D1, D2, or D3) binds to CDK4 or CDK6, thereby activating these kinases and promoting the transition from G1 to S phase. The CDK-activating cyclins are negatively regulated by members of the INK4 family (eg, p16). INK4 family proteins bind to and inhibit CDKs. Thus, within the cell cycle, there exists a regulatory balance between inhibition by INK4 proteins vs activation by cyclins D, E, A, or B. These processes are further controlled by growth inhibitory signals.

Selective targeting of CDK4 and CDK6 is further motivated by data on the prevalence of genetic disruption of the cyclin D-CDK4/6 pathway in multiple types of cancer. Disruptions in the form of amplifications, deletions, point mutations, and even multiple alterations together can occur in the genes encoding cyclin D1-3, CDK4, and CDK6, or those encoding the INK4 proteins p16 and p14 (both encoded by CDKN2A) and p15 (encoded by CDKN2B). The composite frequency of disruptions to the cyclin D and CDK4/6 genes ranges from less than 5% of thyroid cancers to approximately 50% of esophageal cancers. The cyclin D-CDK4/6 pathway can also be genetically disrupted through multiple alterations to the genes encoding the INK4 family proteins; genetic deletion is the most common form of alteration to these INK4 proteins.

Of importance, the genetic disruption of Rb (encoded by RB1), which is the primary target of the CDK4/6 kinases, is also observed in multiple cancers. Rb functionality may ultimately be one of the most critical determinants of this pathway for cell cycle regulation.[3] This multifactorial process presents research motivation for drug development targeting this pathway.

### Inhibition of CDK4/6 in Cancer Disease

Inhibition of CDK4/6 has emerged as an attractive therapeutic strategy.[4] An important theoretical concern is that CDKs play a unique role in the proliferation of normal, and, equally, of cancer cells, creating a narrow therapeutic potential where toxicity would limit the possibility to reach clinically effective exposure levels. Pan-CDK inhibitors (flavopiridol), showed limited clinical benefit and high levels of off-target side effects. Selective CDK4/6 spare CDK2 activity which allows normal cells to continue to function and proliferate, and may therefore have a wider therapeutic efficiency and fewer off-target toxicities than pan-CDK inhibitors. Moreover cellular senescence or senescence-like activity is likely to be important mechanisms associated with clinical activity.

Currently there are three CDK4/6 inhibitors that are either approved or in late-stage development: Palbociclib, Ribociclib and Abemaciclib. All three compounds inhibit CDK4 and CDK6 with IC50 values <40 nM, but they exhibit varying IC50 values against other CDKs. Such differences in selectivity may influence their optimal dosing schedules and side effect profiles. They have also demonstrated preclinical activity in a range of Rb+ tumor models. Note that cell lines with loss or mutation of CDKN2A or loss of p16INK4A protein expression, are particularly sensitive to palbociclib.[5] Preclinical studies have investigated the mechanisms underlying acquired resistance to selective CDK4/6 inhibitors. These preclinical data support the clinical use of CDK4/6 inhibitors in combination regimens with other therapies (phase III trials are ongoing): hormonal therapy, PI3K/AKT/mTOR pathway inhibitors, RAS/RAF/MEK/ERK pathway inhibitors, Chemotherapy and Radiotherapy.[6]

## Conclusion

Gary K. Shwartz, Professor of Medicine, Chief, Division of Hematology and Oncology, Department of Medicine, Columbia University Medical Center, New York, New York, summarizes saying :**"**A defining feature of cancer is the disruption of the cell cycle pathway. As key components of the cell cycle, CDK4 and CDK6 represent important targets for inhibiting the dysregulated tumor cell cycle. At this time (April 2017), 2 selective CDK4/6 inhibitors are approved in combination with endocrine therapy for patients with hormone receptor–positive/HER2-negative advanced breast cancer, and the class of selective CDK4/6 inhibitors offers significant promise for treating patients with multiple other types of cancer.

To advance the potential increasing relevance of selective CDK4/6 inhibitors in additional malignancies, several preclinical and clinical studies are investigating biomarkers that may identify patients with tumors that are sensitive to-or resistant to-CDK4/6 inhibitors. Furthermore, ongoing studies are evaluating combination regimens which may enhance anticancer activity and overcome resistance to CDK4/6 monotherapy**"**.

## Conflicts of interest

There is no conflict of interest.

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