Elevated PARP7 expression in select cancers identifies a target population for RBN-2397 therapy

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INTRODUCTION

PARP7 (TIPARP) is a monoPARP which catalyzes the transfer of single units of ADP-ribose onto substrates to change their function. Its expression is upregulated during cellular stress, including viral infection or through the activation of the aryl hydrocarbon receptor after exposure to cigarette smoke. We and others have shown that PARP7 activity suppresses the Type I interferon (IFN) response following activation by cytosolic nucleic acid sensing pathways. RBN-2397 is a first-in class PARP7 inhibitor, which induces cancer cell autonomous and immune stimulatory effects in preclinical models through enhanced Type I IFN signaling in cancer cells.

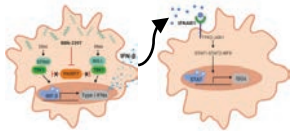

Figure 1. RBN-2397 inhibits PARP7 to restore Type I IFN response.

In characterizing PARP7 copy number and mRNA expression from The Cancer Genome Atlas (TCGA) database, we found the presence of PARP7 copy number amplification in a subset of tumor types, particularly those of squamous histology, as well as ovarian cancer that corresponded to higher mRNA expression levels. High PARP7 expression correlated with poor survival in squamous cancers, while it had no effect on survival in ovarian cancer. Interestingly, tumor types with high PARP7 expression also expressed higher levels of baseline interferon stimulated genes (ISGs). This parallels our findings that cancer cell lines with higher ISGs at baseline are more responsive to PARP7 inhibition.

To explore PARP7 copy number variations (CNVs) in advanced cancer patients, we queried the FoundationCore® (Foundation Medicine, Inc) database. Similar to TCGA, squamous cancers as well as ovarian, breast, and pancreatic ductal adenocarcinoma (PDAC) were among the tumor types with PARP7 amplifications. Moreover, PARP7 was found to be amplified both on the background of chromosome 3q arm-level amplifications as well as focally.

Congruent to our analysis of PARP7 amplifications, we evaluated PARP7 mRNA expression in both squamous and non-squamous non-small cell lung carcinoma (NSCLC), and PDAC primary tumor samples. Using a validated RNAscope ISH probe set, we analyzed over 700 patient samples and found that PARP7 was more highly expressed in tumor cells relative to corresponding normal tissues. Overall, there were varying levels of PARP7 expression across samples with higher expression levels of PARP7 in tumor cells, compared to stroma, across all cancers examined.

CONCLUSIONS

- PARP7 is amplified in cancers of squamous histology in both the TCGA and FoundationCore datasets, and copy number correlates with mRNA expression.
- PARP7 mRNA expression is associated with higher ISG expression and poorer survival in squamous cancers.
- PARP7 mRNA ISH shows PARP7 is expressed in the tumor epithelium of SCCL and PDAC primary tumors.
- These data highlight potential patient selection strategies to identify those patients more likely to benefit from RBN-2397 treatment.

RESULTS

PARP7 is Amplified and Highly Expressed in Squamous Tumors in TCGA

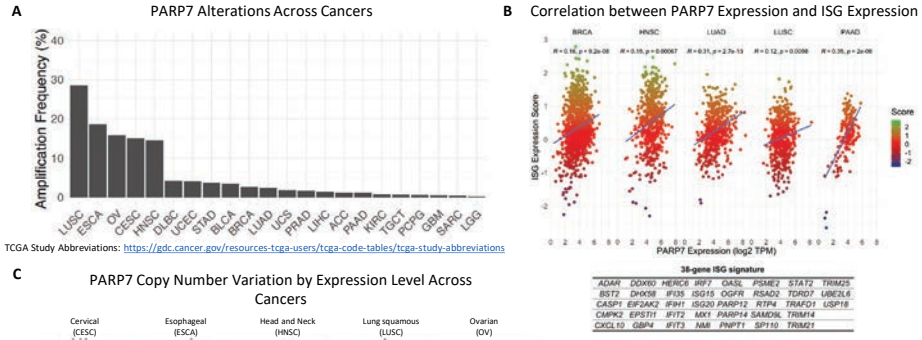

Figure 2. (A) Bar plot of amplification frequency across cancer indication in tumor samples derived from the Cancer Genome Atlas (TCGA) database. PARP7 amplification is most frequently found in squamous tumors. (B) Scatter plots of ISG expression by PARP7 expression across cancer indication in tumor samples. Tumor types with high PARP7 expression express higher levels of ISGs. (C) Scatter plot spearman correlation of copy number variant (CNV) level by expression level (log2TPM). Increased PARP7 copy number correlates with increased mRNA expression. Squamous cancers as well as ovarian cancer correspond to higher mRNA expression levels. (D) Kaplan-Meier survival plots of survival in ovarian cancer (left) and survival in squamous cancers (LUSC, HNSC, ESCA) (right) in mRNA PARP7 high and mRNA PARP7 low individuals. High PARP7 expression correlates with poorer survival in squamous cancers but has no effect on survival in ovarian cancer.

PARP7 is Amplified Focally and on Background of chr3q Arm-Level Amplifications

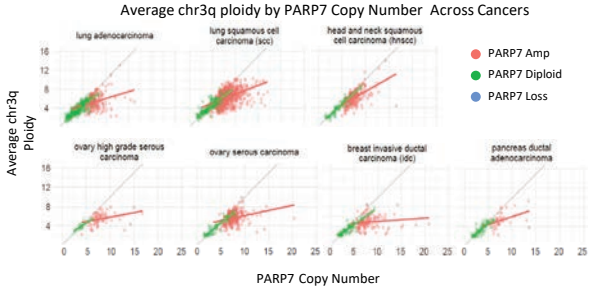

Figure 3. Scatterplots of average chromosome 3q (chr3q) ploidy by PARP7 copy number across cancer indications derived from a custom query in the FoundationCore® database.

Frequency of PARP7 Amplification in Squamous, Ovarian, Breast, and Pancreatic Cancers

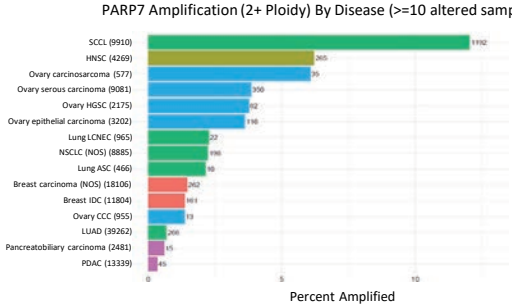

Figure 4. Bar plot depicting PARP7 amplification by disease. Using a custom query in the FoundationCore® database, over 330,000 samples across 95 disease groups and over 400 disease types were analyzed. PARP7 amplification is defined as a PARP7 copy number that is 2 copies over the average sample ploidy.

Abbreviations: SCCL, squamous cell carcinoma of the lung; HNSC, head and neck squamous cell carcinoma; HGSC, high grade serous carcinoma; LCNEC, large cell neuroendocrine carcinoma; NSCLC, non-small cell lung carcinoma; NOS, not otherwise specified; ASC, adenosquamous carcinoma; IDC, invasive ductal carcinoma; CCC, clear cell carcinoma; LUAD, lung adenocarcinoma; PDAC, pancreatic ductal adenocarcinoma.

PARP7 is Expressed in the Tumor Epithelium of Primary Tumor Tissues

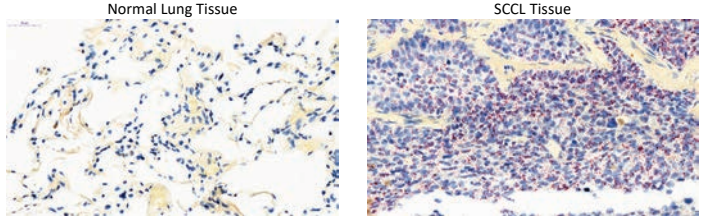

Figure 5. Lung tissue stained with PARP7 mRNA ISH probe (RNAScope) (Left) Normal Lung tissue (Right) SCCL tissue

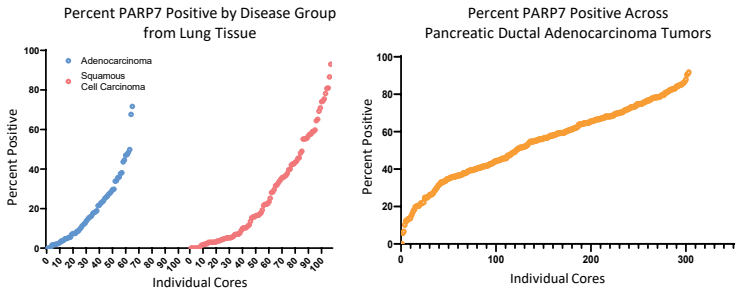

Figure 6. (Left) Scatter plot of percent PARP7 positive from the RNAScope ISH analysis of 345 total tumor core samples across 4 lung tissue microarrays. The median PARP7 positive of adenocarcinoma cores is 16.9% and of squamous cell carcinoma cores is 22%. (Right) Scatter plot of percent PARP7 positive from the RNAScope ISH analysis of over 300 tumor samples from 15 total pancreatic ductal adenocarcinoma (PDAC) tissue microarrays. The median PARP7 positive of PDAC cores is 56.6%.