

**Sequence and Structure Selectivity of Human Lysyl Oxidase-Like 2 (LOXL2)**

L. M. Poller<sup>1</sup>, M. C. Deen<sup>1</sup>, T. Fiala<sup>1</sup>, E. Schönbacher<sup>1</sup>, R. Heeb<sup>1</sup>, H. Wennemers<sup>1\*</sup>

<sup>1</sup>Laboratory of Organic Chemistry, ETH Zurich, D-CHAB, Vladimir-Prelog-Weg 3, 8093, Zurich, Switzerland

Collagen is the dominant structural protein in mammals and its maturation is vital for the integrity of organs and wound healing.<sup>1,2</sup> A key intermediate of collagen biosynthesis and maturation is the so-called tropocollagen.<sup>1</sup> The collagen assembly comprises a proline-rich triple-helical domain and two terminal telopeptide domains which are not assembled into higher-order structures.<sup>1</sup> Tropocollagen undergoes cross-linking into fibrils and fibers. The cross-linking process is induced by the lysyl oxidase enzyme family (LOX and four LOX-like enzymes).<sup>1,2</sup> These copper amine oxidases catalyze the conversion of lysine residues (Lys) to aldehyde-containing allysines that spontaneously undergo aldol and related reactions to form cross-links.<sup>2,3</sup> While the LOX-mediated cross-linking is crucial for the mechanical properties of the extracellular matrix, excessive LOX activity is associated with fibrotic and malignant diseases.<sup>2,3</sup> The isoform LOXL2 is of particular interest as a therapeutic target as it is over-expressed in many types of cancers.<sup>3</sup> In this work, we decipher the sequence and structure selectivity of LOXL2. We will present the selectivity of LOXL2 for Lys derivatives, including Lys-containing single-stranded and triple-helical collagen model peptides.

<sup>1</sup> Matthew D. Shoulders, Ronald T. Raines, *Annual Review of Biochemistry*, **2009**, 78, 929-958.

<sup>2</sup> Matthew R. Aronoff, Paul Hiebert, Nina B. Hentzen, Sabine Werner, Helma Wennemers, *Nature Chemical Biology*, **2021**, 17, 865-871.

<sup>3</sup> Philip C. Trackman, *Expert Opinion on Therapeutic Targets*, **2016**, 20, 935-945.