

### RATIONAL DESIGN OF NEW COMPETITIVE INHIBITORS OF HUMAN CK2 ACTIVITY

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CK2 is a highly conserved serine/threonine kinase that is ubiquitously expressed in both the cytoplasm and nucleus of eukaryotic cells. It exists as a constitutively active tetramer which contains two catalytic subunits, alpha and/or alpha' (37kD–44kD), and two regulatory alpha-subunits (24kD–28kD). The two catalytic subunits are linked through the beta subunits. CK2 is localized in the cytoplasmic and nuclear compartments, and can utilize GTP as well as ATP as a phosphate donor. A large number of cellular proteins are known as substrates of CK2, and this protein kinase has been implicated in the regulation of many cellular processes including DNA replication, basal and inducible transcription, and the regulation of cell growth and metabolism. CK2 was postulated to contribute to tumorigenesis because its activity is enhanced in many human solid tumors and rapidly proliferating tissues. Dysregulated expression of this kinase in cells can be oncogenic, as transgenic expression of CK2alpha can promote lymphoma and breast cancer. CK2 is characterized by the following biochemical properties: it is activated by polyamines; inhibited by heparin, apigenin (chrysin) and DRB (6-dichloro-1-beta-D-ribofuranosylbenzimidazole). Moreover, it is still not clear which structural requirements are crucial for the ligands to inhibit the activity of CK2. Our goal is to better define the CK2 binding site to design new potent and selective CK2 inhibitors. First of all, we have built the complete 3D structure of *human* CK2 using “homology modeling” techniques starting from the *Zea mays* CK2 crystal structure; the second step was the exploration of all possible CK2 inhibitor binding sites using a “flexible docking” methodology; in this way we obtained an identification of the CK2 pharmacophoric pattern. Using *de novo* technique and multiple docking screening methodology, it was possible to design new leads with potential CK2 inhibitory activity. Preliminary results concerning their activity as CK2 poisons seem to be very promising.