Evaluate Vantage

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# Therapeutic focus - Cachexia pipeline gaining weight

Amy Brown

News that GTx is about to start two phase III studies with its novel muscle wasting therapy, Ostarine, is encouraging progress for cachexia research. The condition afflicts a large proportion of cancer patients as well as patients with lung and kidney diseases, carries a significant mortality risk and can severely crimp quality of life, but has few effective treatments.

The complex mechanisms behind cachexia are not completely understood; current treatments include steroids or hormone therapies to build muscle and boost appetite, albeit largely unsuccessfully. Despite this unmet need few therapies are under development – Ostarine will be the only novel drug in final stage testing although a couple of other candidates are progressing through phase II (see table below). Considering many cancers are increasingly being viewed as chronic diseases, clinical progress in cachexia could well translate into significant commercial success, although several challenges remain.

**Loss of strength**

Cachexia is mostly associated with cancer; rates vary with tumour types and the stage of the disease. For example, while around 80% of pancreatic cancer patients are likely to suffer from wasting it is nowhere near as common in less aggressive tumour types.

The loss of muscle and fat can weaken a patient to such an extent that the cachexia is the cause of death in many cancer patients – up to 20% according to some estimates. It also leaves patients less able to fight the underlying disease and tolerate chemotherapy, or other cancer killing agents, as well as increasingly hampering daily activities.

Most cachexia research is being conducted in cancer patients but any successful drug would also likely be used in conditions such as renal disease and chronic obstructive pulmonary disease, where patients routinely suffer from wasting. Broader potential also lies in related conditions such as sarcopenia, muscle wasting in the elderly that is thought to affect a quarter of men over the age of 60.

Currently, only the progesterone therapy Megestrol is cleared by regulators to treat cachexia, when associated with HIV. This is used off-label in cancer patients, and works by boosting hunger. Steroids are also used, to build muscle, but neither of these treatments promotes effective growth of well functioning muscle – a big challenge for any therapy.

“It’s not actually just putting on weight that you want, the goal is to add lean muscle mass, and you also need improvements in muscle function. That’s the conundrum,” says Julian Gilbert, chief executive of Acacia Pharma, which has a product in phase II testing.

“It’s a fairly tough area to work in. The pathology you are trying to overcome is complicated and there are regulatory challenges in proving you have an effective drug,”  he says.

**Thin pipeline**

This mechanistic complexity and lack of a clear regulatory path have contributed to the thin development pipeline for cachexia. A tendency for researchers to focus on cancer therapeutics rather than supportive care has also not helped, Dr Gilbert says.

However, signs are emerging of an increase in activity, particularly in mid-stage candidates. This could in part be due to improving treatments and earlier diagnosis, meaning many people are living longer with cancer.

“Cancer numbers are increasing but it's becoming a chronic condition as well. Therefore supportive care is becoming more important than ever,” Mr Gilbert says.

Ostarine will give the pipeline its first phase III candidate for several years, and importantly test the regulatory waters. The last product to enter pivotal stages was Ark Therapeutics’ Vitor, an lipophylic ACE inhibitor that was put on hold in January 2010, following inconclusive results and a cash crunch at the company.

Ostarine is a selective androgen receptor modulator (SARM), which the company says has the benefits of testosterone treatment while minimising the undesirable side effects. SARMs are anabolic, so build muscle like steroids, but are more selective, hence the improved tolerability.

**Data emerging**

Based on feedback from the FDA, GTx intends to conduct two phase III studies in non-small cell lung cancer patients, using change in lean body mass and stair climb at three months as co-primary endpoints, according to analysts at Leerink Swann. Overall survival is expected to be included as a secondary endpoint, but will likely not be powered or required to show statistical significance.

Each trial will recruit 300 patients and could yield data in late 2012 or early 2013.

In the meantime, data should emerge from the mid-stage pipeline, potentially from Acacia's APD209 before the end of the year. The product is a combination of two repurposed drugs – a beta 2 adrenoreceptor agonist and a progestogen agonist.

"We took a pragmatic approach to look for drugs that would stimulate appetite and be anabolic, but the drugs we identified within those classes also had complimentary cytokine modulatory effects," Dr Gilbert says.

While the mechanisms through which cachexia acts are still not fully understood, inflammatory processes are thought to be involved.

"A complex set of metabolic processes are going on," says Dr Gilbert. "Cachexia has been linked fairly strongly to an inflammatory response, and there are cytokines linked to that. But although it is better understood now, it's not nailed down."

**Targeting inflammation**

With inflammation now considered a viable target for cachexia, a number of companies are targeting this process.

Vicus' VT-122 is an oral combination of propranolol, a non-selective beta adrenergic receptor blocker, and etodolac, a COX2 selective enzyme inhibitor. The company believes by synergistically targeting multiple pathways, cancer-induced systemic inflammation can be attentuated and, hopefully, cachexia reversed. A phase II study was started last December in advanced liver cancer patients being treated with Nexavar. The 80-patient study will measure pain, performance status and lean body mass.

Meanwhile Alder is working on ALD518, an antibody that blocks the pro-inflammatory molecule interleukin-6. The company has put the drug through phase II studies in cachexia – Bristol-Myers Squibb has licensed the compound in indications outside of cancer, specifically RA. Alder's website says further trials are planned, although none appear to be underway currently.

Ohr Pharmaceutical is conducting a phase II trial of OHR/AVR118, a broad spectrum immunomodulator, in 30 patients. The drug inhibits and modulates cellular pro-inflammatory chemokine and cykotine synthesis, including tumour necrosis factor-alpha and interleukin-6. Last December 11 patients had been recruited so final data are unlikely to emerge until 2012. Interim data presented last year showed 7 of 11 patients experienced weight stabilisation or gain.

**Other approaches**

Taking a different approach is PsiOxus with MT-102, an anabolic catabolic transforming agent. Patients are currently being recruited for a double blind, placebo controlled phase II study in 132 patients, with either colorectal or non-small cell lung cancer. Data on endpoints including a six minute walking test and stair climb should be available next year; if positive the company will seek a partner.

MT-102 is unique in that rather than seeking to build muscle and fat, it seeks to prevent tissue being broken down.

"We think this is a more logical approach," says John Beadle, chief executive of PsiOxus. "Some of the products that add muscle only add poorly functioning muscle. We would argue it is better not to lose it in the first place."

Other pipeline candidates include Helsinn's synthetic ghrelin, anamorelin, which is in phase II/III according the company's website. However it is unclear whether trials are ongoing – nothing is listed on www.clinicaltrials.gov. The ghrelins, which work by building appetite, have been widely studied in cachexia but many projects have been abandoned.

Another earlier stage candidate to recently come on the radar is Amgen's AMG 745; although no trials appear to be ongoing at present the company lists it as a phase I candidate. The drug inhibits myostatin, a growth hormone that itself inhibits muscle growth. Animals that lack this protein have overdeveloped muscles.

**Taking a punt**

With much cachexia work in the hands of small companies, it remains to be seen whether big drug developers or specialty pharma will take a punt on this market at this stage. Many of the companies below will need a partner for later stages of development.

History is not encouraging – Merck & Co handed back rights to GTx's Ostarine in 2010, although this arguably was a result of a pipeline review following the Schering-Plough takeover.

Although the companies involved talk about a market worth $1bn, to achieve anything close to this value any product would have to show remarkable efficacy and it seems more likely a number of smaller products will emerge. Given previous clinical experience it does seem more likely that progress in this complex disease will be incremental.

“This is a complex disease and multi-factoral. It will probably end up being treated with a combination of approaches,” PsiOxus’ Mr Beadle says.

**Clearer potential**

The primary aim of cachexia research is to improve the quality of life for cancer patients, many of whom will be in the last few months of life. Although this is hugely important for patients and doctors, the commercial opportunity in this space is harder to quantify than for agents with clear links to cancer progression and survival.

However those working in the field argue that treating cachexia should have clear survival benefits.

“There are two issues with cachexia, firstly supportive care and quality of life: patients want to be able to walk upstairs or put the kettle on. But also there is a clear link to mortality and morbidity. Cachexia is linked to the progression of their disease,” says Mr Gilbert.

“If you build people up, you can treat the cancer more effectively, and by making them stronger, you can prolong life,” says Dr Beadle.

Proving a survival benefit will be tough. But should evidence emerge that these therapies can help prolong life, the commercial potential of cachexia becomes much clearer and more valuable.

| Clinical stage cachexia pipeline | | | | |
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| | **Product** | **Pharmacological Class** | **Company** | **Originator** |
| **Phase III** | Ostarine | Selective androgen receptor modulator (SARM) | GTx | University of Tennessee Research Foundation |
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| **Phase II** | RC-1291 (anamorelin) | Ghrelin agonist | Helsinn Group/Ono Pharmaceutical | Novo Nordisk |
| | VT-122 (etodolac; propranolol hydrochloride) | COX-2 inhibitor | Vicus Therapeutics | Wyeth/Zeneca |
| | OHR/AVR118 | Immunomodulator | OHR Pharmaceutical | Advanced Viral Research |
| | MT-102 | Anabolic catabolic transforming agent | PsiOxus Therapeutics | Myotec Therapeutics |
| | APD209 | Beta 2 adrenoreceptor agonist & progestogen agonist | Acacia Pharma | Acacia Pharma |
| | SUN 11031 | Ghrelin agonist | Daiichi Sankyo | Suntory |
| | BMS-945429/ALD518 | Anti-IL-6 MAb | Alder Biopharmaceuticals | Alder Biopharmaceuticals |
| | | | | |
| **Phase I** | AMG 745 | Myostatin (GDF-8) antagonist | Amgen | Amgen |
| | GLPG0492 | Selective androgen receptor modulator (SARM) | Galapagos | ProStrakan |
| | LGD-4033 | Selective androgen receptor modulator (SARM) | Ligand Pharmaceuticals | Ligand Pharmaceuticals |

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