Atglistatin

PRECLINICAL DEVELOPMENT OF SMALL MOLECULE INHIBITORS TARGETING HUMAN ADIPOSE TRIGLYCERIDE LIPASE

Programm / Ausschreibung	Research Studios Austria, Research Studios Austria, RSA - 5. Ausschreibung 2016	**Status**	abgeschlossen
Projektstart	01.05.2017	**Projektende**	31.10.2021
Zeitraum	2017 - 2021	**Projektlaufzeit**	54 Monate
Keywords	type 2 diabetes, liver steatosis, obesity, drug develoment, adipose triglyceride lipase		

Projektbeschreibung

The global burden of obesity and co-morbitidies, such as type 2 diabetes and non-alcoholic fatty liver disease (NAFLD) is increasing worldwide. Successful therapy of these conditions requires effective treatment strategies. The present application focuses on the development of novel anti-diabetic, lipid-lowering, and anti-steatotic drugs. The molecular target is adipose triglyceride lipase (ATGL), the major triglyceride lipase in adipose tissue. This metabolic role marks ATGL as interesting pharmacological target since deregulated fatty acid metabolism is closely linked to dyslipidemia and metabolic disorders listed above.

Numerous studies from our and other laboratories demonstrate that genetic inactivation of ATGL strongly increases insulin sensitivity and counteracts the development of insulin resistance, type 2 diabetes, and NAFLD. Based on these observations, we developed a competitive inhibitor targeting ATGL called Atglistatin® (granted US patent 8,993,509 and several pending patents EP 2414830, EP 14705288.0 and US 61/755,332). Proof-of-concept studies demonstrated that the pharmacological inhibition of ATGL by Atglistatin® prevents or reverses insulin resistance, NAFLD, and obesity in various murine disease models. Accordingly, the pharmacological inhibition of ATGL may represent a novel strategy to treat metabolic disorders.

Currently we focus on the development of human ATGL inhibitors. After finishing proof-of-concept studies in mouse models, we are now in the stage of clinical formulation development. Further preclinical characterization will include a standardized safety data package including pharmacokinetic and toxicological studies. Within the scope of Research Studios Austria, we plan to convert inhibitors into marketable products.

Our mid-term goal is to establish a start-up company [Diabetes and obesity research and application cooperative Styria (DORACS GmbH), based in Graz, Austria] focusing on the development of inhibitors for lipolytic enzymes up to clinical phase 1. The consortium of the company will comprise experts in lipid metabolism, diabetes research, and medicinal chemistry, as well as an experienced business manager in life sciences.

Selected publications:

• Mayer, N., M. Schweiger, M. Romauch, G. F. Grabner, T. O. Eichmann, E. Fuchs, J. Ivkovic, C. Heier, I. Mrak, A. Lass, G. Höfler, C. Fledelius, R. Zechner, R. Zimmermann, and R. Breinbauer. 2013. Development of small-molecule inhibitors targeting adipose triglyceride lipase. Nat. Chem. Biol. 9: 785–7.

• Schreiber, R., P. Hofer, U. Taschler, P. J. Voshol, G. N. Rechberger, P. Kotzbeck, D. Jaeger, K. Preiss-Landl, C. C. Lord, J. M.

Brown, G. Haemmerle, R. Zimmermann, A. Vidal-Puig, and R. Zechner. 2015. Hypophagia and metabolic adaptations in mice with defective ATGL-mediated lipolysis cause resistance to HFD-induced obesity. Proc. Natl. Acad. Sci. U. S. A. 112: 13850–5.

Projektkoordinator

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