# Project Information

**Project Title**

Definable determinants of chemotherapy resistance and prognosis of intrahepatic cholangiocarcinoma

**Amount Requested**

$50,000

# Applicant Information

**Applicant Name**

Prejesh Philips

**eRA Commons Username**

p0phil02

**Degree (Select all that apply)**

- MD

**Academic Level (Select all that apply)**

- Post-Doc Fellow
- Instructor

# Institution Information

**Institution Name**

University of Louisville Research Foundation, Inc.

**Institution City**

Louisville

**Institution State**

Kentucky

**Institution Country**

United States

**Email**

grntmgmt@louisville.edu

# Mentor Information
The goal of this study is to identify molecular biomarkers that can act as independent prognostic factors for predicting survival outcomes as well as responses to chemotherapy and radiation in intrahepatic cholangiocarcinoma (ICC). Various biomarkers have been investigated for both prognosis and potential for targeting ICC. Given the dense desmoplasia in ICC, local tumor environment of extracellular non-structural proteins, such as tenascin and periostin as well as cellular transport mechanisms such as hENT1 expression could predict prognosis and response to chemotherapy. However, the expression of hENT1 transport protein, periostin, and tenascin by ICC as well as its role as a prognostic marker for survival and chemotherapy response is unclear. In this study, we will attempt to assess the role of tissue hENT1, periostin, and tenascin levels as prognostic markers defined by survival, effect of treatment, and hepatic progression free survival.

Our hypothesis is that high expression of periostin and tenascin as well as low expression of human equilibrative nucleoside transporter 1 (hENT1) are associated with a worse prognosis of intrahepatic cholangiocarcinoma (ICC) and can predict resistance to gemcitabine-based chemotherapy. The Principal Investigator, Dr. Prejesh Philips, is a Coinvestigator of the ongoing DELTIC trial, a Phase II prospective, randomized trial in which samples from ICC patients were, and are continuing to be, obtained in patients receiving cisplatin/gemcitabine in combination with irinotecan-loaded LC beads versus cisplatin/gemcitabine alone. The value of these samples is that they are from a prospective, randomized study with long-term follow up. These samples provide us with a unique opportunity to evaluate determinants to correlate progression and survival. Our aim is to evaluate the prognostic value and expression of human equilibrative nucleoside transporter 1, periostin, and tenascin in relation to overall survival, chemotherapy response, and progression of intrahepatic cholangiocarcinoma using our DELTIC trial population. To achieve this aim, we will measure the serum levels, protein expression, and mRNA expression of periostin and tenascin and tissue levels of hENT1 in patients with advanced ICC. We will evaluate these determinants as prognostic markers for survival and as a marker for efficacy of systemic chemotherapy. Complete research methodology included in supplemental files.
2017 Research Fellowship Application : Entry # 11006

Specific Aims (2500 Max Characters)

AIM: To evaluate the prognostic value and expression of human equilibrative nucleoside transporter 1, periostin, and tenascin in relation to survival, response to chemotherapy, and progression of intrahepatic cholangiocarcinoma using our DELTIC trial population.

Our hypothesis is that high expression of periostin and tenascin as well as low expression of human equilibrative nucleoside transporter 1 (hENT1) are associated with a worse prognosis of intrahepatic cholangiocarcinoma (ICC) and can predict resistance to gemcitabine-based chemotherapy. The Principal Investigator, Dr. Prejesh Philips, is a Coinvestigator of the ongoing DELTIC trial, a Phase II prospective, randomized trial in which samples from ICC patients were, and are continuing to be, obtained in patients receiving cisplatin/gemcitabine in combination with irinotecan-loaded LC beads versus cisplatin/gemcitabine alone. The value of these samples is the fact that they are from a prospective, randomized study with long-term follow up. These samples provide us with a unique opportunity to evaluate determinants to correlate progression and survival. We, therefore, have readily available to us banked tissue specimens and banked serum from which to conduct this study. To achieve this aim, we will measure the serum levels, protein expression, and mRNA expression of periostin and tenascin and tissue levels of hENT1 in patients with advanced ICC and evaluate these determinants as prognostic markers for survival and as a marker for efficacy of systemic chemotherapy. With respect to study outcome, successful identification of these determinants will be a breakthrough in our understanding of cholangiocarcinoma.

Background and Significance (3000 Max Characters)

Cholangiocarcinoma is a primary malignancy of the epithelial lining of the biliary tree, which carries a poor prognosis despite multimodality therapy. A subtype of cholangiocarcinoma is ICC, a primary epithelial cancer of the hepatobiliary tract caused by aberrant cholangiocytc proliferation. There have been noted progressive increases in the incidence and mortality rates of ICC worldwide and in the United States (1, 2). The etiology of the increased incidence is unclear; although it has been hypothesized that long-term biliary inflammation from increased incidence of hepatitis C could be a contributor (2, 3). At present, early detection and surgery remain the only hope for cure; however, recurrence is common after surgery, and few patients are suitable for curative surgery. For patients with unresectable or metastatic disease, the median survival with first-line chemotherapy is still less than a year (4).

Tumor number and differentiation, lymph node metastases, and vascular invasion have been described as independent prognostic factors for ICC and used in the AJCC 7th edition staging system (5). These prognostic factors are far from perfect in understanding and predicting the natural history of ICC. These tumors are highly chemotherapy- and radiotherapy-resistant. In order for chemotherapy to produce its cytotoxic effect, two components are necessary; namely, tissue delivery and cellular permeability. Cellular permeability often involves the presence of key membrane transport proteins, while tissue availability depends on the tissue perfusion or the presence of vascularized tumor tissue. Insight into these molecular mechanisms for resistance could lead to potential therapeutic breakthroughs (4). Tissue perfusion and oxygenation levels are essential for response to radiation. A factor creating such resistance is the overexpression of extracellular matrix proteins, such as periostin and tenascin. A lack of angiogenesis in these tumors also causes a local hypoxic effect, making these proteins radiotherapy-resistant in addition to hampering chemotherapy delivery.

Our emerging data are based on the preliminary evaluation of patients in the DELTIC clinical trial (NCT01648023). As part of the ongoing trial, serum and tissue were banked. The Principal Investigator for this current study is the Coinvestigator in the DELTIC trial, and therefore, will have easy access to specimens and data for this study. Currently, a total of 20 patients are enrolled. The clinical trial is a clinical Phase II randomized, open-labeled study of patients with unresectable intrahepatic CC. Interim analysis of 17 patients showed no unexpected adverse effects, and a majority of patients completed the planned therapy. Therapy included cisplatin/gemcitabine in combination with irinotecan-loaded LC beads versus cisplatin/gemcitabine alone in the treatment of patients with unresectable ICC.

Project Timeline (2500 Max Characters)
Months 1-5 Sample collection/ procurement. Begin experiments with Aim 1.

Months 5-10 Continue and finalize experiments.

Months 10-12 We expect to have supporting data to determine whether these biomarkers for cholangiocarcinoma correlate with prognosis and response to chemotherapy.

Literature Cited

References


Supporting Files - Please upload any supporting files such as charts or graphs in JPG or PDF format.

- Biosketch-combined.pdf
- 2016-LOR-combined.pdf
- Budget-application-form.pdf
- Cholangiocarcinoma-project-description.pdf
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50000