Patient-derived endemic Burkitt Lymphoma avatar mouse models for exploring inter-patient tumor variation and testing targeted therapies

Cliff I. Oduor[1*], Priya Saikumar Lakshmi[2*], Catherine S. Forconi[2], Rachel M. Gerstein[3], Juliana A. Otieno[4], John M. Ong'echa[5], Christian Münz[6], Micah A. Luftig[7], Michael A. Brehm[8], Jeffrey A. Bailey[1], Ann M. Moormann[2]

Department of Pathology and Laboratory Medicine, Brown University, Providence, RI, USA[1]; Division of Infectious Diseases and Immunology, Department of Medicine, University of Massachusetts Chan Medical School, Worcester, MA, USA[2]; Department of Microbiology and Physiological Systems, University of Massachusetts Chan Medical School, Worcester, MA, USA[3]; Jaramogi Oginga Odinga Teaching and Referral Hospital, Ministry of Medical Services, Kisumu, Kenya[4]; Center for Global Health Research, Kenya Medical Research Institute, Kisumu, Kenya[5]; Department of Viral Immunobiology, Institute of Experimental Immunology, University of Zürich, Zurich, Switzerland[6]; Department of Molecular Genetics and Microbiology, Duke University School of Medicine, Durham, NC, USA[7]; Program in Molecular Medicine and the Diabetes Center of Excellence, University of Massachusetts Chan Medical School, Worcester, MA, USA[8]

**co-authors contributed equally*

Email of presenting author: cliff_oduor@brown.edu

Endemic Burkitt Lymphoma (eBL) is a common childhood cancer in sub-Saharan Africa characterized by Epstein-Barr virus (EBV) and malaria-associated aberrant B cell activation and MYC chromosomal translocation. Survival rates for eBL hover at 50% after conventional chemotherapies. Clinically relevant animal models that reflect variation in patient treatment response and tumor heterogeneity are necessary to test additional therapies. Towards this goal, we established five patient-derived BL tumor cell lines and corresponding NSG-BL avatar mouse models. Pairing transcriptomics and protein expression, our BL cell lines (three EBV type 1, two EBV type 2) maintained fidelity from patient tumors to NSG-BL avatar mouse tumors. However, we found significant variation in tumor growth and survival between NSG-BL avatars and observed changes in EBV expression patterns in the absence of host immune pressure. Some oncogenic pathways were differentially expressed between new and long-established BL cell lines such as enriched ATF2-response genes in old cell lines, an alternate MYC-induced growth pathway. We tested rituximab-responsiveness across BL cell lines and found one exhibiting direct sensitivity to rituximab, characterized by gene expression signals associated with apoptosis counterbalanced by unfolded protein response and mTOR pro-survival pathways. This NSG-BL avatar displayed a unique absence of IFN-α responsive gene signature confirmed by protein staining. Our results demonstrate significant variation between eBL patient-tumors and that contemporary patient-derived BL cell lines and corresponding NSG-BL avatars can be used to guide new therapeutic strategies for patients in Africa.

The most appropriate topic area "Burkitt lymphoma".

Oral presentation preferred.