Catabolism of Skeletal Muscle Proteins and Its Reversal in Cancer Cachexia

M.J. Tisdale

Department of Cancer Biochemistry, Pharmaceutical Sciences Research Institute, Aston University, Birmingham, UK

Cancer of the pancreas, stomach, lung and colon often leads to a pronounced wasting of body tissues which, if left unchecked, will eventually lead to the death of the patient. This condition, known as cachexia, has been estimated to be responsible for as much as 22% of all cancer deaths [1] and the poor nutritional status also leads to a propensity to infection leading to death by sepsis, the major cause of death in cancer. Patients with cachexia also show a decreased response to chemotherapy, mainly because they are more susceptible to toxicity and thus receive lower doses, rather than any specifically reduced tumor responsiveness to treatment [2]. Patients with weight loss on presentation have a significantly reduced overall survival compared to those without weight loss, and patients who stop losing weight have a better overall survival [2].

Body composition analysis of lung cancer patients who had lost 30% of their pre-illness stable weight showed an 85% fall in total body fat and a 75% fall in skeletal muscle protein mass, when compared with a group of controls matched for age, sex, height and pre-illness stable weight [3]. In contrast with the decrease in skeletal muscle mass there was no change in the visceral protein compartment. Such body composition changes differ from those found in anorexia nervosa, where the major loss is body fat and where the loss of visceral mass is proportional to the loss of skeletal muscle. During long-term starvation muscle mass is preserved by the use of fat as a fuel, even for organs such as the brain, by an adaption to use ketone bodies formed from fatty acids in the liver. This suggests that, although anorexia is commonly associated with cancer cachexia, a reduction in food intake alone is not responsible for this condition.
Loss of skeletal muscle is the most important factor in the poor prognosis of the cancer patient. Its loss results not only in immobility and a poor quality of life, but also in death from hypostatic pneumonia, due to impaired function of the respiratory muscles. Studies on whole body protein kinetics in cancer patients have been variable. Thus while some studies show an increase in whole body protein turnover [4], an increased hepatic protein synthesis [5], an increased muscle protein degradation and a decrease in muscle protein synthesis, others report no change [6]. The major problem in these measurements is that the non-muscle protein compartment is much larger than the muscle protein and may obscure changes in the latter. In the study where no change in total body protein synthesis was observed in weight-losing cancer patients [6], muscle protein synthesis was found to account for only 8% of total body synthesis compared with 53% for healthy controls. The observed maintenance of the total protein synthetic rate in these patients may be due to a twofold increase in nonskeletal muscle protein synthesis, resulting from the increased hepatic production of acute phase proteins.

The increased protein catabolism in cancer cachexia results in an increased urinary nitrogen excretion and to changes in the plasma concentration of amino acids. Most studies have reported a decrease in the concentration of branched chain amino acids in plasma in contrast with the situation in severe malnutrition where the concentration is normal or even increased.

**Model of Cancer Cachexia**

In order to study the mechanism of protein catabolism in cancer cachexia it is necessary to have an appropriate experimental model. Very few experimental tumors produce cachexia, possibly because this characteristic is selected against during the process of transplantation. Our own studies have utilized a transplantable adenocarcinoma of the colon (MAC16) derived from a primary tumor induced by prolonged administration of 1,2-dimethylhydrazine. The tumor is implanted subcutaneously into the flanks of NMRI mice and weight loss starts to appear 10–12 days after transplantation [7]. Weight loss is evident when the tumor mass comprises more than 0.3% of the host body weight and 30% weight loss is evident when the tumor represents just 3% of the body weight. In humans weight loss occurs when the tumor mass represents less than 1% of the body weight and thus this model approximates quite well to the human situation. Some experimental models of cachexia only produce weight loss when the tumor mass represents 10–20% of the body weight and in these cases anorexia is the principal factor. In animals bearing the MAC16 tumor both carcass fat and muscle mass decrease in direct proportion to the weight of the tumor and without a drop food and water intake [7]. This suggests that tumor-derived products may be responsible for the cachexia.
Evidence for such a product was obtained using cell-free extracts of the MAC16 tumor and plasma from tumor-bearing animals, which was found to cause an enhanced release of amino acids from mouse diaphragm [7]. Tumors and plasma from animals without cachexia had no effect, suggesting that some tumors produce a circulating proteolysis-inducing factor (PIF), which may be responsible for some of the systemic effects. Using an in vitro bioassay PIF was also shown to be present in the serum of cancer patients with weight loss, but not in healthy subjects [8]. While 20% of the bioactivity was attributable to interleukin-1, the rest appeared to be mediated by unidentified factors.

**Isolation of PIF**

A number of cytokines including tumor necrosis factor-α (TNF-α) [9], ciliary neurotrophic factor [10] and interleukin-6 [11] have been shown to induce muscle catabolism in vivo. However, with the possible exception of TNF-α [12] there is no evidence for a direct stimulatory effect of the cytokines on protein catabolism in vitro, which could explain the PIF bioactivity found in serum from cachectic animals and man. This suggests that a different, unidentified catabolic factor was responsible for muscle protein degradation in cancer cachexia. Since the MAC16 tumor has been shown to contain the requisite bioactivity [7], this was the starting point in the investigation.

The initial purification was aimed at fractionating a lipid-mobilizing factor (LMF) from the tumor extracts [13]. Bioactivity was determined by the ability to induce glycerol release from freshly isolated murine epididymal adipocytes. Extracts of the MAC16 tumor were fractionated using a combination of ion exchange, exclusion and hydrophobic chromatography. Some animals transplanted with the MAC16 tumor show a delayed weight loss, which may be indicative of an immunological response to a potential cachectic factor. Thus the fractionated material was subjected to Western blotting using serum from such animals. It was found that a band of apparent Mr 24-kD appeared using serum from animals bearing the MAC16 tumor, but not with serum of mice bearing a related tumor (MAC13), which did not produce cachexia. A similar band of Mr 24-kD was apparent in the urine of cancer patients with cachexia using serum from MAC16 mice, but was not detected using serum from mice bearing the MAC13 tumor. These results suggest that the material of Mr 24-kD was related to the development of cachexia.

Next a monoclonal antibody reactive to the material of Mr 24 kD was obtained from hybridomas produced by fusing splenocytes from mice bearing the MAC16 tumor with mouse myeloma cells [14]. This monoclonal antibody was used to isolate pure 24-kD material using a combination of affinity chromatography and reverse phase HPLC [14, 15]. Interestingly the monoclonal antibody did not neutralize lipid-mobilizing activity in an in vitro assay and the pure 24 kD was shown
to have no effect on lipid catabolism in vivo. Instead the 24-kD material enhanced protein degradation in isolated gastrocnemius muscle, an effect attenuated by the monoclonal antibody [14]. This showed that the 24-kD material was in fact PIF rather than LMF and this was confirmed by the ability to selectively deplete lean body mass after intravenous administration to mice [15, 16]. Using Western blotting with the MAC16 monoclonal antibody PIF was found to be present in the urine of patients with carcinoma of the pancreas, breast, ovary, lung, colon, rectum and liver where the weight loss exceeded 1.5 kg/month, but not in cancer patients without weight loss, or in normal subjects [15, 16]. PIF appears to be specifically associated with cancer cachexia, since it was not detected in the urine of patients with weight loss due to major surgery, sepsis, burns, multiple injuries or trypanosome infection. PIF present in the urine of cachectic cancer patients not only provided a marker for the disease, but it was also biologically active producing a state of cachexia in mice, with loss of body weight and specific depletion of lean body mass [16]. As in the MAC16 tumour, weight loss occurred without a reduction in food and water intake, confirming that PIF was purely catabolic and had no effect on energy intake. The effects of human PIF on body composition in mice was reversed by the monoclonal antibody from the MAC16 mice, showing that both human and murine PIFs are structurally identical.

**Structure and Biological Effect of PIF**

Attempts to digest PIF with pronase, chymotrypsin, trypsin or pepsin were unsuccessful [15], suggesting that it was not a typical protein. The molecule, however, was degraded by both peptide-N-glycosidase F and endo-α-N-acetylgalactosaminidase, suggesting the presence of carbohydrate attached to both asparagine and serine residues. Moreover, complete removal of the carbohydrate residues indicated that the central polypeptide chain was only Mr 4 kD [17] and that the majority of the molecule was carbohydrate. Lectin-blotting studies with PIF showed a strong reaction with *Triticum vulgaris*, wheat germ agglutinin, which has specificity predominately for N-acetylglucosamine and *Erythrina crystagalli* agglutinin, which has specificity for Galβ(1→4)-N-acetylglucosamine [14]. There was no evidence for mannose or fucose residues. The carbohydrate chains were also found to be sulfated and digestion with chondroitinase suggested the material to be a sulfated glycoprotein [17]. Biosynthetic labelling studies together with enzymatic digestion was used to determine the size and attachment of the carbohydrate residues to the polypeptide core. These studies suggested a model for the PIF of Mr 24-kD with one O-linked sulfated oligosaccharide chain containing glucosamine and Mr 6 kD, and one N-linked sulfated oligosaccharide chain of Mr 10 kD, also containing glucosamine. Thus most of the structure of PIF resides in the carbohydrate component. The polypeptide core was shown to be phosphory-
lated [17] and showed no structural homology with other materials in the protein data base.

The carbohydrate chains in PIF were found to be responsible for both biological activity and antigenic reactivity [17]. Thus both the ability to initiate protein degradation in isolated gastrocnemius muscle and antibody reactivity were destroyed by incubation with enzymes capable of removing the N- and O-linked oligosaccharide chains.

The body composition changes induced by PIF were similar to those observed in cancer cachexia. Thus there was a significant decrease in the weight of the soleus and gastrocnemius muscles, with no change in the weight of the heart and kidney, but an increase in weight of the liver [18]. The progressive decrease in skeletal muscle mass involved a decrease in muscle protein synthesis and an increase in protein degradation [16, 18].

There are three major proteolytic pathways believed to be responsible for the catabolism of proteins in skeletal muscle. These are the lysosomal, Ca²⁺-activated and ubiquitin-proteasome-dependent pathways. Of the three the first two are responsible for less than 15–20% of total protein breakdown in muscles of both control and cachectic animals, and are not responsible for the degradation of myofibrillar proteins [19]. The ubiquitin-proteasome pathway has been shown to be mainly responsible for the wasting in cachexia and other diseases. In this process ubiquitin is first activated by a ubiquitin-activating enzyme (E1), which then transfers the ubiquitin to a carrier protein (E2), which either ligates the ubiquitin directly to the carrier protein, or does so in the presence of ubiquitin-protein ligase (E3). The rate-limiting step in the pathway appears to be the conjugation mediated by E2. Such proteins marked for degradation by ubiquitin are digested to small peptides within a 20S proteasome particle. The proteasome contains five peptidase activities and consists of four stacked rings, each of which is composed of seven subunits surrounding a central cavity. The process requires ATP both in the formation of the E1 complex, and to unfold protein substrates to enable them to enter the central cavity of the proteasome.

Evidence has been presented for the activation of the ATP-ubiquitin-dependent proteolytic pathway in animals bearing the MAC16 tumor [18]. Increased levels of mRNA were found for the ubiquitin carrier protein and of the C9 proteasome subunit in gastrocnemius muscle. A monoclonal antibody to PIF attenuated the enhanced protein degradation in soleus muscle from mice bearing the MAC16 tumor, confirming that PIF was responsible for the loss of skeletal muscle. This suggests that PIF may enhance protein degradation in skeletal muscle by activation of the ATP-ubiquitin-dependent proteolytic pathway.

Protein degradation initiated in isolated soleus muscle by PIF was associated with a significant elevation in intracellular prostaglandin E₂ (PGE₂) [20]. While some studies have suggested a role for PGE₂ in muscle protein degradation, its role is still somewhat controversial. Nevertheless the PGE₂ production initiated by PIF was inhibited by the monoclonal antibody, which also attenuated muscle
protein breakdown. In addition the polyunsaturated fatty acid (PUFA) eicosapentaenoic acid (EPA) also inhibited protein degradation induced by PIF and attenuated PGE$_2$ production. These results suggest either that PGE$_2$ is an intracellular mediator for protein degradation induced by PIF or that another metabolite of arachidonic acid formed at the same time as PGE$_2$ is responsible.

**Treatment of Cachexia**

The first indication that $\omega$-3 PUFAs such as EPA may be effective in the treatment of cancer cachexia was obtained from experiments with animals bearing the MAC16 tumor, where the carbohydrate component of the diet was substituted with calories derived from fat in the form of fish oil, while maintaining the total caloric intake constant [21]. The diets containing fish oil significantly reduced host body weight loss, with almost complete protection occurring when the fish oil comprised 50% of the calories. The reduction of host body weight loss was associated with an increase in total body fat and muscle mass confirming that the effect was not due to water retention or accumulation of fat alone. The principal PUFAs found in fish oil are EPA (18.7%) and docosahexaenoic acid (DHA; 13.2%). In order to determine which of the PUFAs was responsible for the antica-chectic effect, the action of the individual fatty acids on tumor lipid-mobilizing activity was determined [22]. Bioactivity was found to be specifically inhibited by EPA and other PUFAs such as DHA were found to be ineffective as inhibitors of the lipolytic process. Administration of the pure PUFA to mice bearing the MAC16 tumor confirmed that only EPA effectively attenuated the development of cachexia, while other PUFAs, DHA, $\gamma$-linolenic and linoleic acids were ineffective [22]. Another study using the Lewis lung carcinoma transfected with IL-6 cDNA showed both EPA and DHA to be equieffective in attenuating the development of cachexia in this model [23]. Such differences could reflect differences in the etiology of the cachexia or arise from differences in the administration of the PUFAs. In the MAC16 study the EPA was only administered after the appearance of cachexia (average weight loss 5%), while in the Lewis lung carcinoma study the PUFAs were administered prior to the development of cachexia. Both studies showed EPA to attenuate the catabolism of muscle proteins. In the MAC16 model treatment with EPA was found to significantly reduce protein degradation without an effect on protein synthesis in gastrocnemius muscle [24], while in the Lewis lung model there was a decrease in the level of a ubiquitinated 180-kD protein, suggesting that the effect may be on the ubiquitin-mediated proteolysis system.

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Clinical Studies

Although anorexia frequently accompanies cachexia, it is not possible to attenuate the wasting process by the provision of calories alone. Attempts to increase energy intake through dietary counselling failed to reverse cachexia, and provision of excess calories in the form of total parenteral nutrition only gave a short-term weight gain, suggesting retention of water. Body composition analysis showed a temporary maintenance of body fat stores, but no evidence for preservation of lean body mass [25].

Most studies with pharmacological agents show similar results. Thus studies with the progestational agent, megestrol acetate, an appetite stimulant, showed a significant weight gain of over 5% in only 15% of the patients treated. Increases in lean body mass were not generally observed, and the weight gain arose from an increase in adipose tissue and possibly an increase in body fluid [26]. In a recent trial 54 patients with non-hormone-sensitive cancer who had lost greater than 5% of their pre-illness weight received either placebo or medroxyprogesterone acetate (MPA) over a 12-week period [27]. Treatment with MPA led to an increase in energy intake and an increase in resting energy expenditure, together with an increase in fat mass, without a significant change in fat-free mass.

Clinical studies with EPA have shown it to be effective in attenuating the development of weight loss in patients with unresectable pancreatic cancer, without the limitations of megestrol acetate and MPA. In a trial of 18 patients receiving fish oil capsules equivalent to a dose of 2 g EPA/day, 11 patients experienced weight gain, 3 became weight-stable, and 4 continued to lose weight, but at a reduced rate [28]. Patients had a median weight loss of 2.9 kg/month prior to supplementation and a median weight gain of 0.3 kg/month 3 months after commencement of the fish oil supplement. Anthropometric and body composition analysis showed stabilization of protein and fat reserves, stabilization of resting energy expenditure and a temporary, but significant reduction in acute phase protein production. In contrast patients receiving another PUFA γ-linolenic acid continued to lose weight. Essentially similar results were obtained when pure EPA as the free acid was administered rather than the fish oil capsules, confirming that the anticachectic effect of fish oil resides in the EPA. These studies confirm the ability of EPA to attenuate the development of weight loss in cachectic patients without large weight gain.

However weight gain was seen in a recent pilot study [29] where EPA (2.1 g/day) was administered together with a caloric (589 kcal/day) and protein (30.6 g/day) supplement. Thus at baseline patients were losing weight at a median rate of 2.9 kg/month, but after administration of the EPA-enriched supplement, patients had significant weight gain at both 3 weeks (median 1 kg) and 7 weeks (median 2.5 kg) of treatment. There was no change in percentage body water, suggesting that weight gain was not due to the accumulation of water. Body composition analysis, however, suggested a significant gain in lean body mass, with no change
in fat mass, opposite to what would be expected from nutritional supplementation alone [25]. Both performance status and appetite were significantly improved and the resting energy expenditure per kilogram body weight fell significantly. Such an effect might be expected to be translated into an improved quality of life and an increased survival time and further studies will test this suggestion. However, in a recent unconnected study 60 patients with generalized solid tumors were randomized to receive dietary supplementation with either fish oil (3.06 g EPA/day and 2.07 g DHA/day) or placebo until death [30]. Each group included 15 well-nourished and 15 malnourished patients. As expected the mean survival time was found to be significantly higher for the subgroup of well-nourished patients, but administration of ω–3 fatty acids was found to prolong the survival of both well-nourished and malnourished patients. These results suggest that EPA may prolong survival in cancer patients as well as reversing the progress of cachexia. Since the action of EPA is to reverse the effect of PIF, which is common to cachexia in a range of carcinomas, the results suggest that EPA may be effective against a broad range of tumor types.

**Conclusion**

Knowledge of the mechanism of cancer cachexia will present fresh opportunities for pharmacological intervention in the treatment of cachexia. Such treatments would be expected to benefit patients not only in an improved quality of life, but also an extended survival time. The relationship between tumor growth and cachexia is not known, but it is possible that catabolism of adipose tissue and skeletal muscle could provide the tumor with essential fatty acids and amino acids vital to tumor growth and metabolism. Understanding the nature of tumor catabolic factors and their action on host tissues may provide important insight into the functioning of solid tumors.

**References**


Discussion

*Dr. Baracos:* How far away are we from a readily available assay, so that I can go into a ward, collect urine from a cancer patient, measure this in an assay with a quick turnaround, and apply an appropriate treatment?

*Dr. Tisdale:* We’ve not tried doing it on a large scale. Our laboratory has done Western analysis of urines from all over the world, and we’ve sent the antibody out, but Western blotting is not the easiest way of measuring anything. You are probably aware of work that’s being done in the USA using capillary electrophoresis/mass spectrometry [1]. Again, this is not the sort of technique that every laboratory would have – not every laboratory has a mass spectrometer. So the answer to your question is that we’ve not spent a lot of effort in refining the assay so that every laboratory could do it, but I’m sure that with an antibody we can label the proteolysis-inhibiting factor (PIF). In fact, we do it biosynthetically by feeding the cells labeled sugars to make labeled PIF. We could develop a radioimmunoassay fairly easily, but the answer to your question is, we haven’t done it.

*Dr. Go:* Have you looked at any other epithelial tumors, particularly in patients who are cachectic with prostatic, lung, or colonic tumors – in fact any other tumor apart from pancreatic cancer?

*Dr. Tisdale:* Yes, PIF does occur in other cancers. We’ve tested a range of epithelial tumors, not only pancreatic. The reason for using pancreatic tumors is that you are more likely to get a positive result with those, but we’ve also investigated patients with lung, breast, colonic, rectal, ovarian, and cervical cancer. If the patient is losing weight, then there’s PIF in the urine; if the patient isn’t losing weight, there’s no PIF in the urine. We’ve looked at a number of other weight-losing conditions, though not AIDS, and in those conditions we can’t find PIF.

*Dr. Go:* How is PIF regulated? I’m interested in the metabolic aspects of it. It seems to play such an important role in muscle metabolism.

*Dr. Tisdale:* We don’t really know. We know it’s present in the cytosol, and we’ve done some preliminary experiments that suggest that it is upregulated by cytokines. The peptide core of the PIF is identical to that of a protein that is produced under oxidative stress, and it may be that oxidative stress induces it. This could explain why patients with cachexia can’t tolerate chemotherapy; they have to be given much lower doses of the drug than patients without cachexia. Possibly the chemotherapy will induce oxidative stress and make the situation worse, but a lot more work needs to be done to answer that question.

*Dr. Go:* We have had long discussions in our center about lean body mass. You were able to show that lean body mass increases after giving eicosapentaenoic acid (EPA), presumably without any specific additional exercise. The key question is, what happens if you exercise as well? And if you could do that, could you reverse the cachexia process, with or without further chemotherapy?

*Dr. Tisdale:* We haven’t specifically asked the patients to do any exercise, and I’ve lost contact with the patients in the supplement trial, so I don’t know. Certainly when we started to do this, we found that some of the patients returned to work, so they were presumably getting some exercise. The clinical trial was done in Scotland on the east coast, and some of the people that came were farmers or crofters even, who were working a 12-hour day. Some of these patients returned to normal farm work, so they were certainly getting a lot of exercise, but we didn’t specifically obtain any exercise measurements.

*Dr. Biswal:* How much difference was there in survival in the patients who were given supplemental EPA in your study?

*Dr. Tisdale:* I only hinted at that because we haven’t done the proper placebo-controlled trial. The trials so far have been phase 1 and phase 2, where there was no control. Average survival of such patients in the hospital is 4.1 months, while the patients on the trial had an average survival of about 8 months, but without a control group this is meaningless. We
need to have double-blind randomization in order to be able to say definitely that the survival time was increased.

Dr. Waitzberg: In relation to the EPA study, I would like to know how lean body mass was measured, and whether docosahexaenoic acid (DHA) was studied in addition to EPA.

Dr. Tisdale: Lean body mass was measured by bioelectric impedance analysis. There have been no clinical studies of DHA. In the MAC16 model we found that DHA was not effective compared with EPA, but we need to remember that this is an acute model. The mice are transplanted with the tumor and they start to lose weight by day 12, after which they will lose 30% of their body weight within 5 days. If an agent is not very effective, if it takes a time for the plasma levels to build up, then it won’t work in this acute model. It has got to achieve maximum efficacy within 24 h if it is to work. It may be that DHA would also be effective in patients, but there has been no separate study.

Dr. Hursting: I was wondering if you’d looked at any other arachidonate modulators?

Dr. Tisdale: Yes, we have. Other arachidonic acid modulators are also effective in the treatment of cachexia. We’ve tried indomethacin in our mouse model, but it tends to be toxic. Ibuprofen has been tested in pancreatic patients and produces an effect somewhat similar to EPA. The nice thing about EPA though, compared with any drug, is that you don’t have to worry about the pharmacokinetics; it’s incorporated into plasma phospholipids and therefore you can maintain a good plasma level to get your biological effect, as compared with nonsteroidal anti-inflammatory agents, and you don’t get the side effects that you get with them.

Dr. Hursting: Do you think it’s a Cox 2-mediated process?

Dr. Tisdale: Yes. There’s an experimental drug from Boehringer that we’ve tested which is a specific Cox 2, and that also has an effect. But I should say that the lipo-oxygenase inhibitors are much more effective than cyclo-oxygenase inhibitors. I think that’s because you have cross-reactivity between inhibitors of two pathways that the Cox inhibitors are also effective in the model.

Dr. Meier: How many grams a day of EPA was given?

Dr. Tisdale: From the mouse study we predicted that a patient would require about 5 g of EPA a day, based on the surface area calculation used for working out cytotoxic drug dosage. The study with pure EPA was done using between 2 and 6 g, and it seemed efficacious even at 2 g. As I said, the model we use is fairly acute, so in the current study we are using only 2 g EPA/day.

Dr. Meier: 2 g/kg body weight?

Dr. Tisdale: No, 2 g per person per day.

Dr. Benes: You said there was a reduction in resting energy expenditure in the patients treated with EPA. Did you measure that by indirect calorimetry, and what was the difference before treatment and after treatment?

Dr. Tisdale: I can’t answer that in great detail. This was part of the clinical study, and we only did the laboratory experiments. But yes, it was measured by indirect calorimetry. I don’t know the before and after values.

Dr. Nitenberg: What proportion of the total fat intake was given as EPA, and were there any side effects?

Dr. Tisdale: We gave EPA as a supplement. We weren’t concerned to calculate the intake as a proportion of the total lipids in this phase-1 trial. It was just given like a cytotoxic drug. There were no side effects.

Dr. Nitenberg: What about the possibility that EPA increases membrane fluidity and increases the sensitivity of cells to cytokine actions? Do you have any data on that?

Dr. Tisdale: I think the nice thing about EPA is it can act in a lot of ways, and therefore I’m not excluding other mechanisms by which it might be efficacious, but we know that in our model there’s no cytokine involvement, yet it works. It seems to have a direct effect on the increased expression of the components of the ATP-ubiquitin-dependent pathway. But it could also attenuate other agents that act on that pathway, cytokines for instance.
Dr. Ang: Were these patients receiving chemotherapy or not?

Dr. Tisdale: No. None of the patients received any treatment. They were all patients who were admitted to the department of surgery at the Royal Infirmary in Edinburgh with pancreatic cancers that were nonresectable. In the UK no treatment is given to those patients. We don’t give them chemotherapy unless they are recruited into a trial, because routine chemotherapy is not thought to be effective in prolonging life or improving the quality of life of patients with pancreatic cancer. I know our colleagues in the USA would disagree with that, but in the UK we reckon the best treatment is nothing.

Dr. Go: Is PIF found in the cachexia of old age?

Dr. Tisdale: We haven’t looked specifically at old people, but we have a hypothesis. We can find receptors for PIF on normal skeletal muscle, but we only find PIF itself in cancer cachexia, so why should ordinary skeletal muscle have the receptor? The only possible reason is that there’s another product produced under conditions of muscle protein degradation that acts through the same pathway. So once we’ve isolated the receptor we’re hoping to find the natural agonist which is responsible for breakdown of skeletal muscle in other conditions. My feeling is that it will be similar but not the same as PIF.

Reference