

**PHARMACOLOGICAL INHIBITORS OF CYCLIN-DEPENDENT
KINASES (CDKS) AND GLYCOGEN SYNTHASE KINASE -3 (GSK-3)**

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Cyclin-dependent kinases (CDKs) regulate the cell division cycle, apoptosis, transcription, differentiation, as well as functions in the nervous system. GSK-3, an essential element of the WNT signaling pathway, is involved in multiple physiological processes including cell cycle regulation by controlling the levels of cyclin D1 and β -catenin, dorso-ventral patterning during development, insulin action on glycogen synthesis, axonal outgrowth, HIV-1 Tat-mediated neurotoxicity, and phosphorylation of tau, a characteristic of Alzheimer's disease.

Deregulation of CDKs and GSK-3 in various diseases has stimulated an intensive search for selective pharmacological inhibitors [1]. Over fifty CDK inhibitors and about ten GSK-3 inhibitors have been identified, among which more than twenty have been co-crystallized with CDK2 and one with GSK-3. They all target the ATP-binding pocket of the catalytic site of the kinases. The actual selectivity of most compounds, and thus the underlying mechanism of their cellular effects, is poorly known. Affinity chromatography using immobilized inhibitors provides one approach to identify the actual targets of kinase inhibitors. Pharmacological inhibitors of CDKs and GSK-3 are currently being evaluated for therapeutic use against cancer, neurodegenerative disorders (Alzheimer's disease, Parkinson's disease, stroke, ...etc.), cardiovascular disorders (atherosclerosis, restenosis), glomerulonephritis, viral infections (HCMV/HIV/HSV) and parasitic protozoa (*Plasmodium*, *Leishmania*). The development of these inhibitors will be presented with two examples, roscovitine and indirubins.

REFERENCE

1. Knockaert, M., Greengard, P. and Meijer, L. Pharmacological inhibitors of cyclin-dependent kinases. **Trends Pharmacol. Sci.** 23 (2002) 417-425.