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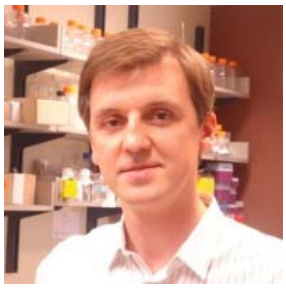

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DNA repair is intimately linked to cancer. On the one hand DNA-repair defects lead to genomic instability and higher risk of cancer development, while on the other, cancerous cells may become dependent on particular DNA-repair pathways for efficient proliferation and for resistance to chemo- and/or radiation therapy. Inhibition of DNA repair may, therefore, expand the therapeutic window of very widely used drugs such as cisplatin, the utility of which is still limited by their toxicity and by acquired resistance. Furthermore, several key proteins in DNA repair have recently been shown to be synthetically lethal with oncogenic mutations, suggesting that DNA repair inhibitors could be used to selectively target cancer cells.

Recently we elucidated the structural basis for the recruitment of XPF-ERCC1 heteronuclease to sites of DNA damage in Nucleotide Excision Repair (NER). XPF-ERCC1 recruitment is enabled by the binding of the independently folded central domain of ERCC1 to the short unstructured segment in the N-terminal region of the damage verification protein XPA. The central domain of ERCC1 has evolved from an endonuclease domain, but its active site is missing catalytic residues and has instead been adapted for XPA binding. We hypothesize that many other protein recruitment events in DNA repair are performed by interaction domains with enzyme-like structural features. These protein-protein interactions may have localized geometries favorable for small-molecule inhibition. We are currently exploring several potential targets for inhibition of DNA repair, one of them is the FancM-FAAP24 heterodimer, a homolog of XPF-ERCC1 that functions in the Fanconi Anemia Pathway of DNA repair.