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# **Synthetic bi-functional degraders of $\alpha$ V integrins**

Stanford scientists have invented protein degraders that induce lysosomal degradation of extracellular cargo. These protein degraders can be used to promote the degradation of integrins, which have implications in several fibrotic diseases, and serve as a highly effective therapeutic for patients suffering from fibrosis.

Organ fibrosis is characterized by excessive deposition and accumulation of extracellular matrix (ECM), which ultimately disrupt normal tissue architecture and functions. For example, renal fibrosis affects 800 million people worldwide and dialysis treatment is becoming a significant economic burden. As the principal ECM receptor, integrins are implicated in diverse fibrotic diseases such as renal fibrosis, cardiac fibrosis, hepatic fibrosis, pulmonary fibrosis, cystic fibrosis, and scleroderma fibrosis. Despite the tremendous interest, the development of inhibitors focusing on integrins has faced substantial challenges such as low in vivo efficacy, undesired effects, lack of tissue specificity, and integrin subtype specificity.

Protein degraders of integrins have resulted in the first known class of integrin inactivators that induce degradation of a cell-surface integrin via lysosomal targeting instead of simply blocking integrin activity. Importantly, targeting integrins in this manner addresses the four key challenges mentioned in the previous paragraph. Consequently, inducing degradation of integrins can drastically improve fibrosis treatment efficacy and transform the fibrotic disease medical field.

## **Stage of Development**

Proof of Concept

## **Applications**

- Induced degradation of integrins associated with fibrosis
- Treatment of fibrotic diseases

## Advantages

- Limits undesired effects associated with direct binding of integrins
- Enhanced tissue specificity and subtype selectivity

## Publications

- Loppinet, E., Besser, H. A., Lee, C. E., Zhang, W., Cui, B., & Khosla, C. (2023). [Targeted lysosomal degradation of secreted and cell surface proteins through the LRP-1 pathway](#). Journal of the American Chemical Society, 145(34), 18705-18710.
- Loppinet, E., Besser, H. A., Sewa, A. S., Yang, F. C., Jabri, B., & Khosla, C. (2023). [LRP-1 links post-translational modifications to efficient presentation of celiac disease-specific T cell antigens](#). Cell Chemical Biology, 30(1), 55-68.

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