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Targeting therapeutic resistance in cancer: From mouse models to human therapy

Therapeutic resistance is a major obstacle in the clinic. Utilizing our novel genetically engineered mouse models (GEMMs) of breast cancer driven by inducible expression of PIK3CA$^{H1047R}$ or a wildtype HER2, coupled with pharmacological approaches, we identified a number of significant resistance mechanisms to PI3K- or HER2-targeted therapy. For example, we found spontaneous focal amplification of Met and Myc, recurrent mutations in Ras and β-catenin, and compensatory activation of the MAPK pathway render resistance to PI3K inhibition. We recently identified Cyclin D1-CDK4 mediated resistance to HER2-targeted therapy through a signaling feedback loop. More importantly, our results led to the design of a randomized phase II trial examining a CDK4/6 inhibitor plus trastuzumab as a regimen for patients with metastatic, refractory HER2+ breast cancer. In addition to GEMMs, we have led the efforts at DFCI to establish and characterize novel breast cancer patient-derived xenograft (PDX) models, with an emphasis on brain metastases, an emerging clinical challenge. I will discuss how we have used these models to discover a therapeutic strategy that overcomes resistance and yields durable remission of brain metastases of HER2+ breast cancer in animals.

STUDENTS: If you would like to attend a lunch with Dr. Zhao following the lecture, please send an email to leah.donnelly@mcgill.ca