

## COMMENTARY

## Wasting away: How to treat cachexia and muscle wasting in chronic disease?

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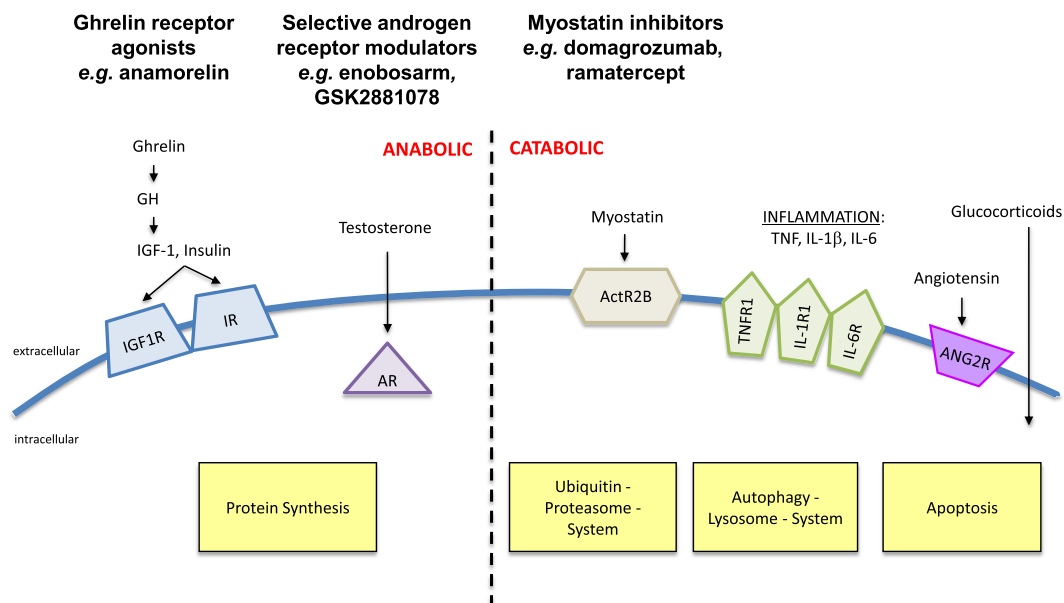
Muscle wasting is an extremely common feature of several chronic diseases associated with inflammatory activation. It can be part of a wasting syndrome known as cachexia [1, 2]. The defining feature of cachexia is overt weight loss, but muscle wasting can also become prevalent without weight loss being detectable. This notion is important, because it highlights the necessity to not only measure weight, but also to assess strength as well as functional and exercise capacity in patients with advanced chronic disease, but also in healthy elderly subjects [3, 4]. Relevant illnesses include, for example, chronic heart failure [5], chronic kidney disease [6], chronic obstructive pulmonary disease [7], rheumatoid arthritis [8], and cancer [9]. Considering these conditions alone, it has been estimated that the number of patients at risk of developing cachexia is 17.5 million in Europe, whereas the number of patients actually being cachectic is close to 4 million [10].

Muscle wasting can be diagnosed, but it is more easily overlooked. Screening measures include the assessment of handgrip strength, the 6-minute corridor walk test, or simple tools such as the short physical performance battery test. All of these are easily performed and take 30 s to no more than 10 min. However, the chances for the patient to actively complain about loss of strength are relatively low, and many elderly subjects consider loss of strength part of the normal ageing process rather than part of advancing disease. Measures to tackle the loss of muscle and strength and, thus, quality of life include nutritional interventions, exercise and, possibly, pharmacotherapy [11–13]. The most promising drug classes in this regard that have seen research endeavour in recent years include myostatin inhibitors, ghrelin receptor agonists, selective androgen receptor modulators and anabolic steroids such as testosterone.

Testosterone was originally described by Károly David and colleagues in 1935 [14]. Its primary site of synthesis are the Leydig cells of the testis, and smaller amounts are released from the adrenal cortex and the ovaries. Therefore, plasma levels of testosterone in men are 10 times higher than those

in women [15]. Testosterone became available for therapeutic use as an injectable drug in the 1940s. In the 1970s, an orally available formulation was approved. Testosterone is metabolized to dihydrotestosterone and estradiol, both of which have feedback effects on luteinizing hormone secretion. This point is worth stressing, because some of the undesired effects of testosterone may be due to the formation of metabolites, rather than due to the effects of testosterone itself. Since steroid receptors just like the androgen receptor are expressed close to ubiquitously in humans, their blockade or activation can be associated with untoward effects. For example, supraphysiological testosterone levels have been associated with acne, dyslipidaemia, sleep apnoea, left ventricular hypertrophy, sodium and water retention, increases in renin-angiotensin-aldosterone system activity and blood pressure as well as increases in erythropoiesis [15–17]. In addition, testosterone administration has been associated with increased cardiovascular mortality, prostate cancer and hepatic toxicity [15, 18, 19]. On the other hand, testosterone can induce bone and muscle growth ultimately leading to increases in strength [20]. Side effects of testosterone have mainly been described in patients who abuse the drug. In clinical settings, adverse effects have generally been mild and reversible [15]. The mixture of desired and undesired effects is present in all steroids; however, it led to the idea of developing selective steroid receptor modulators (Figure 1) [21]. The best known example in clinical use in this regard is tamoxifen, which functions as an oestrogen receptor antagonist in the breast and as an agonist in the uterus. Such selective receptor modulators have been in clinical development also as selective glucocorticoid receptor modulators, selective progesterone receptor modulators and selective androgen receptor modulators [21].

In a recent issue of *BJCP*, Clark and colleagues present a Phase I study of a novel selective androgen receptor modulator (SARM) named GSK2881078 [22]. With the European Medicines Agency's (EMA) rejection of the application for



**Figure 1**

Mode of action of the most promising drugs for the treatment of muscle wasting. Ghrelin receptor agonists such as anamorelin or selective androgen receptor modulators such as enobosarm stimulate protein synthesis in the muscle. Like testosterone, the latter act *via* the androgen receptor. Myostatin is an anti-anabolic substance. Myostatin inhibitors act *via* the ActR2B receptor and inhibit muscle breakdown

marketing authorization of anamorelin, a ghrelin receptor agonist, in May 2017 [23], this class of drugs merits further scrutiny (Figure 1). Indeed, GSK2881078 adds to the list of SARMs in clinical development that include substances like DT-100, enobosarm, ligandrol and MK-0773 [24]. The only one of these to see Phase III testing is enobosarm; however, its development was unfortunately discontinued [25]. Therefore, this new piece in the SARM puzzle comes as a welcome addition. On the other hand, it appears that all drugs that aim at treating muscle wasting struggle with the same problem: to improve both muscle mass and muscle function at the same time. Even though the two – muscle mass and muscle function – appear almost automatically linked, this has not been the case in the two major trials of anamorelin [26] and only partially in the two trials of enobosarm [27, 28]. In fact, these trials have shown significant improvements in muscle mass, but the increase in strength or functional capacity has been less convincing.

Pharmacokinetic data of the new SARM GSK2881078 showed a rapid initial absorption and a long half-life of more than 100 h with slightly higher values in women than men. Pharmacodynamics showed reductions in the serum levels of testosterone, dihydrotestosterone and sex-hormone binding globulin relative to baseline. Overall safety was acceptable. In summary, no major surprises were revealed during Phase I testing, and the data may prompt testing in Phase II. Whatever endpoint the investigators may want to choose in a Phase II study, it should include testing of muscle function using easily applicable tests such as the 6-minute walk test, the stair-climbing power test, the short physical performance battery test or at least handgrip strength. Selecting the right patient population for such a study is another major challenge: patients with cancer cachexia, particularly in cancers of the lung or the pancreas, may simply be too sick to benefit

from pharmacological treatment of muscle wasting. It may be worth selecting patients at an earlier stage such as in pre-cachexia or sarcopenia with the aim of maintaining (rather than improving) muscle mass and function. Such questions are so important that regulators at the EMA or the Food and Drug Administration are requested to provide even more guidance in what they expect to achieve in a clinical trial of muscle wasting [29].

## Competing Interests

S.v.H. has received consultant honoraria from Vifor Pharma, Chugai, Helsinn, Novartis, Pfizer and Boehringer Ingelheim.

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