Protein kinase CK2 (formerly called casein kinase 2), a ubiquitous serine/threonine kinase, regulates a variety of cellular processes including the cell cycle, proliferation, and apoptosis (Allende et al., 1995; Litchfield, 2003; Meggio and Pinna, 2003; Wang et al., 2005; Homma and Homma, 2008; Fig. 1). CK2 is constitutively active and elevated in cancers, and a positive correlation between its over-expression and tumorigenesis has been reported in several cellular and animal models (Prowald et al., 1984; Guerra and Issinger, 1999; Landesman-Bollag et al., 2001; Tawfic et al., 2001; Channavajhala and Seldin, 2002).

Because CK2 inhibition induces apoptotic cell death in tumor cells, this molecule has been considered a promising druggable anticancer target (Slaton et al., 2004; Wang et al., 2005). Several studies suggest that decreasing CK2 activity using either a specific antisense oligonucleotide or a selective small molecule inhibitor attenuates the growth of cancers (Wang et al., 2001; Slaton et al., 2004; Hessenauer et al., 2011; Pierre et al., 2011a, 2011b).

Recently, orally available CX-4945 (Fig. 2), a potent and selective small molecule inhibitor of CK2, has been developed and advanced to testing in human clinical trials. The biological importance of CK2 in the context of cancer as well as the suitability of its small ATP binding site for the design of selective inhibitors has led Cylene Pharmaceuticals to develop orally available CX-4945 as an ATP-competitive inhibitor of CK2 for the treatment of cancer (Pierre et al., 2011). Molecular modeling of CK2 guided the optimization, leading to a form of CX-4945 with a high potency (Ki = 0.38 nM). CX-4945 displays an excellent kinase selectivity profile and is active against a broad range of cancer cell types, including breast, lung, and prostate cancer cells, in which CK2 is reported to be overexpressed (Siddiqui-Jain et al., 2010; Pierre et al., 2011). However, some discrepancies persist, such as the wide-margin difference between the IC50 values of CX-4945 in a kinase enzyme assay and in a cell-based assay. Enzymatic kinase screening data yielded an IC50 at nanomolar-scale concentrations (CK2α IC50 = 1 nM and Ki = 0.38...
nM), but relative EC_{50} values in several cancer cell lines have been in the micromolar concentration range (1.1 to 13.1 µM).

The anticancer activity of CX-4945 correlates with the suppression of CK2-regulated PI3K/Akt signaling, cell cycle arrest, and induction of apoptosis (Siddiqui-Jain et al., 2010); CX-4945 induces early dephosphorylation of Akt (S129; CK2 phosphorylation site) and a subsequent reduction in the number of regulatory sites, Akt (T308) and Akt (S473). In addition, CX-4945 results in decreased phosphorylation of the cell cycle inhibitor protein p21 (T145) and in G2/M or G1 cell cycle arrest. These findings account for the consequent apoptotic response and induction of caspase-3/7 activity in CX-4945–treated cancer cells.

CK2 also regulates angiogenesis by driving the PI3K/Akt signaling pathway (Shiojima and Walsh, 2002; Kramerov et al., 2008). CK2 inhibitors exhibit anti-

Fig. 1. Biological functions of CK2.

Fig 2. Schematic mode of action of CX-4945. CX-4945 inhibits the phosphorylation of PI3K/AKT and p21/p27 and transcriptional activation of HIF1α in the nucleus. These effects might influence cancer survival, angiogenesis, and pro-inflammatory cytokine production.