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YOU ARE INVITED TO ATTEND THE

DEFENSE OF THE DOCTORAL

DISSERTATION

"Target Discovery in Non-Human Primates with Hereditary Colon Cancer"

by

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M.D./Ph.D. Program

B.A. 2018, Rutgers University–New Brunswick, New Brunswick, NJ

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Friday, March 29th, 2024
2:00 P.M.
Cancer Center G1196

https://rutgers.zoom.us/j/97872804403?pwd=OUc4OXk4NUtSOTFkeFA4cTNXMlE1dz09

Meeting ID: 978 7280 4403
Password: 596284

Abstract

Lynch syndrome, a form of hereditary nonpolyposis colorectal cancer (HNPCC) syndrome, affects approximately 1 in 300 people in the United States and heightens the lifetime risk of malignancy. Colorectal cancer can manifest in individuals with this hereditary condition at any age, but it is especially common before the age of 50 years due to the autosomal dominant inheritance of a mutant DNA mismatch repair gene, such as *MLH1*. Moreover, colorectal cancer has recently become the first- and second-leading causes of cancer-related death among men and women, respectively, in this age range throughout the general population. Hence, the discovery of novel targets for therapeutic intervention in this disease is imperative. Bacteriophage (phage) display is a robust platform for the identification of ligands targeting organs and tissues in physiologic and pathologic settings by screening whole organisms via the systemic circulation. To investigate functional ligand-receptor interactions in colon cancer, *in vivo* phage display peptide library screenings were performed in two rhesus macaques with *MLH1*-rheMac HNPCC syndrome that had naturally developed invasive colon adenocarcinoma. Genomic characterization with whole-exome sequencing confirmed germline mutations in key cancer-related genes, high tumor mutational burden, and corresponding mutational signatures. Next-generation DNA sequencing and bioinformatic analysis of phage particles in over 50 tissue types revealed a repertoire of greater than 600 million recovered peptides, assembling the most comprehensive vascular map of ligands in non-human primates to date. A subset of tumor-exclusive peptides shared by both subjects was selected for functional validation through *in vitro* targeting of a human colon cancer cell line. Receptor isolation and identification in tumor specimens from human patients and the rhesus macaques revealed several possible binding partners (n=12). The pursued lead peptide candidate demonstrated specific binding to AP-CRC-006, which was shown to be abundant in human colon adenocarcinoma tissue sections. Together, these findings indicate that integrative and large-scale analysis of *in vivo* screenings in non-human primates can reveal ligand-receptor interactions at the cellular and molecular level that are representative of human disease. Finally, the exploratory panel of novel targets for colon cancer discovered in this unique model presents an opportunity for translation in the clinical setting.