Cancer Target Discovery and Development (CTD^2)

Specific Aims

Institution: Fred Hutchinson Cancer Research Center

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Despite tremendous advances in the molecular understanding of cancer, mainstay cancer therapy has remained essentially unchanged for decades, relying largely on the use of genotoxic agents. While targeted therapies have shown promise, most cancer genes remain undruggable, and the diversity of human cancers limits the utility of the few targeted therapies we have at hand. Our application conceptually stems from the NCI funded Seattle Project, first proposed in 1997 to harness synthetic lethal interactions in order to develop targeted cancer therapies. The result of this local effort, fueled by large Pharma investment, was the development of a best-in-class high throughput screening (HTS) platform, featuring optimized siRNA libraries, miniaturized robotics, and high content readouts, among other innovations. We can now, for the first time, identify synthetic lethal interactions genome wide in mammalian cells.

To date, we have identified novel genes that are synthetic lethal with MYC and TP53 and have confirmed three of these genes as viable drug targets in four different preclinical models of human cancer. Here, we propose to build on this success to identify additional synthetic lethal genes and pathways with known and emerging cancer driver mutations. Using isogenic mouse and human cells carrying genetically defined lesions we will identify novel classes of drug targets that are specific to molecular subtypes of cancer. Cross-species and cell line analyses of synthetic lethal interactions employing state of the art computational and bioinformatics resources will be used to prioritize targets. Patient derived xenografts (PDX) will be utilized to validate targets in systems that mimic the heterogeneity and diversity of human cancer. Implementation of this innovative pipeline will create a menu of targeted cancer therapies matched to the patient, a path which is clearly the future of clinical oncology. The use of PARP inhibitors in clinical trials for treatment of BRCA mutant breast cancer clearly illustrates the clinical promise of synthetic lethality for targeted therapies.

This proposal gathers an integrated and experienced team composed of laboratories with >25 years of experience in cancer biology focused on MYC, RAS, and TP53 tumor suppressor pathways; innovative computational biologists featuring a unique open source data sharing platform; and clinician scientists with expertise in three cancer types in urgent need of targeted therapies, head and neck squamous cell carcinoma (HNSCC), triple negative breast cancer (TNBC), and pancreatic ductal adenocarcinoma (PDAC). Our unifying hypothesis is that synthetic lethal interactions discovered in model systems will be conserved in heterogeneous human cancers and will lead to effective targeted therapies.

Specific Aim 1. *Identify the genome-scale menu of drug targets for known and emerging oncogene and tumor suppressor pathways in isogenic systems*. We will establish a gold standard database of synthetic lethal genes that are specific to driver oncogenic/tumor suppressor gene mutations including RAS, MYC and TP53 in three major epithelial cancers: HNSCC, TNBC, and PDAC. In addition, we will identify synthetic lethal targets that are conditional with frontline therapeutics including cisplatin, doxorubicin, and gemcitabine.

Specific Aim 2. *Prioritize high-confidence, genotype-specific synthetic lethal candidate genes and compound-conditional survival candidate genes*. Through the open source SYNAPSE platform, we will integrate available cancer genomic knowledge and empirical testing in primary cancer samples, to identify the most promising candidates for validation.

Specific Aim 3. *Confirm and validate candidate drug targets*. We will use a combination of cancer cell line and patient-derived xenografts to validate candidate drug targets, focusing on HNSCC, TNBC, and PDAC that carry common driver mutations in MYC, RAS and/or TP53.

We will create and optimize a pipeline to identify, prioritize, and validate targets for three cancer types, validated in the closest possible context to the clinic and matched to the patient.