Dln101 A Naturally Occurring Ghrelin Splice Variant For The Treatment Of Cachexia

Liat Mintz, DiaLean, Ltd.; liat@dialean.com

INTRODUCTION

Unexplained weight loss is a common and vexing problem in many chronic diseases and can lead to the development of cachexia. There are currently no approved medications for cachexia or frailty. Three therapies are approved for treatment of AIDS-related cachexia (megestrol acetate, somatropin, and dronabinol), but adverse effects and questionable efficacy render them poor choices in many cases.

Ghrelin is a 28–amino acid hormone secreted by the stomach that has been extensively studied since its discovery in 1999. It is the natural ligand of the growth hormone (GH)-secretagogue receptor in the pituitary gland, and it is also the only known circulating orexigen (appetite stimulant) to date. In humans, endogenous ghrelin secretion rises before eating and falls afterward, and exogenous ghrelin stimulates hunger and food intake, inducing weight gain. Ghrelin has been administered successfully to over 400 men and women, to date, including patients with cancer, pulmonary disease, diabetes, renal failure, and heart failure.

Dln101, is a proprietary 24–amino acid, acylated peptide that can be easily manufactured at low cost. Extensive preclinical studies have shown that Dln101 acts similarly to ghrelin in increasing food intake, promoting weight gain, and increasing GH release. These extensive preclinical studies also suggest beneficial effects on lean body mass, cholesterol, and glucose that are specific to Dln101. These positive unique metabolic effects of Dln101 makes it a better candidate for the chronic treatment in diabetes, renal failure, heart failure, cancer and COPD related cachexia. Dln101 has also successfully completed the requisite preclinical toxicology, pharmacokinetic, and pharmocodynamic testing and has received approval to start phase 1 clinical trials.

1

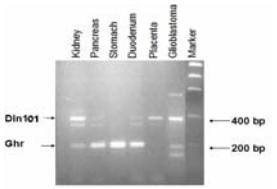


Figure 1: **Human ghrelin mRNA splicing patterns and their respective mRNA variants expression.**
Two splicing patterns of ghrelin mRNA. RT-PCR products. Qualitative RT-PCR was conducted on 6 selected human RNA samples (Stratagene:Kidney, Pancreas, Stomach, Duodenum, Placenta and non commercial A172 glioblastoma cell line). Dln1 and ghrelin (Ghr) cDNA bands, and size markers of 200 and 400 bp are indicated. Interestingly, while ghrelin is predominantly produced and secreted by the stomach and duodenum, the main source of Dln101 appears to be the kidneys and the placenta.

2

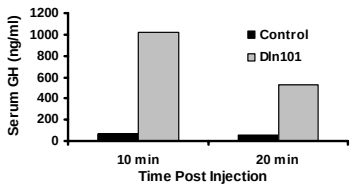


Figure 2: Dln101 stimulates growth hormone (GH) release.
Effect of saline or Dln101 (0.22 µmol kg-1, subcutaneously) on plasma growth hormone at 10 minutes and 20 minutes post injection in 129 SV male mice (n = 5 per group).

3

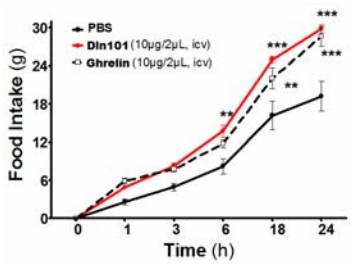
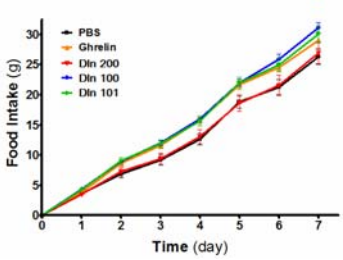
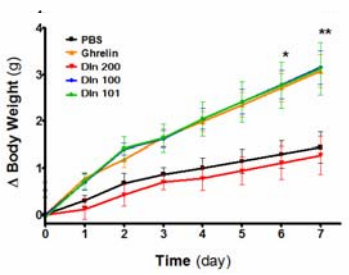


Figure 3: i.c.v. injection of Dln101 increases food intake. Orexigenic effects of i.c.v. injected Dln101 or Ghrelin (10µg of) in male wistar rats (n=9 per group). . **= P<0.01, ***=P<0.001 Two-way ANOVA, Bonferroni *post hoc* test.

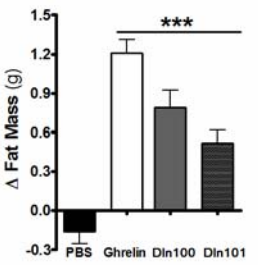
4A



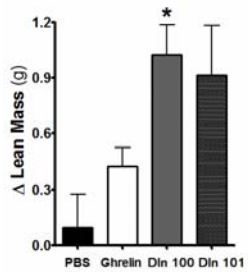
4B



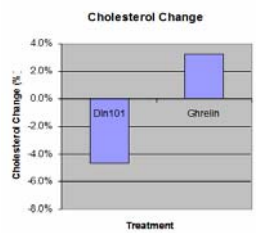
4c



4d



4e



4f

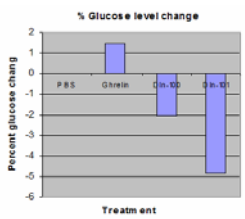


Figure 4: Chronic peripheral administration of Dln 101 increases both fat and lean mass. Effects on food intake (**a**), body weight (**b**), fat mass (**c**), lean mass (**d**) and circulating metabolites (**e&f**) after chronic peripheral (s.c.) injection of Dln100, Dln 101, Dln200 and human Ghrelin (all 7.2mg/kg) in 129 SV male mice (n=8 per group). (**b**) *= P<0.05, **=P<0.01 Two-way ANOVA, Bonferroni *post hoc* test. (**c,d,e,f**) *= P<0.05, **= P<0.01,***=P<0.001 One-way ANOVA, Tukey *post hoc* test.

DIALEAN Peptide therapeutics