Proliferating cell nuclear antigen (PCNA), through its interaction with various proteins involved in DNA synthesis, cell cycle regulation, and DNA repair, plays a central role in maintaining genome stability. We discovered a novel cancer associated PCNA isoform (dubbed caPCNA), which was predominantly expressed in a broad range of cancer cells and tumor tissues, but not significantly in non-malignant cells. We found that the caPCNA-specific antigenic site lies between L126 and Y133, a region within the interdomain connector loop of PCNA that is known to be a major binding site for many of PCNA’s interacting proteins. A cell permeable peptide harboring the L126-Y133 sequence inhibited PCNA function in cancer cells and selectively kills cancer cells and xenograft tumors. Based on these observations, we sought small molecules targeting this peptide region of PCNA as potential broad-spectrum anticancer agents. Our effort led to a drug candidate, AOH1996, which selectively kills a broad range of cancer cells at high nanomolar concentrations, but is not associated with significant toxicity to non-malignant cells. It also works synergistically with DNA damaging chemotherapeutic drugs, such as cisplatin and irinotecan, to selectively kill cancer cells. This compound is orally available to animals and suppresses tumor growth in a dosage form compatible to clinical applications. Importantly, it doesn’t cause significant toxicity at 2.5 times its effective dose. Mechanistically, AOH1996 competes with T3, a known PCNA ligand, for binding to PCNA. However, the mechanism by which AOH1996 exerts its effect on cancer cells may not be identical to what have been reported for the T3 analogs. In particular, we found that AOH1996 interferes with the association of PCNA and MCM7 to euchromatin, leading to DNA replication stress, blockade of homologous recombination-mediated DNA repair, and induction of apoptosis in cancer cells. These findings demonstrated the potential of this compound as a novel therapeutic agent warranting clinical investigation for cancer treatment. We have started planning a phase 1 clinical study for this compound.

Dr. Malkas earned her PhD, in Biochemistry, at City University of New York, and was a postdoctoral fellow at the Worcester Foundation for Experimental Biology, Shrewsbury MA. Dr. Malkas is a candidate for the position of Director of the Johnson Cancer Research Center in the College of Arts & Sciences. Her research laboratory tenure home could be in the Division of Biology.

Coffee & cookies served preceding the seminar in Ackert Hall, Room 225