Faculty Profile
Dr. Melissa C. Srougi

Research Areas:
- Experimental targeted cancer chemotherapies
- Breast cancer
- DNA damage and repair
- Redox signaling
- Transcriptional regulation

Techniques:
Mammalian cell culture, dose-response assays, flow cytometry, SDS-PAGE, Western blot, immunoprecipitation assays, redox signaling, fluorescence microscopy, RNA-seq data analysis, molecular cloning and transfection, comet assays.

The long-term goal of our research is to exploit natural products that target breast cancers for the advancement of precision medicine with notable clinical benefit. β-Lapachone (β-lap) is a naturally occurring antitumor quinone currently in Phase I clinical trials that is selectively bioactivated in tumors expressing NAD(P)H:quinone oxidoreductase 1 (NQO1). NQO1 is constitutively overexpressed in a number of solid tumors including breast (~60%) (1-3), non-small cell lung carcinomas (NSCLCs) (>85%), and pancreatic cancers (~85%) compared to associated normal tissues (4-7). Interestingly, breast tumors with mutations in breast cancer susceptibility genes BRCA1/2 also overexpress NQO1. However, the efficacy of β-lap has not been tested in these or other tumors with inherent defects in DNA repair.

NQO1 metabolizes β-lap via a two-electron oxidoreduction, resulting in the generation of an unstable hydroquinone form that rapidly reverts back to the parent quinone, causing multiple rounds of redox cycling (Fig. 1). β-Lap-induced reactive oxygen species (ROS) cause DNA base damage and DNA breaks (both single (SSB) and double-stranded (DSB)) (8). SSBs and cytosolic Ca²⁺ release from endoplasmic reticulum pools hyperactive poly(ADP-ribose) polymerase-1 (PARP-1) resulting in cell death due to NAD⁺ and ATP loss (8-10). Interestingly, sub-lethal doses of β-lap, in combination with DNA damaging agents such as ionizing radiation, result in tumor sensitization (11,12). Recently, a novel more potent derivative of β-lap, isobutyldeoxynyboquinone (IB-DNQ) has been generated, which kills NQO1⁺ cells in a manner similar to β-lap (13). We hypothesize that sub-lethal doses of β-lap or IB-DNQ will induce low-level DNA damage in NQO1⁺; BRCA1/2-mutant breast tumors. Existing deficits in DNA repair caused by BRCA1/2 mutations in these cells will, therefore, selectively sensitize them to sub-lethal doses of β-lap or IB-DNQ resulting in lethality. Furthermore,
combination treatment with PARP inhibitors (PARPi) will further potentiate β-lap- or IB-DNQ-induced lethality for genotype-driven cytotoxicity, and thereby, circumvent possible resistance mechanisms. Two projects will be pursued to test this hypothesis:

1. To determine the mechanism of β-lap or IB-DNQ-induced cell death in NQO1⁺;BRCA1/2-mutant breast cancers.

2. To elucidate the efficacy of β-lap or IB-DNQ treatment in NQO1⁺;BRCA1/2-mutant breast cancers with or without PARPi combination treatment.

The findings gleaned from our studies will provide insight into the mechanisms of precision targeting of β-lap or IB-DNQ in NQO1-expressing BRCA1/2 mutant breast tumors to increase tumor response to therapy while decreasing normal tissue toxicity.

References