Prevalence of Alternative Lengthening of Telomeres (ALT) in Human Cancer Subtypes

Christopher Heaphy¹, Andrea Proctor Subhawong¹, Seung-Mo Hong¹, Michael Goggins¹,²,³, Elizabeth Montgomery¹,², Edward Gabrielson¹, George Netto¹,²,⁴, Jonathan Epstein¹,²,⁴, Tamara Lotan¹, William Westra¹,², Ie-Ming Shih¹, Christine Iacobuzio-Donahue¹,², Anirban Maitra¹,², Qing Kay Li¹, Charles Eberhart¹,²,⁵, Janis Taube¹, Robert Kurman¹, TC Wu¹, Richard Roden¹,², Pedram Argani¹,², Angelo De Marzo¹,²,⁴, Luigi Terracciano⁶, Michael Torbenson¹ and Alan Meeker¹,²,⁴

Departments of ¹Pathology, ²Oncology, ³Medicine, ⁴Urology, ⁵Ophthalmology, Johns Hopkins University School of Medicine, Baltimore, MD and ⁶Institute of Pathology, University Hospital, Basel, Switzerland

Background: Approximately 10-15% of human cancers do not show evidence of telomerase activity, and a subset of these maintain telomere lengths by a recombination-based telomerase-independent telomere maintenance mechanism termed alternative lengthening of telomeres (ALT). The ALT phenotype, relatively common in sarcomas, astrocytomas and glioblastomas, has only rarely been previously reported in carcinomas. For example, our laboratory recently reported the presence of ALT positive cases in a small subset of breast carcinomas. It has been suggested that telomerase expression is more stringently suppressed in mesenchymal tissues, potentially explaining the higher frequency of ALT in sarcomas; however, the prevalence of ALT has not been thoroughly across all cancer types. Thus, the purpose of this study was to comprehensively survey the ALT phenotype in a broad range of human cancers.

Design: A total of 161 tissue microarrays (TMAs) from the Johns Hopkins Hospital, containing 3,905 primary tumors from 62 cancer subtypes were assessed for ALT status. To validate and extend these findings, a pre-existing set of TMAs was obtained from Europe which contained 2,106 primary tumors from 60 cancer subtypes. In addition, 462 benign neoplasms and 264 normal tissue samples were assessed. Combined telomere-specific fluorescence in situ hybridization and immunofluorescence labeling for PML was conducted to detect ALT positive cases.

Result: Overall, ALT was observed in 3.2% (194/6,011) of all tumor specimens. Conversely, ALT was never observed in benign neoplasms or in normal tissues. This is the first description of the presence of ALT in carcinomas of the bladder, cervix, endometrium, esophagus, gallbladder, kidney, liver, lung, pancreas, and ovary. Additionally, this is the first report of ALT in medulloblastomas and pediatric glioblastoma multiformes (GBM).

Conclusion: This is the first comprehensive survey of the ALT phenotype in a broad range of human cancers. Previous studies have shown that the ALT telomere maintenance mechanism confers a poor prognosis in liposarcomas and neuroblastomas; however, it confers a good prognosis in adult GBM. Further studies are needed to assess the prognostic significance and unique biology of tumors that express ALT. As cancers using the ALT pathway are predicted to be resistant to therapies based on telomerase inhibition, these results may have therapeutic consequences.