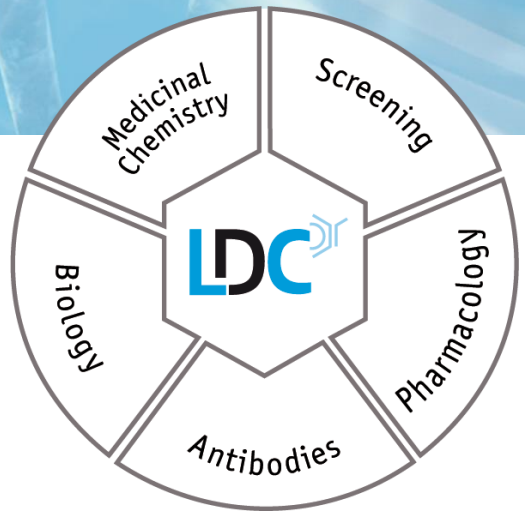
Lead Discovery Center LDC

GDF-15 Antibody



Executive Summary

Target Rationale*:*

- Adressing 2 hallmarks of cancer:
  I. Deregulation of cellular energetics (Inhibition of GDF-15 to prevent cancer associated body wasting)
  II. Immune evasion
- GDF-15 can function as clinically relevant biomarker

Key Achievements:

- DNA Immunization in rats & phage display resulted in 20 antibodies with high affinity
- Lead antibody selected → Antibody shows excellent blocking activity on huGDF-15
- *In vitro* and *in vivo* data package available under CDA

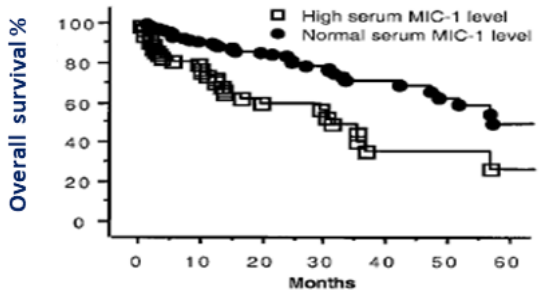
Next Steps:

- Antibody humanisation & selection of CMC-ready candidate
- 30 months away from clinic

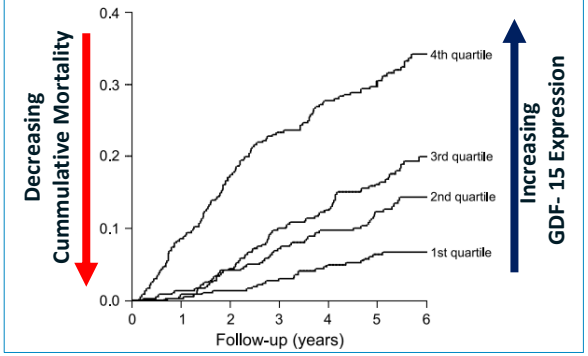
GDF-15 and Cancer

- Growth Differentiation Factor 15 (GDF15) or Macrophage Inhibitory Cytokine 1 (MIC-1); Member of the TGF-β superfamily
- Expression is low under normal conditions (exception: high in placenta)
- GDF-15 serum levels correlate with disease progression and overall survival in CRC patients (Brown et al., Clin can Res, 2003)
  - ➢ CRC > adenomatous polyps > healthy controls
  - ➢ TNM tumor stage 4 > stage 3 > stage 2 ≥ stage 1
- GDF-15 serum levels independently predict poor cancer-specific survival with an almost 3-fold higher cancer death rate in prostate cancer (Brown et al., Clin Can Res, 2009)
- GDF-15 expression is predominantly increased in tumor types with high incidence of body weight loss/cachexia

GDF-15 & Survival in Colon Cancer



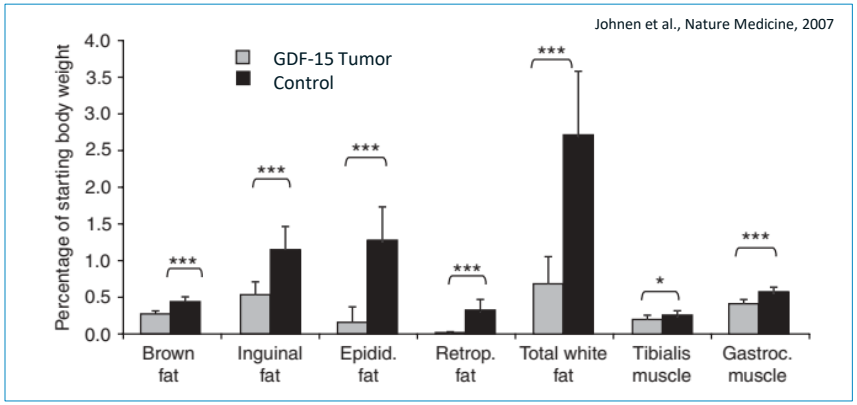
GDF-15 & Mortality in Prostate Cancer



GDF-15 Regulates Fat Mass & Induces Muscle Fiber Reduction

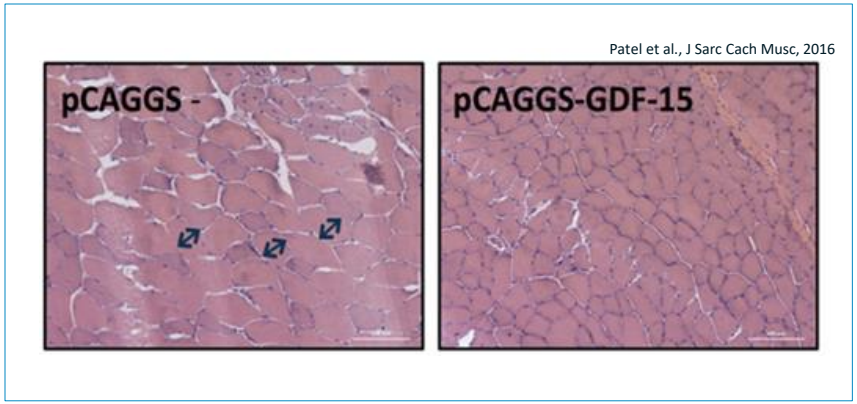
GDF-15 tumors drastically reduced body weight

- 20 nude mice were injected s.c. with DU145 cells expressing human MIC-1 (GDF-15) or empty plasmid vector.
- Mice were killed after loosing approximately 18% body weight.
- Selected fat and muscle compartments were dissected, removed and weighed.
- The results are the mean and s.d. of the specimen weight as a percent of the weight of the mouse at the day of tumor injection



GDF-15 induced muscle fiber reduction

- Mice were electroporated and then left for 14 days with either
  - ➢ control vector into both tibiales anteriores (pCAGGS1/pCAGGS2, n = 8)
  - ➢ a control vector into one tibialis anterior and a GDF-15 expression vector into the contralateral tibialis anterior (Control/GDF-15, n = 8)



25% of Cancer Deaths are due to Cachexia

Cachexia

Defined by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment

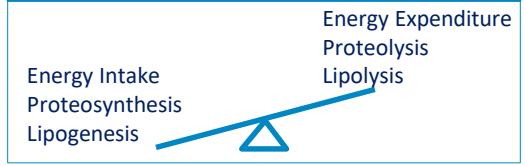
Relevance

- Mortality rates of patients with cachexia range from up to 30% per year in chronic diseases to 80% in cancer.
- 20-30% of all cancer deaths are estimated to result from the effects of cachexia rather than tumor burden
- Particularly common in specific cancer types, e.g. gastric: 85%, PDAC: 83%, NSCLC: 61%, SCLC: 57%, prostate: 57%, colon: 54%

Treatment Options

- Very limited, focus on palliation of symptoms and reduction of the distress of patients rather than prolongation of life
- Treatment approaches using anabolics, anti-catabolic therapies, appetite stimulants, and nutrition supply
- No Target based Therapy available

Metabolic Mismatch

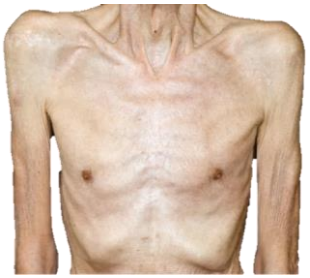


Cancer Cachexia Mortality Rate:

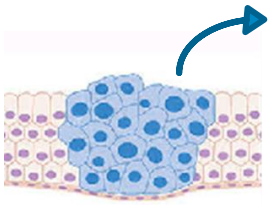
Worldwide Deaths: 8.8 Million (WHO, 2015)

25%

Cachexia related deaths thereof: app. 2,200,000



Dual Role of GDF-15 in Cancer

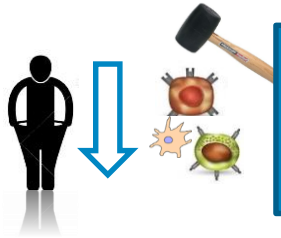


Tumor

GDF-15

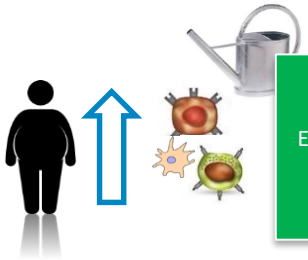
GDF-15 Receptor:
- **GFRAIL/RET**
- TGFbR ?
- Others ?

GDF-15



Increased Morbidity
Reduced Immune Response
Limited Treatment Options
Progressive Disease
Poor Prognosis

GDF-15 Blockade
+ SoC Chemotherapy
+ Next Generation I/O drugs



Improved Health Status
Expanded Therapy Options
Enhanced Immune Response
Better Quality of Life
Better Survival

Next Steps

- **Antibody humanization & engineering of chimeric 1D4 Antibody to**
  - Create additional application opportunities beneficial for chronic treatment
  - Enable broad IP coverage
- **Run analytical package to reconfirm developability of 1D4**
- **Expanding therapeutic potential of 1D4 in pathological muscle wasting and suppression of immune response – Opportunity in Immunooncology**
  - Antibody testing in additional cachexia related *in vivo* models in cooperation with partners in academia (Cancer, COPD, Heart Failure)
  - Evaluate a-GDF 15 treatment in the context of combination therapy with existing or future cancer check point therapies