Defeating checkpoint resistance: Highly specific inhibition of latent TGFβ1 activation renders resistant solid tumors vulnerable to PD-1 blockade

Thomas Schlüpf1, Constance J Martin1, Christopher Littlefield1, Christopher Chapron1, Stefan Wawersik1, Ashish Kaira1, Kevin Dagby1, Allison Simpson1, Francis Dandry1, Christopher Boston1, Anastasia Nikonov1, Susan Lin1, Justin Jackson1, Pichai Raman2, Elizabeth Rainbolt1, Laurie Comfort1, David Harris1, Madelyn Cecil-Taylor1, Lorne Celentano1, Danielle Meadows1, Gregory J Carven1, Alan Bucklin1, Allan Capill1, Abhishek Datta1
1) Scholar Rock Inc., Cambridge MA 2) Independent Consultant, Bryn Mawr, PA 3) Charles River Discovery Services, Montville NJ

Introduction
Despite the profound advances in cancer immunotherapy, primary resistance to checkpoint blockade therapy (CBT) remains a major unmet need for patients; a majority of patients’ cancers still fail to respond to PD-1/L1 inhibition. Retrospective analysis of untreated cancer and melanoma tumors has recently implicated TGFβ activation as a potential driver of primary resistance, very likely via multiple mechanisms including exclusion of cytotoxic T cells from the tumor as well as their expansion within the tumor microenvironment (immune exclusion). These observations and subsequent preclinical validation have pointed to TGFβ pathway inhibition as a promising avenue for overcoming primary resistance to CBT. However, therapeutic targeting of the TGFβ pathway has been hindered by dose-limiting preclinical toxicities, most likely due to inhibition of signaling from multiple TGFβ isoforms.

Upon secretion, TGFβ growth factor is held in a latent complex with its non-covalently associated pro-TGFβ protein. TGFβ activation is triggered by extracellular events that release the growth factor from the latent complex. We previously demonstrated that antibody-based isoform-specific inhibition of TGFβ activation can be achieved by targeting a specific latent TGFβ complex and preventing release of one isoform (e.g., TGFβ1) while avoiding other isoform complexes (e.g., TGFβ2 and TGFβ3), thus creating a potential avenue to avoid the toxicities observed with less selective TGFβ pathway inhibition.

Hypothesis
Delineation and selective targeting of the TGFβ isoform(s) that is most relevant in the tumor microenvironment may enable a pharmacologically tractable approach to overcoming primary resistance to CBT.

Figure 1: TGFβ1 is the predominant isoform in many human tumors
A: TGFβ1 isoform expression by tumor type
B: TGFβ1 isoform expression in individual tumors

Figure 2: SRTβ1-Ab3 is a fully human, isoform-specific anti-lateral TGFβ1 antibody with high affinity
A: Inhibition of TGFβ1 activation by integrins
B: Inhibition of TGFβ1 activation by proteolysis

Figure 3: SRTβ1-Ab3 potently inhibits activation of latent TGFβ1
A: Inhibition of TGFβ1 activation by integrins
B: Inhibition of TGFβ1 activation by proteolysis
C: Inhibition of human Tregs

Figure 4: Selection of murine syngeneic tumor models that best reflect human primary resistance to CBT

Figure 5: Synergistic effects of SRTβ1-Ab3 combination with anti-PD-1 on tumor growth in CBT-resistant tumors
A: MBT-2: Tumor Growth Trajectories
B: MBT-2: Median Tumor Volume
C: MBT-2: Survival
D: MBT-2: Re-Challenge

Figure 6: SRTβ1-Ab3 in combination with anti-PD-1 overcomes immune exclusion by enabling infiltration and expansion of CD8+ T cells in tumors

Figure 7: TGFβ1 isoform specificity of SRTβ1-Ab3 results in improved preclinical toxicity profile
A: Valutopathies confirmed with pan-TGFβ inhibition control reagents in one week tolerability study
B: Improved preclinical toxicity profile of SRTβ1-Ab3

Conclusions
TGFβ1 is the predominant TGFβ isoform expressed in many human tumors, particularly those for which CBT is approved. It is the likely driver of TGFβ pathway signaling that contributes to immune exclusion, which renders a large fraction of tumors resistant to CBT.

SRTβ1-Ab3, a fully human antibody that binds latent TGFβ1 with high selectivity and subnanomolar affinity, potently inhibits multiple mechanisms of activation of this growth factor.

In murine syngeneic tumor models that best reflect human primary resistance to CBT, including the predominance of TGFβ1, treatment with SRTβ1-Ab3 renders tumors vulnerable to anti-PD-1 therapy. SRTβ1-Ab3/PD-1 combination treatment leads to effective T cell infiltration and expansion, resulting in pronounced tumor regression or tumor control, durable immunological memory, as well as a significant survival benefit.

Importantly, isoform-specific inhibition of TGFβ1 activation by SRTβ1-Ab3 results in an improved preclinical toxicity profile versus non-selective TGFβ pathway inhibition.

In summary, the rationale for targeting TGFβ1 in CBT-resistant tumors is derived from analysis of clinically derived human tumors and associated responses. Collectively, our results point to a potential therapeutic avenue for overcoming primary resistance by selectively targeting TGFβ1, the likely driver of this pathway in many human tumors.

A digital copy of this poster can be accessed at [http://www.scholarrock.com](http://www.scholarrock.com) or by scanning the QR code.