ERCC2 Somatic Mutations as Biomarkers of Platinum Chemotherapy Sensitivity in Urothelial Carcinoma and other Platinum-treated Tumors

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Abstract: While platinum-based chemotherapy has long been a standard component of solid tumor oncology, reliable predictive biomarkers for platinum response suitable to direct therapy remain elusive. We have identified somatic mutations in the TFIIH DNA repair complex in muscle invasive urothelial carcinomas (UC) that predict for platinum sensitivity as measured by pathologic complete responses to combination chemotherapy. In an extreme response phenotype cohort, 100% of patients with somatic ERCC2 missense mutations experienced complete responses to platinum-based combination chemotherapy, while none of the non-responders demonstrated these mutations. These mutations are present in other platinum-treated malignancies, but at lower frequencies (generally <10% in TCGA data). Based on these provocative preliminary data, we plan to validate the findings in an independent cohort of muscle invasive UC patients and platinum-treated metastatic UC patients. We will also evaluate extreme responses to platinum chemotherapy in non-UC tumor types to determine whether these mutations are enriched in other platinum-responders across diseases. Exome sequencing will be used for tumors with sufficient high-quality DNA, while a customized exon capture panel (based on the exome sequencing results) will be used for those samples with limited DNA. Finally, the *in vitro* effects of specific ERCC2 mutations on platinum sensitivity will be explored in immortalized XPD fibroblasts, and the impact on the malignant phenotype will be gauged in model systems. If funded, this grant will provide critical evidence that platinum chemotherapy should be considered a biomarker-driven treatment in selected patients, and may lead directly to transformative changes in oncology daily practice.