Mechanistically, signaling events leading to the highly tumorigenic (TME) M2 cross-degrade KTX properties, transcriptionally contributes to the tumor 100000 events. STAT3 degraders show anti-immuno-angiogenesis effects, and several STAT3 DCs (including Pd-l1) inhibit proliferation, is lost. These cell-of-degradation checkpoint subsets in Live cells in the tumor, that highly target immunosuppressive cells to the tumor is potent at advanced stage tumors. In preclinical studies, STAT3 degradation downregulates genes involved with immune suppression and reduces production of pro-inflammatory cytokines. STAT3 is a transcription factor dependent gene expression changes in human PBMCs (including IL-2, -10, and 6) vs pre-culture changes. IL-6 increases in human tumors, and reduces production of pro-inflammatory cytokines and tumor-immune interactions. STAT3 has been implicated in mediating tumor stemness. STAT3 is a transcription factor downstream of multiple signaling events including the IL-6/JAK pathway that has been implicated in multiple aspects of tumorigenesis. In addition to increasing cancer cell proliferation and survival, constitutively activated STAT3 is proposed to regulate cross-talk interactions between tumor, stroma and immune cells to promote immune evasion in the tumor microenvironment (TME). STAT3 activity in tumors promotes the production of immune-suppressive factors that activate STAT3 in diverse immune-cell subsets. Mechanistically, genetic studies support a direct role of activated STAT3 in regulating myeloid cell differentiation to contribute to an immuno-suppressed TME. STAT3 is therefore a highly attractive target for immuno-oncology. However, potent and selective agents that specifically and directly target STAT3 have remained elusive.

Kymera Therapeutics is developing degraders of STAT3 with drug-like properties, represented here with KTX-201 and its related compound KTX-104. These compounds potently and selectively degrade STAT3 protein and reverse immuno-suppression in preclinical models.

**Figure 1** - Overview of Targeted Protein Degradation

**Figure 2** - STAT3 Integrates Multiple Upstream Signaling Events To Regulate Tumor Intrinsic and Extrinsic Functions in The TME

**Figure 3** - KTX-201 is a Potent and Selective STAT3 Degradation In human Immune Cells

**Figure 3A** - Degradation of STAT3 in immune cells

**Figure 3B** - Selectivity in PBMCs

**Figure 4** - STAT3 Degradation Downregulates Genes Involved with Immune Suppression in Both Immune and Tumor Cells

**Figure 4A** - STAT3 degradation inhibits IL-6-dependent gene expression changes in human PBMCs (NanoString analysis)

**Figure 4B** - STAT3 degradation downregulates Pd-l1 mRNA in lymphoma (ALK1+ ALL1+). introduces a NA benchmark marker and changes in cytokine signaling (e.g., decrease in IL-6, -10, and -17A and increase in -17B) as well as genes involved with survival and proliferation (e.g., decrease in Myc).

**Figure 5** - STAT3 Degradation Reverses Immuno-Suppression in a Co-Culture Model of the Tumor Microenvironment in NSCLC

**Figure 6** - STAT3 Degradation Enhances Anti-Tumor Activity

**Figure 6A** - STAT3 degraders show anti-tumor activity at well tolerated doses in the syngeneic CT26 model in vivo and in vitro (48h), 1x10^6 cells per injection

**Figure 6B** - Strategy for Pharmacodynamic and Immune phenotyping

**Figure 6C** - STAT3 degrader increases production of pro-tumoral factors (Vcam and -4). STAT3 is a transcription factor downstream of multiple signaling events including the IL-6/JAK pathway that has been implicated in multiple aspects of tumorigenesis. In addition to increasing cancer cell proliferation and survival, constitutively activated STAT3 is proposed to regulate cross-talk interactions between tumor, stroma and immune cells to promote immune evasion in the tumor microenvironment (TME). STAT3 activity in tumors promotes the production of immune-suppressive factors that activate STAT3 in diverse immune-cell subsets. Mechanistically, genetic studies support a direct role of activated STAT3 in regulating myeloid cell differentiation to contribute to an immuno-suppressed TME. STAT3 is therefore a highly attractive target for immuno-oncology. However, potent and selective agents that specifically and directly target STAT3 have remained elusive. Kymera Therapeutics is developing degraders of STAT3 with drug-like properties, represented here with KTX-201 and its related compound KTX-104. These compounds potently and selectively degrade STAT3 protein and reverse immuno-suppression in preclinical models.