

Pharmacological inhibitors of disease-relevant cyclin-dependent kinases.

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Phosphorylation of serine, threonine and tyrosine residues represents one of the most common post-translational mechanisms used by cells to regulate their enzymatic and structural proteins. Among the 518 human protein kinases, cyclin-dependent kinases (CDKs) (Malumbres and Barbacid, 2005) have inspired considerable interest because of their essential involvement in cell cycle control (Malumbres and Barbacid, 2001), neuronal cell physiology (Cruz and Tsai, 2004), pain signaling (Pareek et al., 2006), apoptosis (Borgne and Golsteyn, 2003, Borgne et al., 2006), transcription and RNA splicing (Garriga and Grana, 2004; Loyer et al., 2005). CDKs are regulated in four different ways: [1] transient association with a regulatory partner (cyclin), [2] various post-translational modifications (phosphorylation, ubiquitin-dependent degradation), [3] transient association with a natural inhibitory protein (Cip1, Kip1/2 or Ink4A-D), and [4] intracellular localization. Although the human genome sequencing program has allowed the detection of about 20 CDKs and 25 cyclins, a more limited number of active CDK/cyclin complexes have been identified (Figure 1).

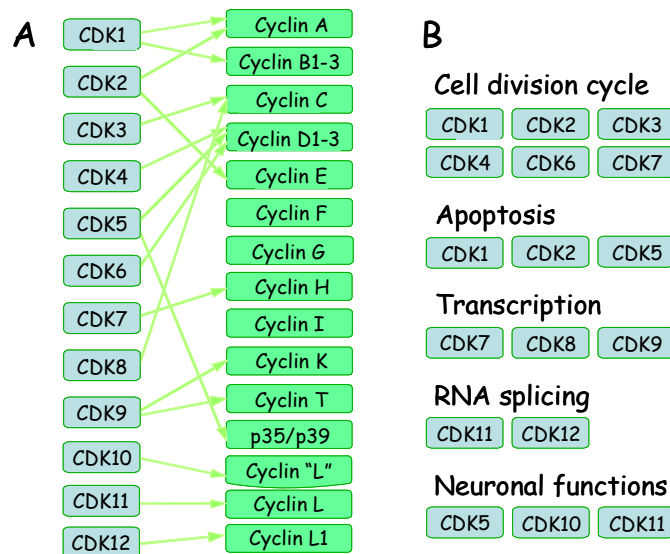


Figure 1 Cyclin-dependent kinases. CDKs (catalytic subunit) associate with regulatory subunits (cyclins and other) to constitute active protein kinase complexes (A). Different CDKs are involved in various physiological processes (B).

Alterations in the phosphorylation of proteins represent a frequent feature associated with human disease. This is the reason for an exponentially growing investment in the discovery, optimization and therapeutic evaluation of small molecular weight, pharmacological inhibitors of protein kinases (reviews in Cohen, 2002; Fischer, 2004; Weinmann and Metternich, 2005). It is estimated that 30-35% of drug discovery programs in the pharmaceutical industry currently target a protein kinase! Presently, 55 kinase inhibitors are undergoing clinical evaluation against diseases such as cancers, inflammation, diabetes, and neurodegeneration.

Abnormalities in CDK activity and regulation in cancers (Vermeulen et al. 2003), viral infections (Wang et al., 2001; Schang, 2004), proliferative renal diseases (Nelson and Shankland, 2005), and neurodegenerative disorders such as Alzheimer's (Tsai et al., 2004), Parkinson's (Smith et al., 2003, 2004) and Nieman-Pick's diseases (Zhang et al., 2004a), ischemia (Wang et al., 2003; Rashidian et al., 2005) or traumatic brain injury (Di Giovanni et al., 2005) have encouraged an intensive search for potent and selective pharmacological inhibitors of these kinases (reviews in Knockaert et al., 2002a; Fischer et al., 2003; Benson et al., 2005; Fischer and Gianella-Borradori, 2005). Over a hundred small molecular weight inhibitors of CDKs have been characterized, most of which appear to act by direct competition with ATP for binding to the catalytic site of the kinase. Over 30 of these compounds have been co-crystallized with CDK2 (Noble et al., 2004) and/or CDK5 (Mapelli et al., 2005), demonstrating their binding in the ATP-binding pocket of CDKs.

The family of 2,6,9-trisubstituted purines encompasses some of the first CDK inhibitors which have been described (review in Haesslein et al., 2002; Meijer et al., 1997; Meijer and Raymond, 2003; Meijer et al., 2006). Among these purines, the (*R*)-stereoisomer of roscovitine is one of the most frequently studied and used CDK inhibitors. Also referred to as CYC202 or Seliciclib, (*R*)-roscovitine is developed by Cyclacel Pharmaceuticals, Inc. (<http://www.cyclacel.com>) (McClue et al., 2002; Guzi, 2004). It has now reached phase 2 clinical trials for B-cell malignancies, lung and breast cancer, phase 2b against non small cell lung cancer, phase 1 trials for glomerulonephritis, and phase 2 trials in IgA nephropathy. It is undergoing pre-clinical animal evaluation against Alzheimer's disease, Parkinson's disease, stroke and Niemann-Pick's disease

type III. The selectivity (Bach et al., 2005, 2006) and intracellular mechanism of action of roscovitine have been extensively studied and will be presented as a representative example of the multiple effects of CDK inhibitors in cells, tissues and organisms.

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