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**POSITRON ANNIHILATION STUDIES OF QUANTUM STRUCTURES**

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Advances in quantum structure science and technology have proceeded in a remarkable manner over the past few years. In addition to basic science issues, imminent applications are occurring in fields as varied as quantum computing and biological sensors and manipulation. It has been stated that nano-structures are able to provide the most perfect crystals, free of impurities, defects and strain. The positron (anti-particle of the electron) appears to be an exquisitely sensitive probe of the quality of nano-structure and in the case of semiconductors, the electronic structure. Electron-positron annihilation produces two collinear γ-rays of equal energy (0.511 MeV) in vacuum and in the rest frame. In a real material the γ rays are slightly momentum Doppler shifted due to the momentum of the electron with which the positron is annihilating. By measuring these Doppler shifts one obtains information about the electronic momentum density. Additionally, the lifetime of the positron in a material is dictated by the electron density in the vicinity of the positron. Data are presented from a variety of quantum systems with emphasis on our measurements on CdSe quantum dots. A model and theory in support of our measurements will also be presented. This model predicts the smearing of the electronic momentum density at the boundary of the Jones zone proportional to the widening of the band gap as the quantum dot size decreases.

**Keywords: QUANTUM STRUCTURES, POSITRON ANNIHILATION SPECTROSCOPY, ELECTRONIC STRUCTURE**

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**STRUCTURE STUDIES ON THE RETINOBLASTOMA TUMOR SUPPRESSOR PROTEIN AND ITS ROLE IN THE CELL CYCLE**

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The retinoblastoma tumor suppressor protein (pRb) regulates the cell cycle, sponsors differentiation and restrains apoptosis. Dysfunctional pRb is thought to be necessary for the development of most human malignancies. As many of the anti-tumorigenic properties of pRb are mediated by its regulation of the E2F transcription factors, we have determined the crystal structure of a fragment of E2F (residues 409-426) bound to pRb. It reveals how E2F acts as a structural sensor of pRb integrity and illuminates the role played by these two proteins in the regulation of apoptosis. We also show that the binding of E2F(409-426) is inhibited by phosphorylation of pRb, but not by the prior binding of human papillomavirus E7 protein to the tumor suppressor.

**Keywords: CRYSTAL STRUCTURE CELL CYCLE REGULATION TUMOUR SUPPRESSOR**

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**PLASMODIUM FALCIPARUM CYCLIN DEPENDENT KINASES**

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The lethal form of human malaria is caused by the protozoal parasite *Plasmodium falciparum*, and may be responsible for 1.5 million deaths per year. The lack of an effective vaccine means that there is an urgent need for novel approaches to prophylaxis and treatment. One such approach is the development of drugs that interfere with *P. Falciparum* cell-cycle regulation. In eukaryotic organisms where it has been studied, cell proliferation is controlled by the action of cyclin dependent kinases (CDKs). Activity of these enzymes is in turn controlled by a network of regulatory interactions and covalent modifications. We are studying CDK-containing complexes of *P. Falciparum* in order a) to characterize the extent to which *P. Falciparum* follows previously identified structural paradigms of cell-cycle regulation, and b) to facilitate the structure-based design of specific *P. Falciparum* CDK inhibitors. We have solved the structure of a monomeric unphosphorylated form of PfPK5, a *P. Falciparum* kinase which displays highest sequence identity with human CDK1 and CDK5. Despite modest sequence homology, the 3D structure of PfPK5 closely resembles that of monomeric unphosphorylated CDK2. We have used the structure to explore potential functional similarities with human CDK2. We have studied PfPK5 mutants, altered at potential sites of phosphorylation to explore the role of phosphorylation in PfPK5 regulation. We have also solved the structures of PfPK5 in complex with tightly binding inhibitors. One of these, indirubine-3'-monoxime-5-sulphonate, induces the PfPK5 structure to approach that of cyclin A-associated CDK2.

**Keywords: CELL CYCLE MALARIA CDK**

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**THE Mad1-Mad2 COMPLEX: IMPLICATIONS OF A 'SAFETY BELT' BINDING MECHANISM FOR THE SPINDLE CHECKPOINT**

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The spindle assembly checkpoint is a surveillance device monitoring sister chromatid attachment to the mitotic spindle. Chromosome separation at anaphase is triggered by the Anaphase Promoting Complex (APC), an Ubiquitin-ligase triggering the degradation of the anaphase inhibitor Securin. Spindle checkpoint protein Mad2 binds to Cdc20, a positive regulator of the APC, thereby inhibiting Securin degradation and delaying anaphase. Another checkpoint protein, Mad1, is required to recruit Mad2 to unattached kinetochores and is essential for Mad2-Cdc20 complex formation *in vivo* but not *in vitro*. The crystal structure of the Mad1-Mad2 complex reveals an asymmetric tetramer, with elongated Mad1 monomers parting from a coiled-coil to form two connected sub-complexes with Mad2. The Mad2 C-terminal tails are hinged mobile elements wrapping around the elongated ligands like molecular 'safety belts'. We show that Mad1 is a competitive inhibitor of the Mad2-Cdc20 complex, and propose that the Mad1-Mad2 complex acts as a regulated gate to control Mad2 release for Cdc20 binding. Mad1-Mad2 is strongly stabilized in the tetramer, but a 1-1 Mad1-Mad2 complex slowly releases Mad2 for Cdc20 binding, driven by favorable binding energies. Thus, the rate of Mad2 binding to Cdc20 during checkpoint activation may be regulated by conformational changes destabilizing the tetrameric Mad1-Mad2 assembly to promote Mad2 release. We also show that unlocking the Mad2 C-terminal tail is required for ligand release from Mad2, and that the 'safety belt' mechanism may prolong the lifetime of Mad2-ligand complexes.

**Keywords: CELL CYCLE SPINDLE CHECKPOINT ANAPHASE**