

Therapeutic focus - Big pharma adds weight to thin cachexia pipeline



[Joanne Fagg](#)

The failure of GTx's enobosarm has robbed the cachexia pipeline of its most advanced hope. And the fact that the remaining drugs in development employ a wide range of mechanisms reflects how the weight loss and muscle wasting disorder, a major cause of death and complication in cancer patients, is poorly understood.

Small private companies are doing much of the work in this area, although in the last couple of years Novartis and Eli Lilly have put monoclonal antibodies into the clinic, suggesting that big pharma has not completely written it off (see table). But with no new treatments for cachexia to emerge in the last 40 years and phase III seemingly a tough barrier to cross, a success story is sorely needed.

"The treatment of cachexia just doesn't exist. It is a miserable frequent event, that every physician knows about and many patients experience, but there is simply nothing available against it and nothing to prevent it" says Stefan Anker, professor of cardiology and cachexia research at the Charité, University Hospital Berlin, Germany.

Wasting

The prominent feature in cachexia is weight loss and muscle wasting that leads to progressive functional impairment; the loss of chest, diaphragm and abdominal muscles that eventually erodes cardiopulmonary function is often the ultimate cause of death for sufferers. It is a multifactorial syndrome with many mechanisms involved, and is associated with several chronic diseases including COPD, kidney disease, heart failure and in particular cancer.

"The rate of cachexia in all cancer patients is anywhere around 40-50%, and in pancreatic cancer it's about 80%. The National Cancer Institute quote 20-40% of cancer death is directly caused by cachexia," says John Beadle, chief executive of PsiOxus Therapeutics which has a drug in phase II.

Current treatments for cachexia are essentially palliative care - nutritional support, medications like steroids to build muscle and exercise to maintain muscle function. Some patients may be given Megace, known generically as megestrol acetate, which was approved over 40 years ago as an appetite stimulant and subsequently used for HIV related wasting. There is little evidence to suggest that it is effective in cancer cachexia but it is often used off label.

Any treatment that could promote weight and muscle gain - or at least stem their loss - would help improve the quality of life of cachexia patients. The ultimate achievement would be to prolong survival.

Late stage

The most advanced pipeline product for cachexia was GTx's enobosarm, a selective androgen receptor modulator (SARM), which last month failed in two phase III trials. It failed to hit either co-primary endpoints of increased lean body mass or improved stair climb ([Cachexia drug failure falls heavily on Gtx, August 20, 2013](#)).

The next late-stage data are due from Helsinn Group's anamorelin, which is in two trials called Romana 1, 2, looking to recruit 954 patients with NSCLC. Primary outcome measures include effect on lean body mass and muscle measured by hand-grip strength, data are expected by mid 2014.

Both of these agents test mechanisms that have been widely trialed in this setting, without success. The SARM class are anabolic, so build muscle like steroids, but avoid the side effects of hormone therapy. Meanwhile anamorelin is a ghrelin receptor agonist, a hormone predominantly produced in the stomach which stimulates appetite.

The only novel mechanism in late stage is Xilonix, from Xbiotech, an anti-IL-1 alpha monoclonal antibody. The drug is testing the hypothesis that by disrupting the systemic inflammation caused by the presence of tumours, muscle wasting can be prevented. According to the company, IL-1 receptors in the hypothalamus detect inflammatory signals that become activated by tumours. This induces a hypermetabolic state, in which the central nervous system continuously demands glucose and swiftly leads to weight loss and muscle

breakdown.

As such, blocking IL-1 may be ways of interrupting the danger signals emanating from the tumour cells. Xbiotech is testing this theory in a trial looking to recruit 656 colorectal cancer patients and has gone for the gold standard primary outcome measure of overall survival. Secondary measures include change in lean body tissue and quality of life, while the active comparator is megestrol acetate.

Data is expected mid 2014 and the drug has fast track designation from the FDA in this use. However, the trial is not blinded or placebo controlled. So even if the outcome shows a big improvement in survival – which would be a big step forward for cachexia – the regulator is likely to closely scrutinise this trial design for robustness.

Next in line

The dominance of private companies in the mid-stage pipeline means disclosure and updates are patchy from many of these candidates.

Phase II data on PsiOxus' MT-102 is expected at the 7th Cachexia Conference in Japan in December.

MT-102, an anabolic catabolic transforming agent, has a dual mode of action with anti-catabolic and pro-anabolic activities; it seeks to both reduce muscle tissue breakdown and increase muscle build-up. The phase II trial is in 87 patients with cachexia related to stage III and IV NSCLC and colorectal cancer. The primary outcome is rate of weight change compared to placebo at 16 weeks.

"We don't have the data yet so I can't confirm any [phase III] plans at this stage but we would be looking for a partner for phase III" says Mr Beadle.

More phase II data is expected from OHR Pharmaceuticals before the end of the year on OHR/AVR118, an immunomodulator. The company has already said that the primary end point of weight gain was not achieved but patients did achieve stabilisation of body weight, body fat and muscle mass. Over 60% of the patients – the open-label trial recruited 18 patients – chose to remain on the drug after the initial treatment period.

Meanwhile Acacia's drug APD209, a combination of megestrol and the beta 2 agonist formoterol, generated encouraging results from a phase I/II open-label trial in 2011. However the regulatory challenges that cachexia presents prompted the company to rule out further work without a partner on board.

"Cachexia is a clear unmet need. The difficulty is proving it as there is no precedent," says Julian Gilbert, Acacia's chief executive. With nothing reaching regulators to date, the endpoints they might like to see are unclear, he says; a risky proposition for a small company.

Bigger players

After years of research neglect, the presence of big pharma in the table below is an encouraging sign. It seems likely that they also have their eyes on the bigger prize of sarcopenia, muscle wasting in the elderly, and cachexia would be the natural segue way into this market.

Novartis and Morphosys have BYM338 - an antibody also known as bimagrumab. It binds to type II activin receptors on the surface of muscle cells, preventing the inhibitory molecules myostatin and activin from binding, therefore stimulating muscle growth. It was recently given breakthrough therapy designation by the FDA for sporadic inclusion body myositis, a rare muscle-wasting condition.

In cachexia a phase II study looking to recruit 50 patients with lung or pancreatic cancer is on-going; the primary endpoint of increase in thigh muscle volume will be measured by MRI at 8 weeks.

Meanwhile another MAb, LY2495655 from Eli Lilly, which has shown to inhibit myostatin activity, is in a phase II trial trying to recruit 120 pancreatic cancer patients. The primary outcome is overall survival at 31 months, while changes in lean body mass and physical performance are included in secondary measures; data are due in July next year.

So despite cachexia losing its most advanced lead product, the clinical pipeline has a diverse range of targets in the offing. But clinical success now needs to follow.

"In two to three years, I would hope that we have one successful phase III program and at least three or four more promising new candidates that have successful phase II studies," says Professor Anker. "Given the current study landscape I think there is a good chance for that."

Selected late stage cachexia pipeline

	Product	Company	Pharmacological Class	Originator	Trial
Phase III	Anamorelin	Helsinn Group	Ghrelin agonist	Novo Nordisk	NCT01387269 NCT01387282 NCT01395914
	Xilonix	XBiotech	Anti-interleukin-1 alpha (IL-1a) MAb	-	NCT01767857
Phase II	Solorel	Æterna Zentaris	Growth hormone secretagogue/Ghrelin receptor agonist	Europeptides	NCT01614990
	APD209	Acacia Pharma	Beta 2 adrenoreceptor agonist & progestogen agonist	-	NCT00895726
	MT-102	PsiOxus Therapeutics	Anabolic catabolic transforming agent	Myotec Therapeutics	NCT01238107
	OHR/AVR118	OHR Pharmaceutical	Immunomodulator	Advanced Viral Research	NCT01206335
	BYM338	MorphoSys	Anti-activin receptor type IIB (ActRIIB) MAb	Novartis	NCT01433263
	LY2495655	Eli Lilly	Anti-myostatin (GDF-8) MAb	-	NCT01505530
	ALD518/BMS-945429	Alder Biopharmaceuticals	Anti-interleukin-6 (IL-6) MAb	-	NCT00866970

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