Actimed Therapeutics
actimedtherapeutics.com

The cancer cachexia company in the making

Actimed Therapeutics is developing anabolic/catabolic transforming agents: a new class of agents to treat cachexia, an often fatal condition associated with many chronic diseases including cancer.

Cachexia is a serious yet under-recognized consequence of many chronic diseases, including heart disease, kidney disease, chronic obstructive pulmonary disease and, most notably, cancer. The pathophysiology and etiology is complex but has been shown to involve failure of normal anabolic drive and responsiveness, accentuated catabolism, immune dysfunction and neurohormonal over-activity. Given the complexity of these overlapping pathophysiological pathways, it is unlikely that selective intervention in any single pathway can reverse cachexia.

Patients suffer weight loss, anemia and other symptoms that diminish their quality of life and drive negative outcomes. In the absence of effective therapies, cachexia accounts for an estimated 20% of all cancer deaths[1]. The condition is a major unmet medical need. Actimed Therapeutics is working to address this major unmet medical need by developing a new class of agents to treat cancer cachexia.

The potential for a new class of agents is illustrated by cachexia statistics. Between 50% and 80% of patients with cancer suffer from cachexia[1], equating to 9–14.5 million cases of cachexia globally in new cancer patients each year. Cachexia ultimately kills a significant proportion of those patients. In colorectal cancer, weight loss of 10% or more is associated with a 3.3-fold higher probability of death[2]. The presence of cachexia is also a strong predictor of poorer survival in patients with lung cancer[3]. Furthermore, it can reduce tolerability to and response to both chemotherapeutic and radiotherapeutic regimens[4,5].

The American Society of Clinical Oncology (ASCO) has identified the management of cachexia as an opportunity to 'improve treatment tolerability, improve survival, and optimize the quality of life of patients with advanced cancer'. However, in its guidelines on the treatment of cachexia, ASCO said the absence of robust evidence makes it impossible to recommend any pharmacological interventions, highlighting the need for a new class of effective agents[6].

As patients with other chronic diseases—including kidney, cardiovascular and respiratory diseases—also suffer from cachexia, the lack of effective therapies is negatively affecting the lives and health outcomes of many millions of people every year. Researchers that want to bring relief to those patients need to grapple with the complexity of cachexia.

Treating a multifactorial disorder

Cachexia is a multifactorial disorder with a complex pathophysiology involving alterations in homeostatic control of energy balance, food intake, body composition and cellular growth/death control. It can also cause an increase in drug side effects and altered metabolism. The primary driver is an imbalance between catabolism (the breakdown of tissues such as muscle or fat) and anabolism (the build-up of tissue). This imbalance occurs against a backdrop of poor appetite and reduced food intake in many patients, as well as a general state of inflammation.

Researchers have previously tried to treat cachexia using molecules that promote pro-anabolic activity. Knowledge of the role the build-up of tissue plays in the pathogenesis of cachexia suggests pro-anabolic therapies could do some good. Yet, while the molecules promote anabolic activity, they are unable to address catabolism, leaving a key part of the pathophysiology of cachexia unaffected. Molecules that are both anti-catabolic and pro-anabolic are needed.

S-pindolol, lab-code ACM-001 (previously called MT-102), may be such a molecule. This drug candidate is the first example of a new class of agents—the anabolic/catabolic transforming agents (ACTAs)—that are designed to address the complex pathophysiology that defines cachexia[7]. ACTAs directly target the pathophysiology of cachexia in three different, complementary ways to correct the disease-driving metabolic imbalance and thereby save muscle and fat tissue while improving appetite.

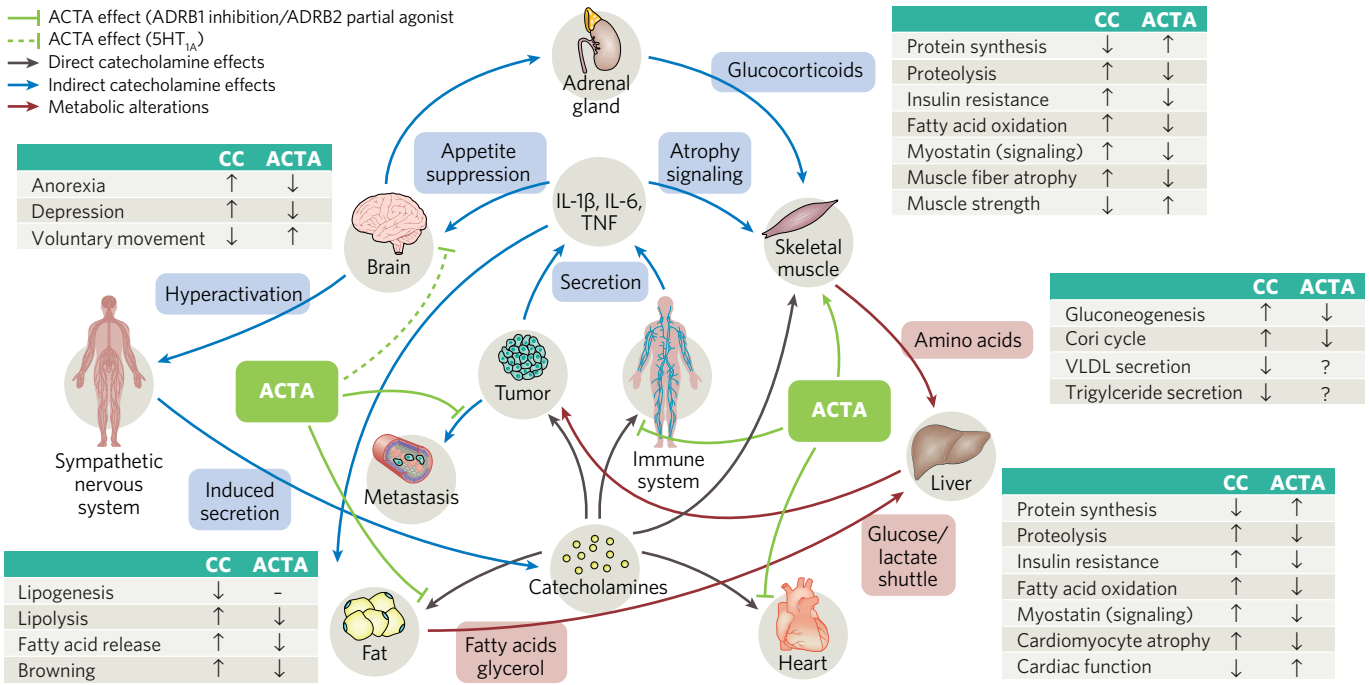

Fig. 1 | Hypothesized mode of action of the anabolic-catabolic transforming agents in reducing cancer cachexia. ACTA, anabolic-catabolic transforming agent; ADRB, β-adrenergic receptor; CC, cancer cachexia; IL, interleukin; TNF, tumor necrosis factor; VLDL, very low-density lipoprotein.

It has been observed in nonclinical models that, firstly, S-pindolol reduces catabolism via non-selective β-blockade. Secondly, it increases anabolism via partial β2-agonism[8]. Finally, it helps reduce fatigue and increase appetite via central 5-HT1A activity[9]. The ability of ACTAs to act on several elements of the disease causality, and thereby directly address the causes of cancer cachexia via multiple routes, potentially makes lead candidate S-pindolol and the broader class unique among the products currently in development (Fig. 1).

The ACTAs have other characteristics that make them attractive drug candidates. For example, S-pindolol is being developed as an oral dosage form for storage and transport under ambient conditions, thereby increasing patient convenience and limiting the burden on supply chains.

Andrew Coats and Stefan Anker, world-leading physicians in cachexia research, co-founded Actimed in 2017 to realize the potential of ACTAs. Coats is joint professor in the faculties of medicine at the University of Warwick, UK and Monash University in Melbourne, Australia. Anker is a professor of tissue homeostasis at Charité University Hospital, Berlin. Having recruited a management team and board, Actimed is now building on early evidence of the efficacy of S-pindolol.

Validating a new class of agents

Researchers first demonstrated the potential utility of S-pindolol in cachexia in preclinical models of cancer cachexia, including in studies that linked the drug to increased survival. In one study, S-pindolol outperformed the β-blocker bisoprolol and the angiotensin-converting enzyme inhibitor imidapril (which itself had been tested in a phase 3 cachexia trial) in terms of lean muscle tissue gain, physical activity, appetite and survival in a rat model of cancer cachexia.

In another study, aged rats gained weight, particularly lean mass, after taking S-pindolol, providing yet more evidence of the potential of the compound to prevent and reverse muscle wasting[8]. This study also generated data to support the mechanism of action of S-pindolol, linking use of the molecule to reduced expression of key catabolic regulators and decreased proteasome and caspase 3 proteolytic activities.

This early-stage pre-clinical work supported the advance of S-pindolol into clinical development and a phase 2a proof-of-concept study of S-pindolol has been conducted (ACT-ONE)[10]. A total of 87 patients with late-stage colorectal or non-small-cell lung cancer (NSCLC) who had been diagnosed with cachexia were enrolled into this study and were randomized to receive either 10 mg S-pindolol, 2.5 mg S-pindolol or placebo, each administered orally twice daily.

Over the 4 month duration of ACT-ONE, subjects on the twice-daily 10 mg dose of S-pindolol had a median weight gain of 2.83 kg, compared with a median weight loss of 0.99 kg in the placebo cohort, a statistically significant difference. This difference meant that ACT-ONE met the primary end point of the rate of weight change over a 16-week period.

Subjects on the high dose of S-pindolol also performed better against placebo in multiple secondary end points. Lean body mass increased significantly in the high dose arm, as did an important measure of muscle function; hand grip strength. Such improvement in muscle function could translate into outcomes important for the quality of life and independence of patients with cancer, such as walking or their ability to climb stairs.

S-pindolol was generally well tolerated in this population of patients with advanced cancer, although an excess of dsypnea was observed in patients treated with S-pindolol. The safety profile seen in the ACT-ONE trial has added to the reassurance provided by results from two earlier phase 2 clinical trials of S-pindolol in functional dyspepsia and irritable bowel syndrome.

ACT-ONE: Median weight change over 4 months (mITT)[1]

Median weight change (kg) [IQR] at Day 112

High-dose S-pindolol	= +2.83 [1.00–3.68]
Low-dose S-pindolol	= +0.10 [−1.31–2.75]
Placebo	= −0.99 [−3.97–1.52]

High-dose S-pindolol vs placebo
*P = 0.0010

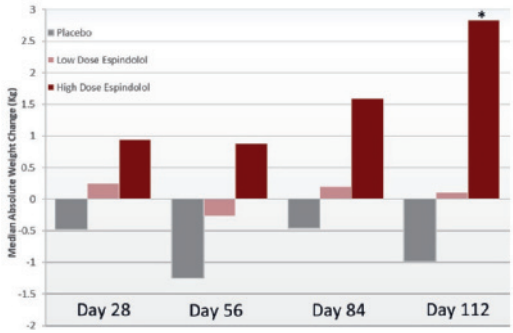

Fig. 2 | ACT-ONE: S-pindolol, successful proof-of-concept trial[10].

Future S-pindolol clinical development program

Actimed has the global rights to S-pindolol and has funded the development work to date using the proceeds of a £1.25 million seed A round. A seed B round is ongoing and Actimed is preparing to run a global clinical development program to further validate the ACTAs in the treatment of cachexia. The planned development program will feature a pharmacodynamic/pharmacokinetic and dose-ranging study, followed by a phase 2b study of S-pindolol in patients with NSCLC or colorectal cancer.

The NSCLC and colorectal cancer cachexia indications that Actimed plans to target in its phase 2b program represent major opportunities. The addressable market for cachexia in NSCLC and colorectal cancer alone in the USA and European Union is conservatively estimated at between $3 billion and $4 billion. Actimed has plans to unlock further opportunities by developing S-pindolol in other cancers and sarcopenia without cachexia.

Actimed's pipeline also features a preclinical prospect, S-oxprenolol. Like S-pindolol, S-oxprenolol is an ACTA, potentially targeting anabolism, catabolism, and fatigue and appetite, the three key biological mechanisms related to cachexia. Actimed has the global rights to S-oxprenolol in cancer cachexia.

In addition, S-oxprenolol has also exhibited a positive effect in animal studies on amyotrophic lateral sclerosis (ALS). Actimed also owns the global rights for S-oxprenolol in ALS and is investigating the potential to develop the compound for this indication.

With both S-pindolol and S-oxprenolol, Actimed has the opportunity to develop effective treatments for cancer cachexia and other muscle-wasting conditions, which have the potential to bring multiple benefits to patients and the health-care systems that treat them.

Building the cancer cachexia company

Treating cachexia has the potential to prolong the independence and improve the quality of life of patients with cancer, for example, by delaying or preventing hospitalization. In doing so, an effective cachexia therapy could reduce health-care costs. Treating cachexia may also improve the tolerance of patients to their anti-cancer therapies, and could enable more patients to receive the sustained, effective doses they need to shrink their tumors and potentially improve their survival.

Actimed is uniquely well positioned to deliver those benefits. In the ACTAs, Actimed has a new class of therapeutic agents[7] that, for the first time, have the potential to equip physicians to tackle the complex pathophysiology of cachexia, rather than simply acting on one element of this multifactorial disease. The rationale for using the ACTAs was validated in the phase 2a ACT-ONE trial given the magnitude and highly significant effect in body weight gain observed[10].

Actimed is committed to developing its portfolio further. The company will draw on the expertise of its founders, who are world-leading physicians in cachexia and other muscle-wasting diseases, and a management team and board that is well versed in pharmaceutical development and commercialization.

The combination of this deep expertise and the unique properties of the ACTAs[7] positions Actimed to deliver on its central mission to improve the lives of millions of patients by developing medicines that establish it as the cancer cachexia company.

1. Argilés, J. M. et al. *Nat. Rev. Cancer* **14**, 754–762 (2014).
2. Zacharakis, M. et al. *Anticancer Res.* **30**, 653–660 (2010).
3. Shiono, M. et al. *Cancer Med.* **5**, 2641–2648 (2016).
4. Dewys, W. D. et al. *Am. J. Med.* **69**, 491–497 (1980).
5. Ross, P. J. et al. *Br. J. Cancer* **90**, 1905–1911 (2004).
6. Roeland, E. J. et al. *J. Clin. Oncol.* **38**, 2438–2453 (2020).
7. Ebner, N. et al. *Maturitas* **75**, 199–206 (2013).
8. Pötsch, M. S. et al. *J. Cachexia Sarcopenia Muscle* **5**, 149–158 (2014).
9. Newman-Tancredi, A. et al. *Neuropsychopharmacology* **18**, 395–398 (1998).
10. Stewart Coats, A. J. et al. *J. Cachexia Sarcopenia Muscle* **7**, 355–365 (2016).

CONTACT
Actimed Therapeutics
Ascot, Berkshire, UK
Email: info@actimedtherapeutics.com