MCRI Internally Funded Research Award

2019 Application Face Page

TITLE OF PROJECT **Deep Learning Prediction of Chemotherapy Response using Multi-Omics Features**		
MCR/SP Code		
Principal Investigator		
NAME *(Last, first, middle initial)*: Guo, Shicheng		DEGREE(S): Ph.D.
POSITION TITLE & DEPARTMENT: Postdoctoral Fellow-Research		ROUTING ADDRESS: ML4611
TEL: 93508	E-MAIL ADDRESS: Guo.Shicheng@marshfieldresearch.org	
Key Personnel		
NAME *(Last, first, middle initial)*: Steven J Schrodi		DEGREE(S): Ph.D.
POSITION TITLE & DEPARTMENT: Assoc. Research Scientist-Genetics in CPMR, MCRI		ROUTING ADDRESS: ML4807
PROJECT ROLE: Co-I		
NAME *(Last, first, middle initial)*: Mehdi Maadooliat		DEGREE(S): Ph.D.
POSITION TITLE & DEPARTMENT: Assoc. Research Scientist in in CPMR, MCRI		ROUTING ADDRESS:
PROJECT ROLE: Co-I		
NAME *(Last, first, middle initial)*:		DEGREE(S):
POSITION TITLE & DEPARTMENT:		ROUTING ADDRESS:
PROJECT ROLE:		
PROPOSED PROJECT PERIOD: 03/01/2020-03/01/2022		REQUESTED FUNDING AMOUNT: $65,000
Does the project involve the following:		
HUMAN SUBJECTS: ☒ No ☐ Yes		RNA ☒ No ☐ Yes
VERTEBRATE ANIMALS: ☒ No ☐ Yes		

MCRI Administrative Review

I certify that I have reviewed this proposal and that it meets MCRI budgetary guidelines and scientific priority requirements.

_____ _____

ORSS Director Date

_____ _____

MCRI Executive Director Date

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ABSTRACT Form

PI Last Name: Shicheng Guo

Project Title: Deep Learning Prediction of Chemotherapy Response using Multi-Omics Features

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 provide a high dimensional feature space—exceeding ~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.

Specific Aim 1: To accurately predict overall chemotherapy response and identify the specific chemotherapy regimen for each individual based on multi-omics data.

Specific Aim 2: To identify novel pharmacogenomic biomarkers and understand the underlying mechanisms by gene ontology, pathway and multi-omics interaction network analysis.

Design: We have collected 1,109 cancer patients with multi-omics genomic and image data. We will apply Sure Independence Screening (SIS) and Gini-Simpson 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. A predictive 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 gene ontology and pathway enrichment analysis to investigate the molecular function, pathway, cellular component and biological process of the biomarkers to reveal shared pharmacogenomic mechanism for drug response. Additionally, we will build a functional network with multiple interaction forms including miRNA-mRNA, methylation-mRNA and methylation-miRNA networks to understand the interactions across different molecular dimensions in drug response and pharmacogenomic mechanism.

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

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Signature Page

CERTIFICATION AND ACCEPTANCE

I certify that the statements herein are true and complete to the best of my knowledge and accept, as to any funds awarded, the obligation to comply with MCRI Internally Funded Research Award terms and conditions in effect at the time of the award.

1. Shicheng Guo — 09/26/2019
   MCRI Principal Investigator's Signature — Date

   Guo, Shicheng
   Printed name of Investigator

2. _____ — 09/28/2019
   MCRI Co-Investigator's Signature — Date

   Schrodi, Steven, J
   Printed Name of Co-Investigator

3. Mehdi Maadooliat — 09/30/2019
   MCRI Co-Investigator's Signature — Date
   Maadooliat, Mehdi
   Printed Name of Co-Investigator

4. _____ — 09/27/2019
   MCRI Co-Investigator's Signature — Date

   _____
   Printed Name of Co-Investigator

5. _____ — _____
   MCRI Lead Unit Research Administrator or Designee — Date

   _____
   Printed Name of MCRI Lead Unit Research Administrator or Designee

If this is a collaborative effort, please obtain external collaborator(s) (i.e. co-investigator) certification via email stating that they have read and approve of the proposed investigation. Include email(s) with your application.

Research Center Director Review

Please include a signature by Research Center Director indicating that the Center has reviewed this proposal and affirms and supports it.

Sanjay K. Shukla — 10/01/2019
Center Director Signature — Date

Sanjay K Shukla
Printed Name of Center Director