Systematic Rational Identification of Sex-Linked Molecular Alterations and Therapies in Cancer

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Though patient sex influences response to cancer treatments, time-consuming trial-and error screening currently hinders prediction of sex-disparate drug effects. We developed a novel framework combining genomic, pathway, and connectivity map analyses to rationally predict sex-disparate molecular alterations and treatment responses. Through analyses of genomics data collected from thousands of patients, we identified significant genomic differences between the sexes in 17 cancers as well as between neoplastic and nonneoplastic tissue within each sex in 7 cancers. Using these genomics results, we discovered sex-disparate pathway associations with neoplastic expression. Constructing sensitivity and resistance signatures from our genomics results, we then used connectivity maps to predict perturbagens to which both sexes are sensitive and perturbagens to which one sex is sensitive while the other is resistant in each of 7 cancers. Notably, we correctly predicted that females are sensitive and males are resistant to tamoxifen treatment of lung adenocarcinoma. Furthermore, we made several novel predictions, including that CDK1 knockdown would be more effective in males and that midostaurin would be more effective in females, which were supported by mechanistic knowledge of the processes involved. Thus, our approach is a valuable tool for large-scale discovery of sex-differentiated molecular alterations and for rational prediction of sex-disparate and sex-independent perturbagen sensitivity and resistance.

Awards Won:

Second Award of $2,000