Suppression of Carcass Weight Loss in Cachexia in Rats Bearing Leydig Cell Tumor by the Novel Compound NO-1886, a Lipoprotein Lipase Activator

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The Leydig cell tumor has been reported to produce tumor necrosis factor (TNF) and induce cachexia in rats. TNF is thought to reduce lipoprotein lipase (LPL) activity, decrease fat deposits, induce emaciation, and worsen cachexia. Therefore, we thought emaciation might be prevented and thus cachexia improved by increasing LPL activity. We administered NO-1886, a lipoprotein lipase activator, to rats bearing Leydig cell tumor and observed its effect on improving the cachexia induced by the tumor. In Leydig cell tumor–bearing rats, the emaciation progressed after tumor inoculation and the general condition worsened daily. Plasma levels of total protein, albumin, and glucose, which are biological parameters of malnutrition, were found to decrease soon after tumor inoculation in tumor-bearing rats. In contrast, rats given NO-1886 showed less malnutrition than tumor-bearing rats. LPL activity of rat adipose tissue was decreased, the weight of adipose tissue was decreased, carcass weight was reduced, and food consumption was decreased after Leydig cell tumor inoculation. NO-1886 increased adipose tissue LPL activity and suppressed the decrease in the weight of adipose tissue, carcass weight, and food consumption due to cachexia without influencing tumor growth. The present results suggest that the novel compound NO-1886 may suppress carcass weight loss in rats bearing Leydig cell tumor by suppressing the decrease in food consumption and LPL activity.

CACHEXIA is defined as an extreme wasting condition with marked weight loss, anorexia, and lassitude.[1] It is observed in patients with cancer and severe infectious diseases, and is a terminal manifestation of these diseases. It is associated not only with a deterioration of the quality of life but also with shorter survival. However, the causes of the body weight loss, anorexia, and wasting condition that occur during cachexia have not been adequately elucidated. Although it is important to improve cachexia, no appropriate method has been satisfactorily established, and it is expected that an effective drug will be found. Adipose tissue atrophy is marked in cachectic patients and animals. Fat deposition is accomplished by the action of lipoprotein lipase (LPL) in adipose tissue and by de novo lipogenesis in the liver and adipose tissue.[2] LPL activity in adipose tissue has been reported to be depressed in tumor-bearing animals.[2-4] Vlassara et al[5] reported that LPL activity in cancer patients was less than in healthy persons and that the degree of the decrease was closely correlated with the degree of weight loss when LPL activity was determined in the postheparin plasma of 28 patients with cancer associated with weight loss. These phenomena show that cachexia may be improved if a means of elevating LPL activity is found.

Research on cytokines and cachexia has recently advanced, and it has become clear that certain cytokines are involved in the onset of cachexia.[6,7] Tumor necrosis factor (TNF),[6,7] interleukin-1 (IL-1),[8] and IL-6,[9] in particular, are thought to inhibit the activity of LPL, a key enzyme in lipoprotein metabolism, thereby suppressing hydrolysis of very–low-density lipoprotein triglyceride, decreasing the supply of fatty acids to adipose tissue and muscle and eventually inducing weight loss as a result of reduction of fat accumulation in the tissues.

We have found the novel compound NO-1886, which increases LPL activity, and have previously reported the effects of this compound on lipid metabolism and arteriosclerosis in rats.[10,11] The purpose of the present study was to assess the possibility of improving cachexia by increasing LPL activity with NO-1886 in rats bearing Leydig cell tumor.

MATERIALS AND METHODS

Animals

Male Fisher rats were obtained at 4 weeks of age from Charles River Japan (Yokohama, Japan), and were used at 6 weeks, when they weighed 140 to 155 g. The animals were maintained on a 12-hour light/dark cycle at a constant temperature of 23° ± 2°C. They were fed a breeding diet (CRF-1; Oriental Yeast, Tokyo, Japan) and water ad libitum.

Tumor

Leydig cell tumor was provided by the Maryland Research Laboratories of Otsuka America Pharmaceutical (Rockville, MD). Leydig cell tumor was inoculated subcutaneously into the right inguinal flank of the Fisher rats (10^5 cells/rat). The rats were divided into groups according to tumor weight 7 days after tumor inoculation. Administration of the drug was started after grouping.

Drug

NO-1886, diethyl 4-[(4-bromo-2-cyanophenyl)carbamoyl]benzylphosphonate, was synthesized in the New Drug Research Laboratory of Otsuka Pharmaceutical (Tokushima, Japan), and the chemical structure is shown in Fig 1. NO-1886 suspended in 5% gum arabic was orally administered at 100 mg/5 mL/kg body weight in the NO-1886 group. The control group received 5% arabic gum solution alone at 5 mL/kg body weight. A normal group uninoculated with tumor was also prepared, and 5% gum arabic was administered at 5 mL/kg. The period of administration was 35 days.

Biochemical Parameters

Blood samples were collected from some rats under sodium pentobarbital anesthesia 14, 21, and 35 days after cancer inoculation for

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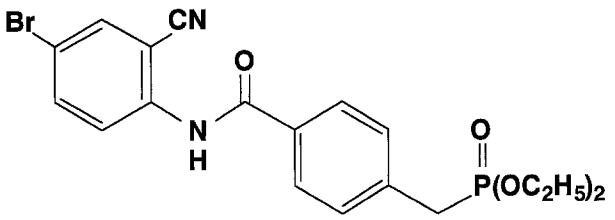

Fig 1. Chemical structure of NO-1886.

nutritional evaluation. Plasma cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, glucose, total protein, and albumin were determined with an Automatic Analyzer (Hitachi 705; Hitachi, Tokyo, Japan).

Tumor Weight, Body Weight, Carcass Weight, and Food Consumption

Body weight, tumor weight, and food consumption were measured once per week. The weight of the tumor was calculated as follows: tumor weight (g) = [longest diameter (cm) × shortest diameter $(cm)^2$]/3. Carcass weight was measured as the difference between the weight of the whole body and tumor. Food consumption was determined in each cage and divided by the number of rats housed per cage to calculate food consumption per animal. Some rats were killed during the experiment for blood collection to determine tumor weight, body weight, carcass weight, and food consumption.

LPL Activity

Epididymal adipose tissue samples were collected in blind fashion at the time of dissection from animals under sodium pentobarbital anesthesia, weighed, and examined for LPL activity on the final day of the experiment. Adipose tissue LPL activity was measured as described by Murase et al.[12] A specimen of epididymal adipose tissue weighing 100 mg was minced into small pieces and placed in Krebs-Ringer bicarbonate buffer (pH 7.4) in the presence of heparin for 60 minutes at 37°C. The incubation medium was then assayed for LPL activity.

Statistical Analysis

The results are expressed as the mean ± SD. Significant differences between the experimental groups were calculated by Dunnett's test.

RESULTS

Biochemical Parameters

When Leydig cell tumor was inoculated into the rats, plasma total protein, albumin, and glucose levels began to decrease 14 days later (Table 1). Plasma cholesterol tended to decrease 35 days after tumor inoculation (Table 2). These findings show that malnutrition develops early (14 days) after inoculation of Leydig cell tumor.

Although there was no difference in plasma HDL cholesterol between tumor-bearing rats and normal rats 14 days after inoculation, it was decreased 8% and 37% at 21 and 35 days, respectively, after tumor inoculation (Table 2). Plasma triglyceride levels in tumor-bearing rats tended to higher than in the normal rats.

Tumor-bearing rats given NO-1886, in contrast, showed decreases in plasma total protein and albumin as in the tumor-bearing control rats, but to a much smaller extent. These findings show that the nutritional condition of rats treated with NO-1886 was better than that of control rats. Plasma cholesterol and HDL cholesterol levels in rats given NO-1886 were higher than in normal rats. Plasma triglyceride levels did not differ after NO-1886 administration.

Tumor Weight, Body Weight, Carcass Weight, and Food Consumption

At the time of dissection of tumor-bearing rats, there were no signs of edema and ascites.

The tumor weight of tumor-bearing control rats showed a daily linear increase starting 14 days after inoculation, and tumor weight accounted for 10%, 17%, and 26% of body weight 21, 28, and 35 days, respectively, after tumor inoculation (Fig 2). Tumor-bearing rats began to become leaner as tumor weight increased, and body weight stopped increasing 21 days after tumor inoculation (Fig 3). Carcass weight started to decrease considerably 28 days after tumor inoculation (Fig 4). Although there was no difference in food consumption between tumor-bearing rats and normal rats for 14 days after tumor inoculation, it decreased daily from 21 days onward. Tumor-bearing rats exhibited 29% less food consumption than normal rats 35 days after tumor inoculation (Fig 5).

Table 1. Plasma Total Protein, Albumin, and Glucose Levels After Tumor Inoculation

Parameter	Days After Tumor Inoculation		
	14	21	35
Total protein (g/dL)			
Normal rats	4.87 ± 0.12 (n = 9)	5.11 ± 0.11 (n = 8)	5.33 ± 0.13 (n = 8)
Tumor-bearing control rats	4.31 ± 0.27† (n = 10)	4.51 ± 0.29† (n = 9)	4.00 ± 0.87† (n = 9)
NO-1886–treated rats	4.51 ± 0.20† (n = 10)	4.61 ± 0.28† (n = 9)	4.49 ± 0.63† (n = 8)
Albumin (g/dL)			
Normal rats	2.68 ± 0.07 (n = 9)	2.78 ± 0.09 (n = 8)	2.88 ± 0.08 (n = 8)
Tumor-bearing control rats	2.26 ± 0.23† (n = 10)	2.31 ± 0.21† (n = 9)	1.89 ± 0.45† (n = 9)
NO-1886–treated rats	2.37 ± 0.19† (n = 10)	2.36 ± 0.18† (n = 9)	2.26 ± 0.43† (n = 8)
Glucose (mg/dL)			
Normal rats	172 ± 8 (n = 9)	179 ± 9 (n = 8)	201 ± 35 (n = 8)
Tumor-bearing control rats	163 ± 8* (n = 10)	162 ± 23 (n = 9)	136 ± 80* (n = 9)
NO-1886–treated rats	164 ± 12 (n = 10)	162 ± 23 (n = 9)	158 ± 51 (n = 8)

NOTE. Data are the mean ± SD.
*$P < .05$, †$P < .01$: *v* normal rats.

Table 2. Plasma Lipid Levels After Tumor Inoculation

Parameter	Days After Tumor Inoculation		
	14	21	35
Cholesterol (mg/dL)			
Normal rats	63 ± 5 (n = 9)	62 ± 8 (n = 8)	62 ± 13 (n = 8)
Tumor-bearing control rats	62 ± 5 (n = 10)	59 ± 6 (n = 9)	56 ± 11 (n = 9)
NO-1886–treated rats	119 ± 8† (n = 10)	113 ± 8† (n = 9)	109 ± 10† (n = 8)
HDL cholesterol (mg/dL)			
Normal rats	61 ± 5 (n = 9)	51 ± 4 (n = 8)	57 ± 2 (n = 8)
Tumor-bearing control rats	61 ± 3 (n = 10)	47 ± 10 (n = 9)	38 ± 16† (n = 9)
NO-1886–treated rats	117 ± 7† (n = 10)	89 ± 18† (n = 9)	95 ± 22† (n = 8)
Triglycerides (mg/dL)			
Normal rats	69 ± 17 (n = 9)	111 ± 36 (n = 8)	155 ± 47 (n = 8)
Tumor-bearing control rats	99 ± 26† (n = 10)	150 ± 70 (n = 9)	142 ± 155 (n = 9)
NO-1886–treated rats	99 ± 33* (n = 10)	166 ± 115 (n = 9)	187 ± 75 (n = 8)

NOTE. Data are the mean ± SD.
*$P < .05$, †$P < .01$: *v* normal rats.

By contrast, tumor-bearing rats given NO-1886 showed approximately the same changes in body weight as the normal rats, and a lesser decrease in carcass weight than the control rats. Food consumption was also approximately the same as in normal rats for 28 days after tumor inoculation, and even at 35 days after inoculation, food consumption was only 10% less than in normal rats. NO-1886 did not suppress the increase in tumor weight.

Weight per Total Fat Depot of Epididymal Adipose Tissue

The total amount of adipose tissue in the body was evaluated on the basis of the weight per total fat depot of epididymal adipose tissue. The weight of epididymal adipose tissue was 71.5% less than in normal rats 35 days after inoculation of Leydig cell tumor. NO-1886 suppressed the reduction in weight per total fat depot of epididymal adipose tissue (Table 3).

LPL Activity of Adipose Tissue

LPL activity of epididymal adipose tissue was 67% less than in normal rats 35 days after inoculation of Leydig cell tumor. NO-1886 suppressed the decrease in LPL activity of epididymal adipose tissue, and maintained the same activity as in normal rats (Table 3).

DISCUSSION

Cachectic patients and cancer-bearing animals show decreases in LPL activity in postheparin plasma and adipose tissue, and a number of reports have indicated that the decrease in LPL activity is presumably attributable to the emaciation in cachexia.[2-5] This suggests that emaciation can be prevented and cachexia improved by suppressing the decrease in LPL activity. However, there have been no reports on the suppression of the decrease in LPL activity and improvement in cachexia. We therefore administered an LPL activator, NO-1886, to a rat model of cachexia to investigate its effects.

There have been almost no animal models that adequately reflect human cachexia. Obeid and Emery[13] have reported that the Leydig cell tumor is a model that resembles human cachexia

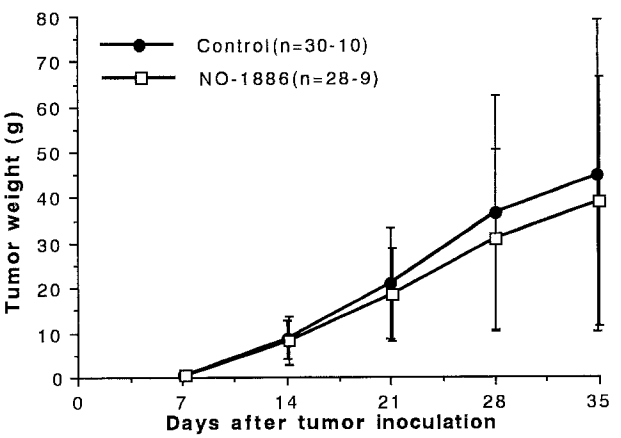

Fig 2. Effect of administration of NO-1886 on tumor weight in Leydig cell tumor–bearing rats. NO-1886 was administered to the rats at a daily dose of 100 mg/kg body weight for 35 days. Tumor-bearing control rats: ●, n = 30, 30, 20, 20, and 11 on days 7, 14, 21, 28, and 35, respectively; tumor-bearing NO-1886–treated rats: □, n = 28, 28, 18, 18, and 9 on days 7, 14, 24, 28, and 35, respectively. Data are the mean ± SD.

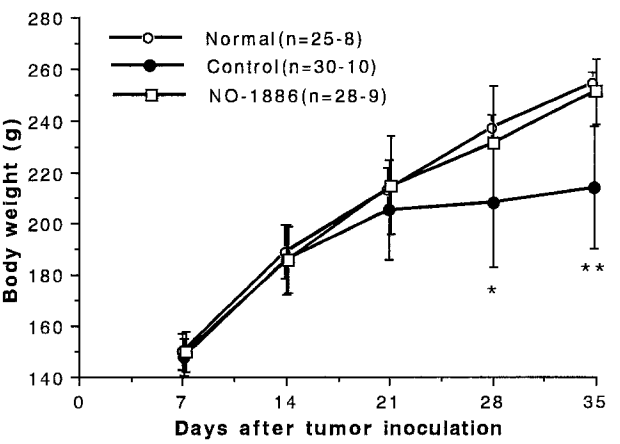

Fig 3. Effect of administration of NO-1886 on body weight in Leydig cell tumor–bearing rats. NO-1886 was administered to the rats at a daily dose of 100 mg/kg body weight for 35 days. Normal rats: ○, n = 25, 25, 16, 16, and 8 on days 7, 14, 21, 28, and 35, respectively; tumor-bearing control rats: ●, n = 30, 30, 20, 20, and 11 on days 7, 14, 21, 28, and 35, respectively; tumor-bearing NO-1886–treated rats: □, n = 28, 28, 18, 18, and 9 on days 7, 14, 21, 28, and 35, respectively. Data are the mean ± SD. *$P < .05$, **$P < 0.01$: *v* normal rats.

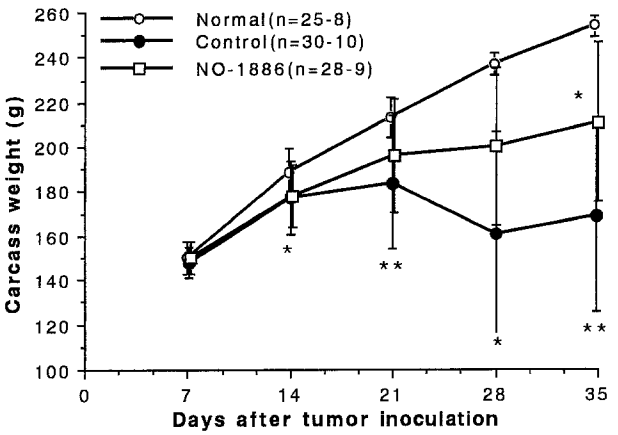

Fig 4. Effect of administration of NO-1886 on carcass weight in Leydig cell tumor–bearing rats. NO-1886 was administered to the rats at a daily dose of 100 mg/kg body weight for 35 days. Carcass weight was measured as the difference between the weigh of the whole body and tumor. Normal rats, ○; tumor-bearing control rats, ●; tumor-bearing NO-1886–treated rats, □. Data are the mean ± SD. *$P < .05$, **$P < .01$: *v* normal rats.

rather well, because the tumor induces a slow progression of anorexia, as well as marked weight loss. Sabatini et al[14] have reported that Leydig cell tumor produces TNF, and TNF induces cachexia. Furthermore, NO-1886 did not suppress TNF and IL-1 production in peritoneal exudate macrophages in experiments using an in vitro assay (H. Nishikawa, unpublished data, January 1994). Therefore, we adopted Leydig cell tumor–bearing rats as the model of cachexia for use in this study.

When Leydig cell tumor was inoculated into the rats, there was an early decrease in plasma total protein and albumin levels 14 days after inoculation followed by a decrease in plasma glucose and HDL cholesterol 35 days after inoculation, with the animals showing signs of malnutrition throughout. Food consumption had not yet decreased 14 days after inoculation. In other words, the malnutrition may have occurred before the

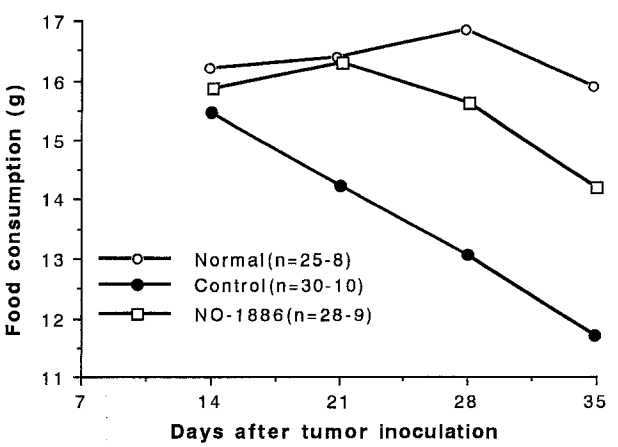

Fig 5. Effect of administration of NO-1886 on food consumption in Leydig cell tumor–bearing rats. NO-1886 was administered to the rats at a daily dose of 100 mg/kg body weight for 35 days. Food consumption was determined in each cage and divided by the number of rats housed per cage to calculate food consumption per animal. Normal rats, ○; tumor-bearing control rats, ●; tumor-bearing NO-1886–treated rats, □. Data are the mean.

Table 3. Effects of NO-1886 on Epididymal Adipose Tissue LPL Activity and Adipose Tissue Wt

Group	LPL Activity (μmol FFA/min/g tissue)	Weight per Total Fat Depot (g)
Normal rats (n = 8)	0.282 ± 0.100	3.30 ± 0.45
Tumor-bearing control rats (n = 10)	0.093 ± 0.074*	0.94 ± 1.11*
NO-1886–treated rats (n = 9)	0.289 ± 0.170	2.02 ± 0.36

NOTE. Data are the mean ± SD.
*$P < .01$ *v* normal rats.

decrease in food consumption. Food consumption started to decrease 21 days after tumor inoculation, and thereafter the rats rapidly became leaner.

One of the causes of cachexia in cancer patients is inadequate food consumption. Exogenous administration of nutrients by intravenous hyperalimentation has been used in an attempt to treat this condition, but no distinct effect has been observed.[15] When megesterol acetate, which possesses the ability to increase appetite, was administered to tumor-bearing mice, there was no increase in carcass weight, but tumor weight increased.[16] When considering these reports along with the present results, it seems difficult to improve cachexia merely by supplying nutrients or administering appetite stimulants without improving the metabolic abnormality.

Based on evaluation by biological parameters, tumor-bearing rats given NO-1886 also exhibited malnutrition similar to that of the tumor-bearing control rats, but the degree was milder. NO-1886 was also found to exert an inhibitory effect on anorexia due to cancer inoculation, but no appetite-stimulating effect has been found even in a long-term treatment study using normal rats.[17] Therefore, NO-1886 probably does not have an effect on the central nervous system. More interestingly, the tumor did not enlarge even when the appetite and anorexia were improved by administration of NO-1886, although we have no data at this time to explain why these phenomena occurred.

In general, there is a positive correlation between LPL activity and plasma HDL cholesterol.[10,18,19] LPL activity may possibly be indirectly evaluated by determining HDL cholesterol. In the present experiment, HDL cholesterol was increased 14 days after administration of NO-1886, implying that NO-1886 increased LPL activity soon after administration to Leydig cell tumor–bearing rats. At 35 days, the LPL activity of rat adipose tissue and adipose tissue weight were decreased by Leydig cell tumor inoculation. NO-1886 increased the LPL activity of adipose tissue that was decreased by Leydig cell tumor inoculation, and the activity was the same as in normal rats. NO-1886 prevented the decreases in adipose tissue weight and carcass weight attributable to Leydig cell tumor. NO-1886 did not affect plasma triglyceride levels in tumor-bearing rats despite increasing adipose tissue LPL activity, because the influence on increasing food intake may have been too considerable compared with control rats.

Fat catabolism in adipose tissue increases and fat synthesis decreases in cachexia. As a result, the total body fat depot decreases. LPL is an enzyme that hydrolyzes triglycerides in the blood and releases fatty acids, that are used for triacylglycerol synthesis by adipocytes. Therefore, the decrease in LPL activity

diminishes the fatty acid supply to adipocytes and decreases the fat depot. On the other hand, some reports have shown that LPL levels are high during obesity.[20,21] The fat depot and body weight would be expected to increase in response to the increase in LPL activity. However, NO-1886 did not increase body weight in the long-term treatment study in normal rats even though it is an LPL activator.[17] Shimada et al[22] have reported that none of the mice in which human LPL gene expression was induced became obese, and that the storage and decomposition of fat were balanced in mice as a result of the increased activity of hormone-sensitive lipase in adipose tissue. In other words, because of homeostasis, body weight may not be increased in normal animals even by an elevation of LPL activity. We calculated the fat pad weight of epididymal adipose tissue divided by carcass weight (F/C ratio) in each group. The F/C ratio was 0.013, 0.006, and 0.010 in normal, tumor-bearing control, and NO-1886–treated rats, respectively. These data show that NO-1886 may simply increase body fatness. In the present experiment, NO-1886 suppressed the decreases in fat weight, carcass weight, and body weight due to tumor inoculation, suggesting that the fat depot may be increased by the increase of LPL activity in cancer-bearing animals. Although NO-1886 did not suppress TNF production (H. Nishikawa, unpublished data, January 1994), it increased LPL activity in adipose tissue, perhaps directly by acting on LPL activity and indirectly by increasing appetite. Further experiments to determine if other mechanisms are involved need to be performed.

The results of the present experiment also show that LPL is involved in the onset of cachexia induced by Leydig cell tumor and that cachexia can be prevented by restoration of LPL activity. Vlassara et al[5] have reported that the postheparin plasma LPL activity of cancer patients who exhibit weight loss is lower than in normal persons, and that the degree of decrease is correlated with the degree of weight loss. When considering the results of our experiment along with the report of Vlassara et al,[5] cachexia may be prevented and improved by increasing LPL activity.

In summary, the novel compound NO-1886 suppressed the decrease in carcass weight and food consumption caused by Leydig cell tumor inoculation. This compound may suppress carcass weight loss in tumor-bearing rats by suppressing the decrease in food consumption and LPL activity. NO-1886 may therefore play a role in improving cachexia caused by cancer.

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