

BC INNOVATIONS | TRANSLATION IN BRIEF

GHRELIN'S LEAP FORWARD

BY LAUREN MARTZ, SENIOR WRITER

NGM and MedImmune researchers have discovered a liver peptide, LEAP2, that is a natural antagonist of the metabolic target ghrelin. The peptide could serve as a new handle for either boosting or dampening ghrelin signaling to treat a variety of metabolic conditions ranging from diabetes and obesity to cachexia.

The results are the most recent fruit of a 2013 partnership between the MedImmune LLC unit of AstraZeneca plc (LSE:AZN; NYSE:AZN) and NGM Biopharmaceuticals Inc. to learn more about the hormones involved in the regulation of metabolism and glucose homeostasis.

Ghrelin is well known for its function as the "hunger hormone." It also plays roles in glucose homeostasis, particularly during calorie restriction. At least seven companies are developing analogs of the hormone or modulators of its receptor.

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Last week in *Cell Metabolism*, the partners published data from a study in which they screened obese mice that underwent bariatric surgery for changes in metabolic regulators. They found a 52-fold increase in expression of liver enriched antimicrobial peptide 2 (LEAP2) in the stomach and a 94% decrease in the intestine, compared with sham-operated controls.

Daniel Kaplan, associate director of biology at NGM, told BioCentury the same target was also identified in enteroendocrine (EEC) cells, a small subset of cells in the gastrointestinal tract responsible for producing gastrointestinal hormones such as glucagon-like peptide-1 (GLP-1). The MedImmune partnership was originally designed to develop peptide and antibody drug candidates for Type II diabetes and obesity based on hormones identified in NGM's EEC discovery program.

"LEAP2 popped up in a number of different models, but it really caught our attention in the mouse model of bariatric surgery. It is expressed in EECs, but also in enterocytes," said Kaplan. "In addition to the EEC model, we have a number of different programs focused on hormones including different surgical models," he added.

The group confirmed that LEAP2 plays a role in metabolism and glucose homeostasis, with a series of *in vitro* and *in vivo* studies showing it acts by selectively antagonizing GHSR -- the ghrelin receptor.

Against a panel of GPCRs, LEAP2 selectively antagonized GHSR, and its antagonistic effect was independent of ghrelin concentration, suggesting it is a noncompetitive inhibitor.

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In mice, pretreatment with LEAP2 decreased ghrelin-induced growth hormone release, which occurs downstream of GHSR activation, and completely prevented the ghrelin-induced increase in food intake compared with vehicle. Conversely, anti-LEAP2 antibodies increased growth hormone release in fasted mice, compared with vehicle.

Kaplan told BioCentury next steps might include studying the molecular pharmacology behind the hormone, such as where exactly it binds GHSR and how it works. He added that his group saw counter-regulation of LEAP2 and

GHSR expression in response to surgery and fasting, so studying the underlying feedback mechanisms is important.

He declined to comment on potential ways to increase the safety of targeting LEAP2 or related metabolic systems.

For NGM, the program would add to a solid pipeline of hormone-targeting candidates for treating metabolic and liver diseases. The lead product, NGM282, is an engineered variant of the fibroblast growth factor 19 (FGF19) hormone in Phase II testing to treat nonalcoholic steatohepatitis (NASH) and cholangitis. NGM313, a mAb that agonizes the klotho β (KLB)-fibroblast growth factor receptor 1c isoform (FGFR1c) complex, is in Phase I testing to treat Type II diabetes and obesity.

NGM also has several preclinical programs, including NGM386 and NGM395, engineered variants of growth differentiation factor 15 (GDF15) to treat metabolic conditions including Type II diabetes, obesity and NASH, and NGM120, an antibody antagonist of the GDF15 receptor GDNF family receptor α like (GFRAL) for anorexia and cachexia. The company also has NGM217, a humanized mAb against an undisclosed target for diabetes. Merck & Co. Inc. (NYSE:MRK) has an option to NGM120 and all other programs except NGM282 are partnered with Merck .

Under the deal with MedImmune, the pharma has an exclusive option to license worldwide rights to the candidates. MedImmune will be responsible for further preclinical and clinical development and commercialization of licensed candidates. The biotech received an undisclosed upfront payment and research funding and is eligible for undisclosed milestones and royalties.

Kaplan declined to disclose whether NGM will pursue a LEAP2-based candidate, or whether MedImmune is interested in the program. The IP status of the LEAP2 research is undisclosed. *Ge, X., et al. "LEAP2 Is an endogenous antagonist of the ghrelin receptor." Cell Metabolism (2017)*