

Background

Preliminary clinical data suggest that D1/VEGFA bispecifics may be more effective than PD-inhibitors in NSCLC patients.

To be effective, PD1-inhibitors requires activated CD8+ T-Cells, that are primed against tumor antigen by Dendritic Cells (DCs).

- VEGFA exerts Vascular Effects: Angiogenesis promoting.
- VEGFA may also exert Immune Suppressive Effects, namely Inhibition of DCs, thus preventing CD8+ T-Cell activation
 - If so, overcoming immune suppression by VEGFA-inhibition may enhance effectiveness of PD1-inhibitors when combined.

Objectives

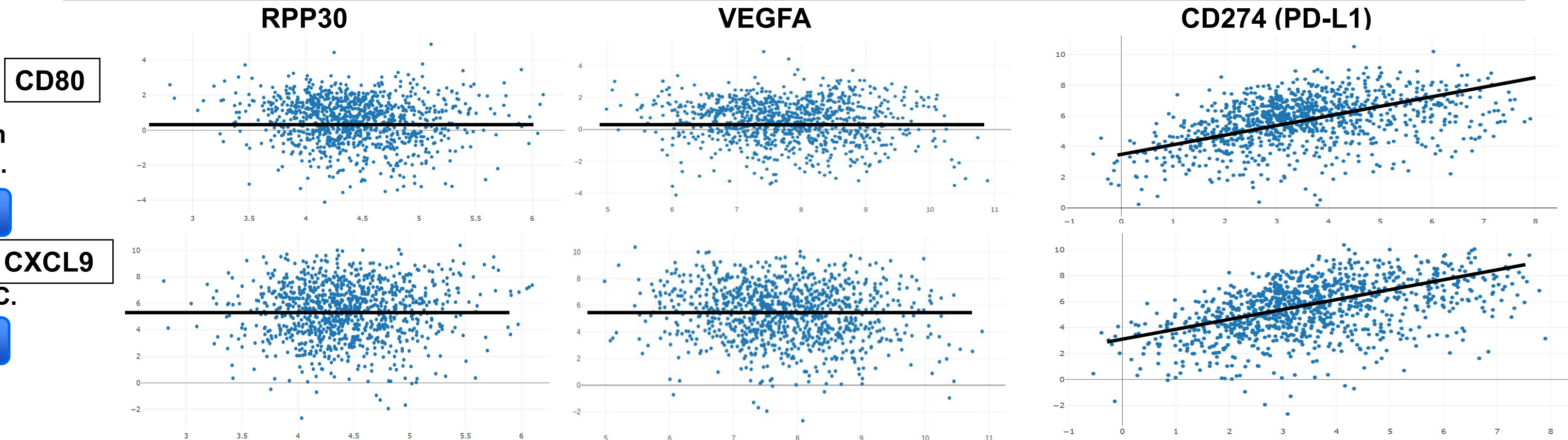
We investigated whether VEGFA exerts immune-suppressive effects on DCs and CD8+ T-Lymphocytes in patients with NSCLC.

Methods

- RND Inc. employed an in-silico bioinformatics ('AI') approach with gene expression profiling/mining of immune markers in baseline (prior to therapy) tumor issue and microenvironment (TME) from NSCLC patients (n=1027) using The Cancer Genome Atlas (TCGA) database.
- Gene Expression levels of VEGFA, were correlated with markers of DC activation (CD80, CD86, CD163) and CD8+ T Cell activation (CXCL9, IL2RA) on a within-subject basis.
 - We included a 'negative' control (RPP30, a house-keeping gene) and a 'positive' control (CD274 [PD-L1], an established marker of immune-activation).
 - Pearson correlation coefficients (r-values) were calculated after linear regression.

Results

Correlation between Gene Expression of Immune Markers of Interest (RPP30 [left column], VEGFA [middle column], CD274/PD-L1 [right] column) and CD80 (Activation Marker of DCs; top panel) and CXCL9 (Activation Marker of CD8+ T-Cells; bottom panel). Y-Axis: CD80 (top panel) and CXCL9 (bottom panel); X-Axis: RPP30 (left), VEGFA (middle) and CD274 (right). RPP30: house-keeping gene; 'negative control'; CD274/PD-L1: 'positive control'; CD80: Dendritic Cell Activation Marker; CXCL9: CD8+ T-Lymphocyte Activation Marker.



r-Values	CD80	CD86	CD163	CXCL9	IL-2RA
VEGFA	-0.089	-0.144	-0.088	-0.11	-0.109
RPP30	-0.114	-0.017	-0.156	+0.044	-0.031
PD-L1	+0.503	+0.442	+0.426	+0.477	+0.506

Table 1: A summary of Correlation Coefficients ('r-value') of Activation Markers of Dendritic Cells (CD80, CD86, CD163) and CD8+ T-Lymphocytes (CXCL9, IL2RA) versus Immune Markers (RPP30 (negative control), VEGFA, CD274/PD-L1 (positive control)).

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Results

Interpretation :

- CD274 (PD-L1), an established marker of immune activation, demonstrated a positive correlation (positive r-value and slope of the linear regression line in black) with DC (CD80) and CD8+T-Cell (CXCL9) activation markers, as can be expected. This is important model validation data.
- RPP30 ('negative control') did not correlate with CD80 and CXCL9 (flat slope and a r-value around zero of the linear regression line), as can be expected. This is also important model validation data.
- The correlations (r-value) of VEGFA versus CD80 and CXCL9 were similar to those of the negative control RPP30. If VEGFA would exert immune-suppression, the r-value would be strongly negative.
- Table 1, shows consistent findings for other DC (CD86, CD163) and CD8+ T-Cell (IL-2RA) markers.

Conclusion:

VEGFA does not appear to exert immune-suppressive effects in the NSCLC TME. The perceived benefit of VEGFA inhibition with PD1/VEGFA bispecifics is unlikely due to reversing immune suppression, but rather due to other VEGFA-related mechanisms of action (such as anti-angiogenesis).