Small molecule modulators of the tumor necrosis factor alpha signaling pathway for the inhibition of inflammatory processes and the enhancement of cancer immunotherapy

The research objective of our project is to characterize the mechanism of degradation of the tumor necrosis factor alpha (TNF) by lysosome-targeting chimeras (LYTACs). In particular, we are interested in studying how these TNF-LYTACs modulate the tumor immune microenvironment and whether they could synergize with the immune checkpoint blockade (ICB)-induced responses in cancer.

LYTACs are bifunctional conjugates that bind to both the extracellular domain of the target protein and the cell surface lysosome-targeting receptor. The target protein is then degraded in the lysosome. Elimination of the target protein by protein degradation, using LYTAC molecules, has many advantages. Compared to traditional direct inhibitors that rely on occupancy-driven pharmacology, LYTACs exhibit sub-stoichiometric activity where one LYTACs molecule is capable of inducing multiple rounds of degradation. Deactivation, i.e. removal, of an oncoprotein occurs at lower concentrations compared to traditional small-molecule inhibitors. As a result, LYTACs generally exhibit less toxicity than conventional direct inhibitors.

Our TNF-LYTAC conjugates will be used in immuno-oncology, both alone and in combination with antibodies against immune checkpoint receptors such as PD-L1 and PD-1. Blockade of immune checkpoint receptors (for example, PD-1, PD-L1 or CTLA-4) has revolutionized cancer therapy and have fundamentally changed the treatment regimen and prognosis for many cancers, providing long-term clinical responses and even cures in a subset of cancer patients (Sharma, P., et al. (2021). The Next Decade of Immune Checkpoint Therapy. Cancer Discov. 11, 838–857). It is now used in clinics around the world and was recognized with the 2018 Nobel Prize in Physiology or Medicine to James P. Allison and Tasuku Honjo. Immune checkpoint blockers (ICBs) based on antibodies against the PD-1/PD-L1 pathway are currently the cornerstone of this cancer immunotherapy. Despite the success of immune checkpoint inhibitors, resistance limits the number of patients who can achieve durable responses, and most patients develop immune-related adverse events (irAEs). These include colitis, an inflammatory bowel disease that can be treated with anti-TNF antibodies such as infliximab. The mechanism of irAEs is unclear, but in the case of TNF, it is thought that TNF contributes to resistance to anti-PD-1 therapy. TNF blockers have been shown to enhance the antitumor therapeutic activity of ICBs in mouse models. Reducing TNF expression is considered a promising strategy and has become an area of intense research.

TNF alone is of enormous therapeutic importance. It is a pleiotropic cytokine with both proinflammatory and immunoregulatory functions. TNF is dysregulated in autoimmune diseases such as psoriasis, rheumatoid arthritis, ankylosing spondylitis, and inflammatory bowel disease. In fact, TNF-neutralizing biologics have been in clinical use for decades for the treatment of many inflammatory conditions. There is also increasing evidence that the TNF system plays an important role in the immune aspects of cancer (Chen, A.Y., Wolchok J.D., Bass, A.R. (2021). TNF in the era of immune checkpoint inhibitors: friend or foe? Nat. Rev. Rheumatol. 17, 213–223). Thus, the clinical promise of TNF LYTAC degraders also motivated our studies of their mechanism of action and the role of TNF in cancer.