**Stem cell directed pan cancer analysis reveals a human adult stem cell signature that defines aggressive epithelial cancer subtypes**

Bryan A. Smith[1], Nikolas G. Balanis[2], Avinash Nanjundiah[2], Katherine M. Sheu[2], Qingfu Zhang[3,4], Jung Wook Park[1], Michael Thompson[2], Jiaoti Huang[3], Thomas G. Graeber[2,5,6], and Owen N. Witte[1,2,6,7,8]

[1]Department of Microbiology, Immunology, and Molecular Genetics, [2]Department of Molecular and Medical Pharmacology, UCLA, Los Angeles, CA 90095, USA. [3]Department of Pathology, Duke University School of Medicine, Durham, NC 27710, USA. [4]Department of Pathology, The First Affiliated Hospital of China Medical University, 110001 Shenyang, China. [5]Crump Institute for Molecular Imaging, [6]Jonsson Comprehensive Cancer Center, [7]Molecular Biology Institute, [8]Eli and Edythe Broad Center of Regenerative Medicine and Stem Cell Research, UCLA, Los Angeles, CA 90095, USA.

Background
Cancer progression often co-opts features of normal stem cell biology including activation of signaling pathways that regulate stem cell function. Further, pan-cancer efforts by The Cancer Genome Atlas and others have shown that cancers originating from different tissues share similar genomic signatures. It is unclear if stem cell associated transcriptional programs are conserved across different cancers and if these programs are specific for certain stem cell populations.

Methods
We used a rank-rank hypergeometric overlap algorithm to develop gene expression signatures for different human normal stem cell populations. These signatures were applied to a pan-epithelial cancer gene expression dataset consisting of 19 epithelial cancers. We further assessed the signatures' abilities to predict survival outcome. To gain insight into genomic alterations associated with the signatures, we performed a hypergeometric test between stem cell signature status and genomic alteration. We also interrogated datasets consisting of small cell neuroendocrine (SCN) prostate and lung cancers for their enrichment in the normal stem cell signatures. DNA methylation datasets of SCN prostate and lung cancers were mined to identify methylation patterns common to SCN cancers.

Results
We generated gene signatures specific for human epithelial adult stem cells (ASC) and different embryonic stem cell populations. Across 19 epithelial cancers, we found that tumor stage and tumor grade was significantly, positively correlated with ASC signature score and not with other stem cell signatures. The ASC signature provided prognostic information independent of proliferation and cancer type. The ASC signature selected for cancers associated genomic alterations in oncogenic drivers and small cell neuroendocrine cancers. We found that SCN lung and prostate cancers were more enriched for the ASC signature compared to non-SCN phenotypes. We found that DNMT expression was highly associated with the ASC signature within the SCN datasets. Interrogation of DNA methylation data revealed that SCN cancers from different tissues share a DNA methylation profile. The inferred activities of the differentially methylated genes were significantly anti-correlated with their methylation status in both prostate and lung cancer datasets. Further, ASC signature scores were significantly anti-correlate with methylation status and positively correlated with gene expression within these datasets.

Conclusions
Our results demonstrate a molecular link between human adult stem cells and aggressive cancers from multiple epithelial tissues. The ASC-linkage is particularly strong in small cell neuroendocrine lung and prostate cancers and in part involves a core set of differentially methylated and activated genes.

Conflict of Interest
None

Funding Acknowledgements
This work was supported by an American Cancer Society postdoctoral fellowship PF-16-082-01-TBE and Prostate Cancer Foundation Young Investigator Award (to B.A.S.), and a Eli and Edythe Broad Center of Regenerative Medicine and Stem Cell Research-Hal Gaba Director's Fund for Cancer Stem Cell Research Award (T.G.G. and O.N.W.).