SYSTEMS MODELING OF TUMOR HETEROGENEITY AND THERAPY RESPONSE IN COLORECTAL CANCER

PROJECT SUMMARY/ABSTRACT Colorectal cancer (CRC) has one of the highest worldwide incidence (>1.3 million new cases) and mortality rates (~610,000 deaths annually). Genotoxic chemotherapy in stage II and III confers minimal treatment benefit (im- proved survival in 3-4% stage II patients and 15-20% patients in stage III), and predictive markers for therapy response are lacking. CRC patients would strongly benefit from novel prognostic and predictive biomarkers that identify patients who will not benefit from 5-FU-based chemotherapy, redirecting them towards targeted or novel interventions and intensified disease monitoring. One of the challenges in implementing such a biomarker approach is that CRC is a highly heterogeneous disease, with evidence for multiple subtypes emerging. The pur- ported causes of chemotherapy resistance are complex and multi-factorial, including dysfunctional apoptosis pathways, immune cell cytotoxicity (in turn, negatively affecting apoptosis and reducing immune-competency) and presence of cancer stem cells (and expression of multi-drug resistance proteins). The numbers, spatial dis- tribution and pathway status of these cells in the tumor and stromal area (and their heterogeneity) is an import- ant consideration, but the significance is not understood. The central hypothesis under investigation in this pro- posal is that modeling of apoptosis pathways at a cellular level and integration with tumor heterogeneity mark- ers in stage II and III CRC patient samples will better predict chemotherapy response, compared to standard biomarkers and treatment algorithms. While the immediate application would be for stage II patients, the re- sults will provide much needed new mechanistic insights into stage III outcomes and diagnostic opportunities for new therapies. We will use a novel single cell imaging technology to profile up to 50 proteins in a single tis- sue micro array (TMA) sections and quantify cellular and spatial distribution in tumor and stromal regions. in >1500 stage II and III CRC patients. These proteins will represent the apoptosis pathway, tumor microenviron- ment, stem cells, stroma and epithelial cells and be quantified at single cell level. Established models will be used to convert single cell apoptosis data into apoptosis competency scores. Heterogeneity in cellular apoptosis will be correlated with recurrence risk in treated and untreated patients. Tumor microenviroment measures (stroma, immune, endothelial), stem cells and available molecular subtype data will be combined with apoptosis scores to further elucidate therapy response. We will validate significant predictive biomarkers in a randomized controlled trial with chemotherapy treated and untreated patients. Finally, in a subset of patients with available cell lines, we will experimentally investigate mechanisms of drug resistance and test whether novel apoptosis- inducing therapies could potentially provide an alternative to chemotherapy. Predictive biomarkers in CRC could potentially save hundreds of thousands of patients per year from treatments with limited benefit and pro- vide oncologists with greater ability to direct patients towards other therapies.

PROJECT NARRATIVE Colorectal cancer (CRC) has one of the highest worldwide incidence and number of deaths per year. The proposed US, Ireland, and Northern Ireland collaboration (funded by each jurisdiction) will focus on understanding why chemotherapy provides limited benefit to most stage II and III patients and identify biomarkers that better predict patients who will respond.