Technology offer: Highly selective and high-affinity autophagy inhibitors for development in oncology

The University of Antwerp has discovered the most potent and selective small molecule autophagy inhibitors reported to date. Compounds target autophagy in a highly specific manner, via inhibition of the cysteine protease Atg4B. Target audience for the technology: pharma/biotech partners that are looking for a development candidate in oncology.

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Situation before

In oncology, autophagy has been reported to play distinct and functionally ambiguous roles, depending on the stage of the disease. Inhibition of autophagy has been shown to increase and restore sensitivity to cytotoxic therapy and to promote tumor cell death, both in vitro and in vivo. All currently known autophagy inhibitors have low intrinsic potency and act in a non-specific manner, mostly interfering upstream of autophagosome formation and affecting a variety of processes. Atg4B is a cytosolic enzyme that processes so called Light Chain Proteins (LCPs), essential chaperones for autophagosome formation. Interference with LCP-processing via blocking of Atg4B activity, has been shown to be an effective means for autophagy inhibition. To date, only low-affinity Atg4B inhibitors without practical value in translational settings have been reported in literature.

Technology

Lead compound UAMC-2526 is currently the most advanced candidate for further development. The compound induces complete resistance to starvation-induced autophagy in liver cells of healthy mice. More importantly, in a mouse HT29 tumor xenograft model of human colorectal cancer, the compound significantly increased therapeutic response to the cytostatic standard of care, oxaliplatin. So far, during a 28-day treatment regimen in mice, UAMC-2526 did not cause any observable toxicity. Our data demonstrate that UAMC-2526 could be a very promising candidate for oncology drug development. It has the potential to act as a booster for targeted oncology therapies by increasing and restoring sensitivity to cytotoxic therapy, thereby promoting tumor cell death. We are currently planning further studies where UAMC-2526 is tested in 4 additional models of human cancer. At the same time, we are preparing additional analogues of UAMC-2526 that could serve as eventual back-up candidates.

About the researchers

The Medicinal Chemistry (contact: Prof. P. Van der Veken), the Physiopharmacology (contact: Prof. W. Martinet), the Molecular Imaging Center Antwerp (contact: Prof. S. Stroobants) and the Center for Oncological Research (contact: Prof. M. Peeters) groups have a durable joint multidisciplinary collaboration on inhibitor discovery for Atg4B in the field of oncology. Previous collaborations between these groups have already resulted in several publications and a joint patent application, and combine expertise from three different preclinical disciplines: basic drug discovery, pharmacology and in vivo biology.