ImmunoTools *special* Award 2026





Fara Berghmans, PhD-student, Brussels Center for Immunology, VUB, Brussels, BELGIUM

Benoit Stijlemans, PhD, Professor, Brussels Center for Immunology, VUB, Brussels, BELGIUM

Receptor-specific single-domain-antibody-based targeting of Lipocalin-2 to treat cachexia and improve cancertherapy

Cachexia is as a multifactorial syndrome characterized by severe body weight, fat and muscle loss and increased protein catabolism due to underlying disease(s) that can have devastating results. Given that, so far, there is no effective treatment, cachexia presents an area of major global public health burden with an urgent unmet therapeutic need. Cachexia frequently occurs in patients with end-stage chronic heart failure, malignant cancer, chronic kidney disease, chronic obstructive pulmonary disease, neurological disorders and rheumatoid arthritis. Besides non-infectious diseases, cachexia is also frequently observed in infectious diseases, such as tuberculosis and HIV.

Cancer-associated cachexia (CAC) severely impairs the quality of life of patients, causing weakness, fatigue, increased chemotherapy toxicity and decreased efficacy, and reduced emotional and social well-being. It affects up to 74% of cancer patients and accounts for 20–30% of cancer deaths yet remains underdiagnosed. CAC is most prevalent in pancreatic and gastric cancers (70-90%), followed by lung cancer

(~ 60%). Different factors play a role in the development of cachexia including, increased and systemic inflammation, profound alterations in carbohydrate, protein and lipid metabolism and an increase of muscle proteolysis. Importantly, cachexia is frequently accompanied by inflammation-driven anemia and functional iron deficiency due to inflammation-induced iron sequestration in macrophages and impaired erythropoiesis.

CAC is managed with multimodal supportive care, combining (i) nutritional support and appetite stimulants to stabilize the weight of the patients, but which fail to restore lean muscle mass, (ii) different pharmacological treatments targeting inflammation, anorexia and gastrointestinal dysfunction, yet these show limited and inconsistent benefit, (iii) exercise can improve patients' function but is often difficult in advanced disease, and (iv) anemia treatments with iron or erythropoiesis-stimulating agents that reduce symptoms without reversing inflammation-driven iron sequestration. As no approved therapy effectively targets the upstream immune–metabolic drivers of cachexia, targeting these central mechanisms may provide a promising strategy for developing effective disease-modifying treatment.

Emerging evidence identifies the adipokine Lipocalin-2 (Lcn-2) as a central orchestrator of CAC. Lcn-2 integrates metabolic and tumor-promoting signals by (i) suppressing appetite via the Lcn-2–MC4R axis, (ii) inducing adipocyte cell death through Lcn-2–24p3R signaling, and (iii) regulating iron availability to sustain tumor progression. In our project, we propose a first-in-class Single-Domain Antibody (sdAb)-based strategy to selectively and receptor-specifically block Lcn-2 signaling. By simultaneously restoring appetite, preserving adipose tissue integrity, and attenuating tumor-promoting mechanisms, this approach aims to redefine therapeutic interventions in CAC. Targeting Lcn-2 at the receptor level may establish a dual metabolic–oncologic treatment paradigm that enhances the efficacy of current cancer therapies while directly addressing cachexia.

As a first step, it is crucial to characterize the Lipocalin-2 signalling through its receptors (24p3R and MC4R) in different cell types such as adipocytes, myeloid cells and neuronal cells *in vitro*, under both pro-inflammatory and anti-inflammatory conditions, established using recombinant murine cytokines and chemokines. **A selection of murine recombinant cytokines and chemokines from ImmunoTools** is of great benefit here: in the first instance for stimulating these cell cultures and evaluating whether the Lcn-2–receptor interaction is activated, and in the second whether our anti-Lcn-2 sdAbs interfere with that activation. Because the sdAb efficacy is largely assessed through cytokine read-outs by ELISA, concentration-dependent titrations with the named cytokines and chemokines will allow more

accurate quantification of the Lcn-2 produced upon stimulation, and thereby define the sdAb dose required to block its effects.

Once we have established which molecules trigger Lcn-2–receptor activation and which cytokines and chemokines are induced, we will test whether our panel of anti-Lcn-2 sdAbs can modify these responses and identify a lead blocking sdAb. These *in vitro* assays allow us to gauge sdAb effectiveness and select a lead compound prior to establishing *in vivo* models.

ImmunoTools *special* AWARD

for **Fara Berghmans** and **Benoit Stijlemans** includes:

Recombinant murine cytokines: rm IFN-gamma, rm IL-1alpha, rm IL-1b / IL1F2, rm IL-2, rm IL-4, rm IL-6, rm IL-10, rm IL-17A, rm IL-27A (IL-27/p28), rm IL-33, rm IP-10 / CXCL10, rm KC /CXCL1, rm LIX / CXCL5, rm MCP1 / CCL2, rm MCP-5 / CCL12, rm MIP-1a / CCL3, rm PF4 / CXCL4, rm SDF-1alpha, rm CXCL12a, rm TNF-alpha

DETAILS more AWARDS