Margaret E. Larsen
L2
LSU Health Sciences Center, New Orleans, LA

Dr. Bolin Liu
LSUHSC, Stanley S. Scott Cancer Center, Department of Interdisciplinary Oncology

"Investigating the role of HER3 in the resistance to EGFR tyrosine kinase inhibitors in non-small cell lung cancer"

The majority (80%) of lung cancer patients suffer from non-small cell lung cancer (NSCLC), which has a 5-year survival rate of about 19%. Prior research has shown the importance of studying epidermal growth factor receptor (EGFR) activating mutations to better understand NSCLC. These studies have led to the development of tyrosine kinase inhibitors (TKIs) that target the EGFR mutations to combat tumor growth and metastases. First and second-generation EGFR-TKIs are effective in NSCLC patients with the most common EGFR mutations (exon 19 deletion (Del19) and exon 21-point mutation (L858R)); however, resistance in the form of a T790M point mutation has become prevalent. A third generation EGFR-TKI, osimertinib (AZD9291), has been developed to target the T790M resistance mutation. This drug has been beneficial in the clinic, but patients are starting to show resistance to this line of therapy as well. Our study aims to elucidate the mechanism(s) behind how these NSCLC cells are becoming resistant to EGFR-TKIs with specific interest on the involvement of human epidermal growth factor receptor 3 (HER3). We hypothesize that EGFR mutant receptors are working in conjunction with HER3 and other membrane receptors to continue activating the MEK/ERK pathway in order to evade the effects of osimertinib, resulting in therapeutic resistance. To perform our experiments, two parental NSCLC cell lines, PC-9 and HCC827, with the L858R EGFR activating mutation as well as the established cell lines that are resistant to the EGFR-TKIs were used. Cell proliferation (MTS) assays, Western blot analysis, and quantitative reverse transcriptase polymerase chain reaction (RT-qPCR) were performed with these cell lines. From our preliminary analysis, we found that both HER3 and mesenchymal-epithelial transition factor (MET) were upregulated in the EGFR-TKI-resistant cell lines as compared to their parental counterparts. Further studies showed an increased level of phosphorylated STAT3 (p-STAT3) and ERK1/2 (p-ERK1/2) in the resistant cell lines, suggesting possible involvement of HER3 and/or MET in the activation of downstream signaling pathways to compromise the efficacy of osimertinib. Additional work is underway to continue to define the role of HER3-mediated signaling in the resistance to EGFR-TKIs in NSCLC.