NMR study of ribosomal protein L35, a therapeutic target for systemic therapy of the rare disease Epidermolysis bullosa

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The rare disease Epidermolysis bullosa (EB) is a genetic spectrum condition causing severe blistering of the skin. One of the variants is caused by a premature termination codon (PTC) mutation of protein laminin β3 (LAMB3-PTC). This results in severe reduction of full length Lamb3 protein and loss of formation of skin anchor proteins. A novel route to increase the synthesis of full length Lamb3 protein employs specialized ribosomes. Targeted alteration of ribosomal protein rpL35/uL29, one of the 80 eukaryotic ribosomal proteins, triggers increase in basal readthrough of the LAMB3-PTC mutation. This results in increased expression of full length Lamb3 protein. Importantly, this customized repair of Lamb3PTC expression is achieved with minimal interference on bulk protein expression [1].

We have over-expressed uniformly ^{15}N labeled, soluble rpL35 in *E. coli* and obtained first 2D solution NMR spektra thereof. These indicate native fold of rpL35, which consists of 60% alpha helical and 40% disordered parts, consistent with crystallographic data [2]. Titration studies of rpL35 with small molecules which might serve as future therapeutic agents for EB have been conducted.

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[1] Bauer, J. W., Brandl, C., Haubenreisser, O., Wimmer, B., Weber, M., Karl, T., Klausegger, A., Breitenbach, M., Hintner, H., von der Haar, T., Tuite, M. F., Breitenbach-Koller, H.; PLOS One, 2013, 8 (7): e67609,

[2] Natchiar, S. K., Myasnikov, A. G., Kratzat, H., Hazemann, I., Klaholz, B. P.; Nature, 2017, 551: 472 - 477