SELECTED TALK:

Gabrielle Tender

Targeted degradation of tumor associated mucins

Gabrielle S. Tender[1], Kayvon Pedram[1], D. Judy Shon[1], Natalia R. Mantuano[2,3], Jason J. Northey[4], Kevin J. Metcalf[6], Davey Huang[1], Valerie M. Weaver[4,8], Heinz Laübli[2,3], Carolyn R. Bertozzi[1,9]

[1]Stanford University, Department of Chemistry and ChEM-H, Stanford, CA, USA
[2]Cancer Immunology Laboratory, Department of Biomedicine, University Hospital, Basel, Switzerland
[3]Division of Oncology, Department of Internal Medicine, University Hospital, Basel, Switzerland
[4]Center for Bioengineering and Tissue Regeneration, Department of Surgery, University of California, San Francisco (UCSF), San Francisco, CA, USA
[5]Institute for Stem Cell Biology and Regenerative Medicine, Stanford University School of Medicine, Stanford, CA, USA
[6]Ludwig Center for Cancer Stem Cell Research and Medicine, Stanford University School of Medicine, Stanford, CA, USA
[7]Department of Comparative Medicine, Stanford University, Stanford, CA, USA
[8]Departments of Radiation Oncology and Bioengineering and Therapeutic Sciences, Eli and Edythe Broad Center of Regeneration Medicine and Stem Cell Research, and UCSF Helen Diller Comprehensive Cancer Center, University of California San Francisco, San Francisco, CA, USA
[9]Howard Hughes Medical Institute, Stanford, CA, USA

Mucins are densely *O*-glycosylated proteins that have been shown both clinically and experimentally to play important roles in cancer progression. Their upregulation and altered glycosylation status are some of the most common cancer-associated changes, and they are therefore leading prognostic and diagnostic makers for different carcinomas. Mucins adopt a rigid and extended bottle-brush like secondary structure, which has previously been shown to alter membrane biophysics to promote survival in low adhesion settings *in cellulo* and metastasis *in vivo*. The combined glycan and peptide epitopes presented on mucins are also immune inhibitory ligands that reduce immune cell killing when overexpressed.

Despite the multitude of data supporting depletion of mucins as a strategy to reverse tumor progression, mucins have remained canonically undruggable, because they are a large class of proteins with multiple repeated domains and complex biosynthesis. Additionally, many of their effects are driven by the combination of both the glycan epitopes and the underlying amino acid scaffolds. These properties complicate attempts to reverse their tumor progressive effects via small molecule inhibition or antibody blockade.

Here we present a novel way for depletion of cancer associated mucins through engineering and targeting of a protease to cancer cells. In mixed cell assays, we observe specific degradation of mucins on only the target cells. The targeted degrader also specifically reverses both biophysical and immune evasive effects of mucins on only the target cells *in cellulo*. Finally, the targeted degrader reduces tumor burden and metastasis in two different mouse tumor models.