Summary of Lecture

Development of an Anticachexia Therapeutic Agent: Application to Cancer and Renal Failure

Kenneth A. Gruber, Ph.D.
Tensive Controls, Inc.
& University of Missouri-Columbia

Cachexia-anorexia syndrome is a life-threatening aspect to many diseases, including cancer and chronic kidney disease. The symptoms of cachexia are different from malnutrition. The latter is a result of insufficient food intake. Malnutrition is characterized by hunger, whereas a lack of appetite/anorexia is commonly found in patients with cachexia. Malnutrition lowers metabolic rate. In contrast, energy expenditure in cachexia is greater than normal, exceeding any attempt at supplemental calorie administration.

Cachexia produces multi-organ failure due to apoptosis: whole body high metabolic rate initiated “programmed cell suicide.” The loss of skeletal muscle mass (the most obvious symptom of effects on lean body mass) is a metric of the consequences in other organ systems. This effect is not widely appreciated. For example, many anti-cachexia approaches under development target restoration of skeletal muscle mass and strength. Loss of skeletal muscle mass, as opposed to lean body mass, is not a fatal disorder: e.g. Stephen Hawking. Further, significant intestinal effects of cachexia include a reduction of protein absorption, loss of tissue protein content**,** and leakage of bacterial toxins into blood, with the latter effect producing a potentiation of cachexia. Anti-cachexia therapies that only target high metabolic rate effects in a single organ [i.e. skeletal muscle will probably fail as long-term therapeutic agents.

Activation of the central (CNS) melanocortin system appears to be a common mechanism in cachexia. Melanocortin receptor antagonists alleviate cachexia in all experimental models of the disease, including chronic uremia. If the melanocortin system is a critical factor in the etiology of cachexia, then it is a logical drug target.

Previous attempts to develop melanocortin drugs for several medical applications failed due to cardiovascular side effects.

We designed and synthesized a new family of melanocortin receptor antagonist peptides. These compounds lacked cardiovascular activity, produced a reversal of cachexia in several aggressive experimental cachexia models, including renal failure and cancer, suppressed cachexia-induced lethargy, and were orally active.

Safety/efficacy studies of our lead compound (TCMSB07) were performed in normal beagles. Body weight increased during drug administration, consistent with a drug that lowers metabolic rate/enhances energy storage, and was reversed when drug administration ended. Cardiovascular, blood chemistry (MAP, HR, ECGs) values remained within the normal range throughout drug administration.

We are currently performing a canine cachexia clinical trial in client owned dogs. Daily TCMCB07 administration. Canine patients being considered for euthanasia due to a wasting disorder was placed on TCMCB07, and within 6 weeks recovered their lost weight. Their body condition scores from Poor-Emaciated (scores of 4-5) to Ideal to near Ideal (scores of 1-2). The underlying condition that caused the cachexia is still present, but is no longer an immediate threat to a relatively normal life. Our lead compound is a potential candidate for a clinically useful anti-cachexia therapeutic.