**Background:** Chemotherapy is currently the most common treatment for human cancers. However, usually less than 35% patients respond well to chemotherapy, especially patients with advanced cancer. Cancer progression typically does not offer enough time for the patients to try different chemotherapy regimens. Therefore, a method that predicts chemotherapy response prior to treatment would have profound impact on treatment efficacy. In the previous studies, a single or sparse clinical or biological feature rather than multi-omics data was utilized with traditional machine learning approaches for drug response prediction and therefore limited prediction accuracy was obtained. In this proposal, we have collected a large chemotherapy treatment and response dataset from Cancer Genome Atlas (TCGA) project that includes 274 patients with clinical progressive disease, 156 with stable disease, 76 with partial response, and 603 with complete response. In addition, somatic-mutation, DNA-methylation, microRNA, mRNA-seq and digital pathology image data have been collected for all 1,109 TCGA cancer patients. These data provided high dimensional feature space (totally large than ~0.57 million) from which investigation of multi-omics chemotherapy response prediction can be conducted.

**Hypothesis:** In our preliminary analysis of this high-dimensional dataset, we found that traditional machine learning approaches such as support vector machine (SVM) and random forest could achieve good response prediction (AUC~0.7), indicating that we can identify a uniform prediction system for across multiple chemotherapy drugs. We hypothesize that cancer cells, regardless of tissue-of-origin, have a uniform molecular network and pattern to indicate the response to chemotherapy treatment. Therefore, we expect that a deep learning approach could provide improved predictive performance for chemotherapy drug response.

**Aims:** 1)identify a uniform multi-omics based deep-learning prediction model for overall chemotherapy response and specific chemotherapy regimen. 2) Reveal biological mechanism of cancer cell response to chemotherapeutic drug and identify novel targets for cancer drug development.

**Design:** We have collected1,109 cancer patients with multi-omics genomic and image data. We will apply Sure Independence Screening (SIS) and Gini impurity index (SII) for feature selection from the ultrahigh dimensional genomic feature set followed by conditional generative adversarial networks (CGAN) to produce predictive models for chemotherapy response, internally validated by 10-fold cross-validation. Prediction model of response status to overall and specific chemotherapeutic drug (including cisplatin, carboplatin, gemcitabine and 5-fluorouracil) will be established simultaneously. Efficiency and contribution of the different molecular features will be evaluated. We will apply multiple gene ontology and pathway enrichment analysis to investigate the molecular function, pathway, cellular component and biological process of the biomarkers to reveal shared molecule mechanism for drug response. Meanwhile, we will build a functional network with multiple interaction forms including miRNA-mRNA, mRNA-mRNA, methylation-mRNA and methylation-miRNA networks, which will help us to understand the interactions across different molecular dimensions in drug response.

**Significance/Impact:** This study will establish deep-learning based multi-omics prediction models to assistant physicians on chemotherapy regimen selection that will significantly increase the outcome and prognosis of the cancer patients and decrease unnecessary side effect. In addition, predicted biomarkers would be novel targets for cancer drug development and understanding drug response mechanisms.