Surfaceome and cancer testis antigen profiling of lung adenocarcinoma by large-scale transcriptomic analysis

Andrew Swartz[1], Andrew Elliott[2], George Sledge[2], Stephen V. Liu[3], Balazs Halmos[4], Vincent K. Lam[5], and Taofeek K. Owonikoko[1]

[1]UPMC Hillman Cancer Center, Division of Hematology/Oncology, University of Pittsburgh School of Medicine, Pittsburgh, PA. [2]Clinical & Translational Research, Medical Affairs, Caris Life Sciences, Phoenix, AZ. [3]Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC. [4]Department of Oncology, Montefiore Medical Center, Bronx, NY. [5]Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins School of Medicine, Baltimore, MD

Background

- Antibody drug conjugates (ADC's), bispecific engagers and adoptive cell therapy are novel therapeutic approaches that rely on targeting tumor specific and tumor associated antigens in solid tumors. These are underutilized treatment modalities in thoracic oncology
- Prior studies have identified differential expression of surface expressed proteins ('the surfaceome') and cancer testis antigens in SCLC translational subtypes. We sought to expand this approach to include molecular subtypes of NSCLC

Objectives

- Compare the surfaceome and CT antigen profile of NSCLC Molecular subtypes (EGFR, KRAS, ALK) using published dataset of cancer surfaceome and CT antigens
- Generate a hierarchical priority of surface membrane proteins as potential therapeutic targets

Methods

- We examined differential expression of surfaceome genes (Fonseca et al., 2016) and cancer testis (CT) antigen genes (Almeida et al., 2009) among major lung adenocarcinoma genomic subtypes
- Conducted comprehensive surfaceome/CT antigen profiling of 9002 NSCLC adenocarcinoma samples using data generated by RNA sequencing (whole transcriptome) at Caris Life Sciences (Phoenix, AZ).
- NSCLC tumors were stratified into 5 subgroups based on the presence of specific driver mutations: *ALK* fusion (N=325), *EGFR* mutant (N=1739), *KRAS* mutant (no *STK11* or *KEAP1* mutation; N=2561), *KRAS* + *STK* or *KEAP1* mutation (N=1264), and Pan-WT (no mutation in *ALK*, *EGFR*, *KRAS*, *STK11*, or *KEAP1* detected; N=3113).
- Fold-change in expression was calculated by dividing the median value for a specific subgroup by the median of all other groups combined.
- Significance was tested by Mann-Whitney U test, with p-values adjust for multiple hypothesis testing (Benjamini-Hochberg).

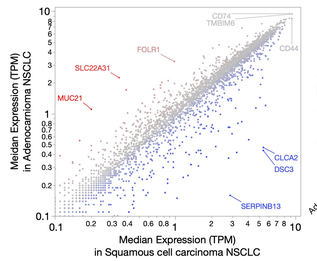
Table 1.1 – Baseline Demographics

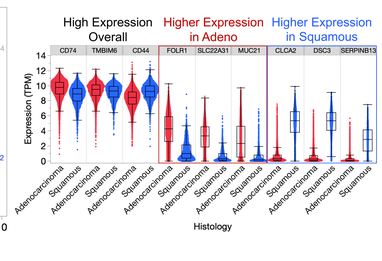
Subgroup	ALK+ (Fusion+)	EGFR-mut	KRAS-mut	KRAS+STK11|KEAP1-mut	Pan-WT
Samples, N (%)	374 (2.7%)	1947 (13.9%)	3169 (22.6%)	1499 (10.7%)	7042 (50.2%)
Median Age (range) [N]	*61.0 (21 - >89)	69.0 (28 - >89)	70.0 (24 - >89)	67.0 (37 - >89)	70.0 (25 - >89)
Sex					
Male	47.3% (177)	28.7% (558)	41.1% (1303)	46.5% (697)	57.6% (4056)
Female	52.7% (197)	71.3% (1389)	58.9% (1866)	53.5% (802)	42.4% (2986)
Histology					
Adenocarcinoma	87% (325)	89% (1739)	81% (2561)	84% (1264)	44% (3113)
Squamous	1% (4)	2% (31)	3% (90)	1% (22)	36% (2519)
Other/NOS	12% (45)	9% (177)	16% (518)	14% (213)	20% (1410)
Tumor mutational burden (TMB)					
Median TMB (range)	*3.0 (0 - 22)	4.0 (1 - 227)	9.0 (0 - 71)	8.0 (0 - 59)	7.0 (0 - 223)

Note: Pan-WT = ALK, EGFR, KRAS, STK11, and KEAP1 wildtype.

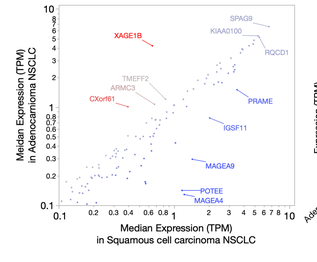
Results

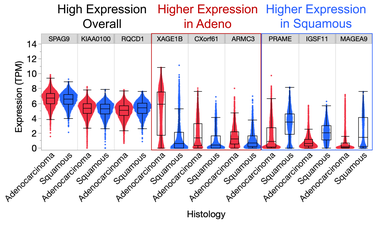
Surfaceome gene expression profiling (N=3699):



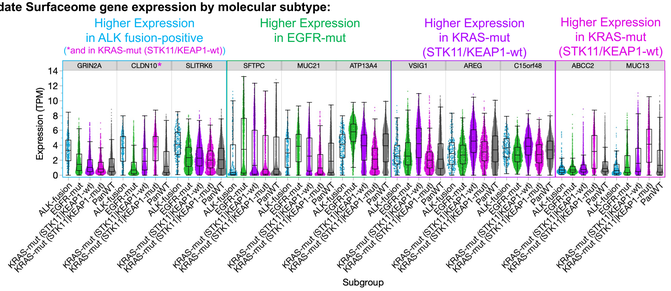


CT antigen gene expression profiling (N=210):

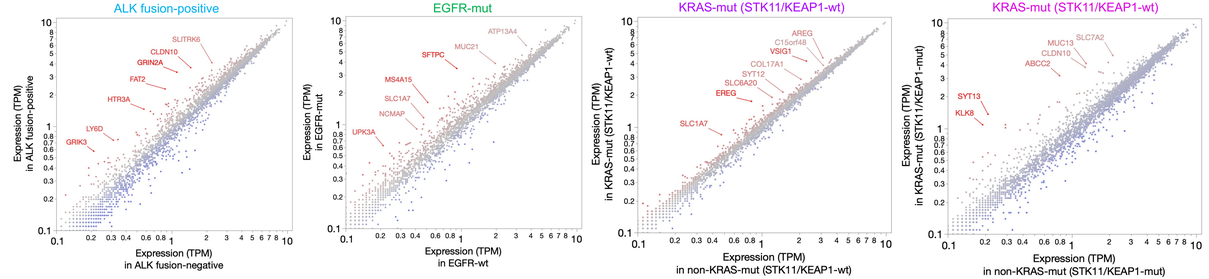




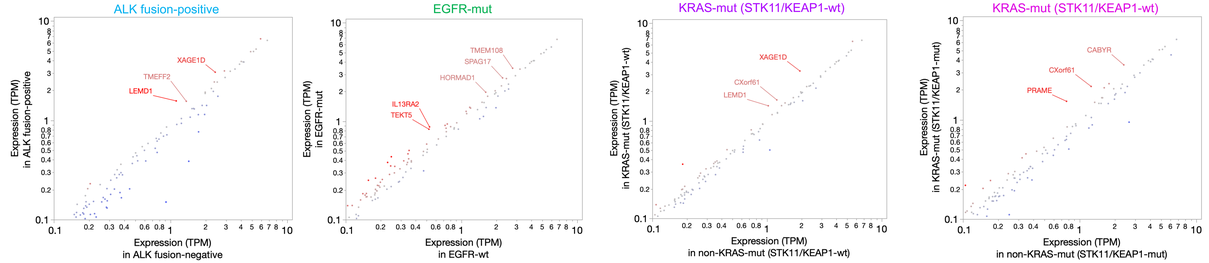
Candidate Surfaceome gene expression by molecular subtype:



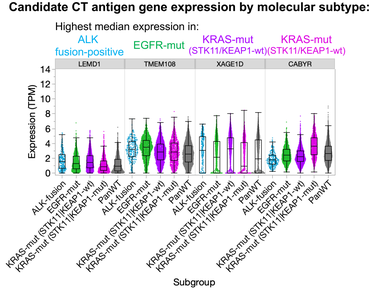
Surfaceome gene expression profiling among driver-positive adenocarcinoma NSCLC:



CT antigen gene expression profiling among driver-positive adenocarcinoma NSCLC:



Candidate CT antigen gene expression by molecular subtype:



Conclusions

- Our analysis revealed several surfaceome and CT antigen candidate genes with relatively high expression across lung adenocarcinoma, as well as differential expression of candidate genes within specific genomic subtypes.
- These findings can help prioritize the validation and development of novel therapeutic targets in lung adenocarcinoma.