Development of Small-molecule Inhibitors of Adipose Triglyceride Lipase (ATGL)

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Adipose Triglyceride Lipase (ATGL) is the first and rate-limiting enzyme in the catalytic cascade of lipolysis.[1] Hence, ATGL is primarily responsible for the mobilization of fatty acids (FAs) from cellular triglyceride stores[2] and in consequence the level of circulating FAs.[3] As high levels of serum FAs are closely linked to the development of non-alcoholic fatty liver disease (NAFLD) and insulin resistance, ATGL represents an interesting pharmacological target. This is strongly supported by the results of ATGL knock out studies in mice.[3,4]

Recently, we described the first potent inhibitor of murine ATGL, Atglistatin (IC50 = 0.7 µM). Treatment with Atglistatin effectively reduces FA mobilization *in vitro* and *in vivo*, which leads to a tremendous increase of insulin sensitivity and resistance against the development of NAFLD in mice on a high fat diet. Still, mice showed no loss in muscle weight or accumulation of TGs in ectopic tissue such as skeletal muscle or heart in contrast to ATGL-k.o. mice.[4]

The structure of Atglistatin has been developed from the hit compound in an intense optimization process and is designed to overcome toxicity and solubility issues while increasing potency. It can be produced in a three-step-synthesis. However, Atglistatin inhibits only murine ATGL. To overcome this issue, we are currently working on a 2nd generation inhibitor.

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[1] A. Lass, R. Zimmermann, M. Oberer, R. Zechner, *Prog. Lip. Res.* **2011**, *11*, 14-27.

[2] N. Mayer, M. Schweiger, M. Romauch, G. Grabner, T. Eichmann, E. Fuchs, J. Ivkovic, C. Heier, I. Mrak, A. Lass, G. Höfler, C. Fledelius, R. Zechner, R. Zimmermann, R. Breinbauer, *Nat. Chem. Biol.* **2013**, *9*, 785-787.

[3] N. Mayer, M. Schweiger, M.C. Melcher, C. Fledelius, R. Zechner, R. Zimmermann, R. Breinbauer, *Bioorg. Med. Chem.* **2015**, *23*, 2904-1916.

[4] M. Schweiger, M. Rommauch, G.F. Grabner, R. Schreiber, T.O. Eichmann, S. Yamada, S. Hütter, O. Knittelfelder, C. Diwoky, C. Doler, N. Mayer, W. De Cecco, R. Breinbauer, R. Zimmermann, R. Zechner *Nature Commun.* **2017**, *8*, 14859.