Development of new chemical tools to investigate the lysosomal TRPML1 ion channel

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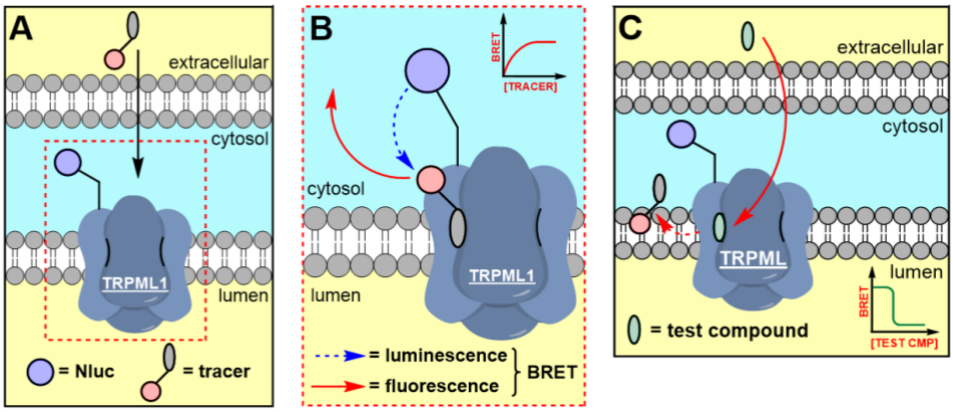
We recently developed a Bioluminescence Resonance Energy Transfer (BRET) [1] assay as a novel technique to investigate the binding of small-molecules to the transmembrane pocket of the human Transient Receptor Potential Mucolipin 1 (*h*TRPML1), a lysosomal ion channel involved in several genetic diseases and cancer progression. To attest the usefulness of this BRET assay, we determined the binding parameters of TRPML1-related compounds [2] as well as novel chemical tools in live cells. Currently, studies of ligand binding to TRPML1 are often performed using mutated or deleted versions of the ion channel that localize to the cell surface [3]. We expect this new assay will accelerate the identification and optimization of potent ligands able to permeate cells and interact with hTRPML1 at the lysosomal membrane.



[1] Hall, M. P., Unch, J., Binkowski, B. F., Valley, M. P., Butler, B. L., Wood, M. G. Otto, P. Zimmerman, K. Vidugirs, G., Machleidt, T., Robers, M. B., Benink, H. A., Eggers, C. T., Slater M. R., Meisenheimer, P. L., Klaubert, D. H., Fan F., Encell, L. P., Wood, K. V. *ACS Chemical Biology*, **2012**, *7*, 1848-1857.

[2] Schmiege, P. Fine, M. Li, X., *Structure*, **2021**, *29*, 1295-1302.

[3] Leser, C. Keller, M. Gerndt, S. Urban, N. Chen, C. C. Schaefer, M. Grimm, C. Bracher, F. *European Journal of Medicinal Chemistry,* **2021,** *210,* 112966.