

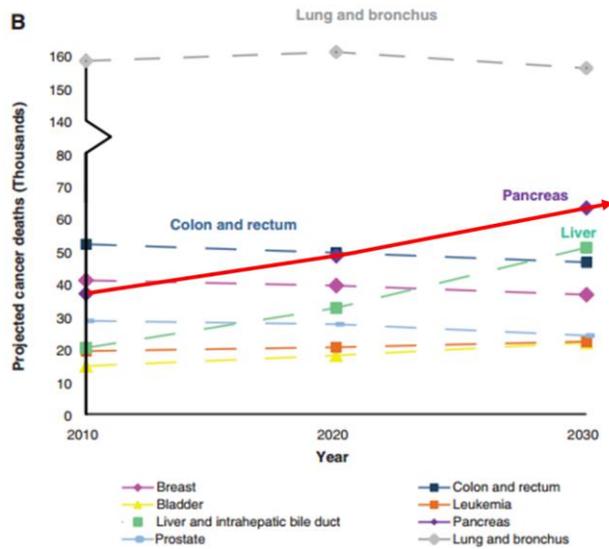
Sarcopénie et cancer du pancréas

Angélique Vienot

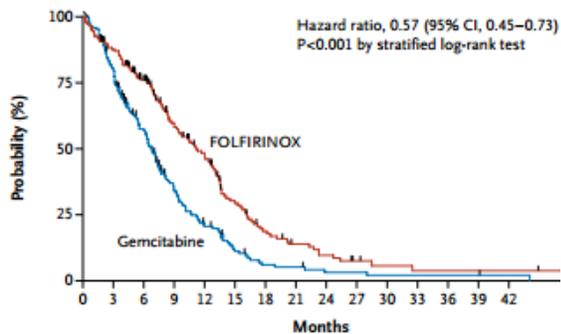
Oncologie digestive – CHU Besançon
UMR1098 RIGHT, INSERM, EFS, UFC

Cancers du pancréas

Maladie hétérogène



Résistance aux traitements



| No. at Risk | 0 | 3 | 6 | 9 | 12 | 15 | 18 | 21 | 24 | 27 | 30 | 33 | 36 | 39 | 42 |
|-------------|-----|-----|-----|----|----|----|----|----|----|----|----|----|----|----|----|
| Gemcitabine | 171 | 134 | 89 | 48 | 28 | 14 | 7 | 6 | 3 | 3 | 2 | 2 | 2 | 2 | 1 |
| FOLFIRINOX | 171 | 146 | 116 | 81 | 62 | 34 | 20 | 13 | 9 | 5 | 3 | 2 | 2 | 2 | 2 |

Comment optimiser la prise en charge ?

→ Identification de facteurs pronostiques

Marqueurs chirurgicaux

| | |
|---|---------|
| Nombre de ganglions réséqués > 11 | HR 0,98 |
| Centre < 25 interventions/an | HR 1,3 |
| Complications post-opératoires grade III-IV | HR 3,69 |

Marqueurs histologiques

| | |
|----------------------------|---------|
| Taille tumorale > 2 cm | HR 5,69 |
| Ratio ganglionnaire > 0,4 | HR 2,55 |
| Caractère peu différencié | HR 2,7 |
| Envahissement péri nerveux | HR 2,77 |
| Marges < 1 mm | HR 1,55 |

→ Autre marqueurs applicables en pratique clinique ?

Marqueurs cliniques

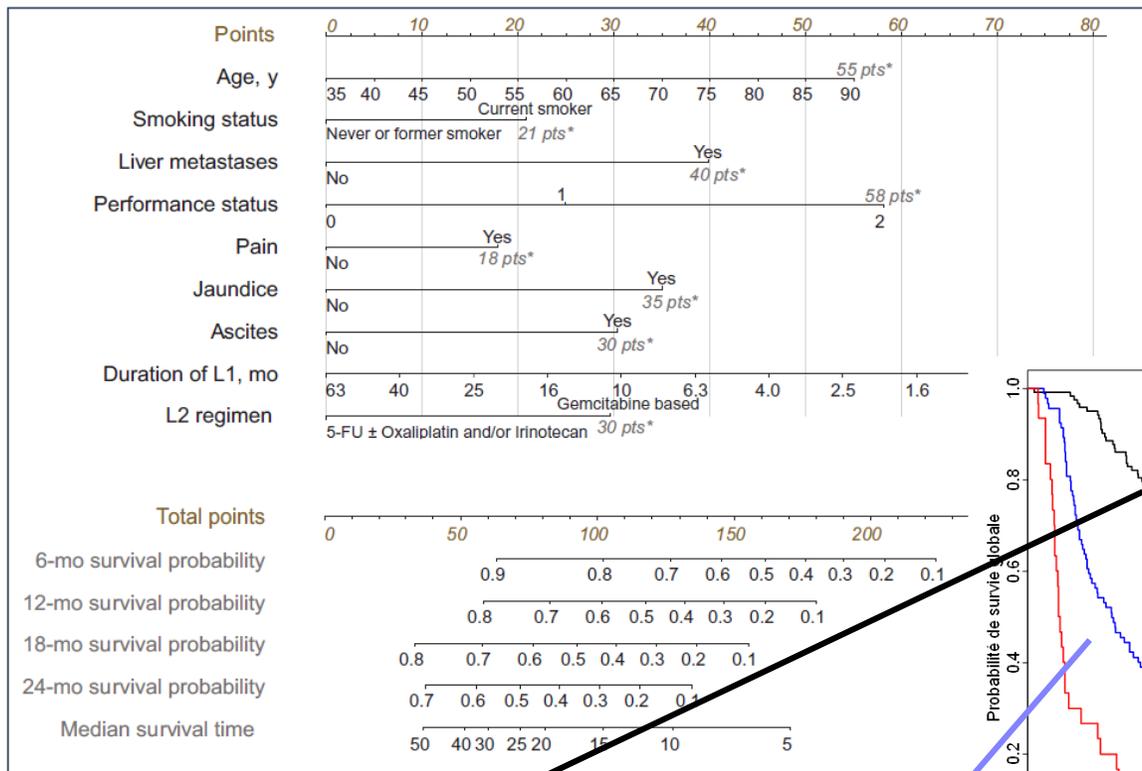


Cohorte RECAP
Base de données régionale
900 cancers du pancréas

Modélisation pronostique

➔ Outils informatiques

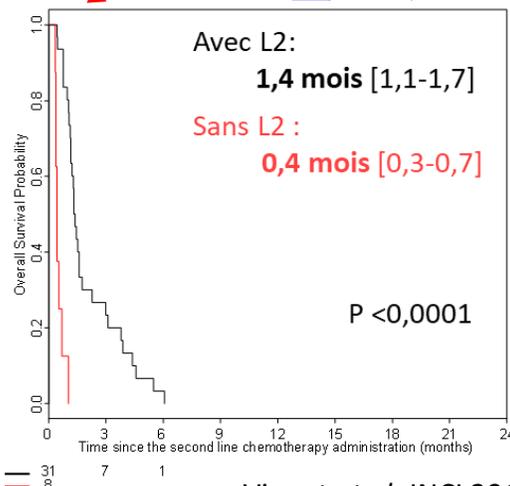
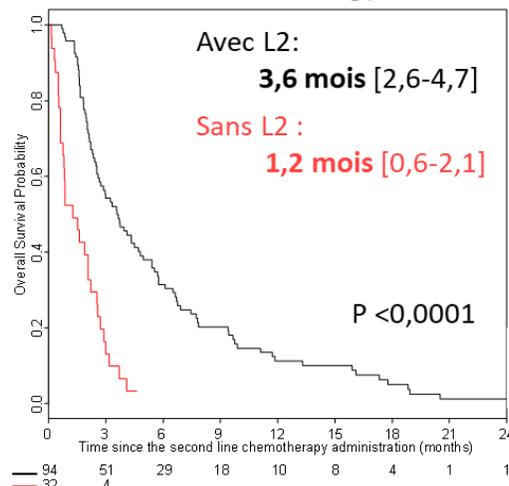
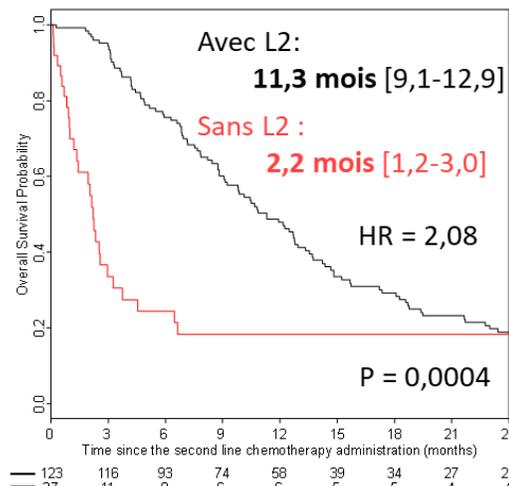
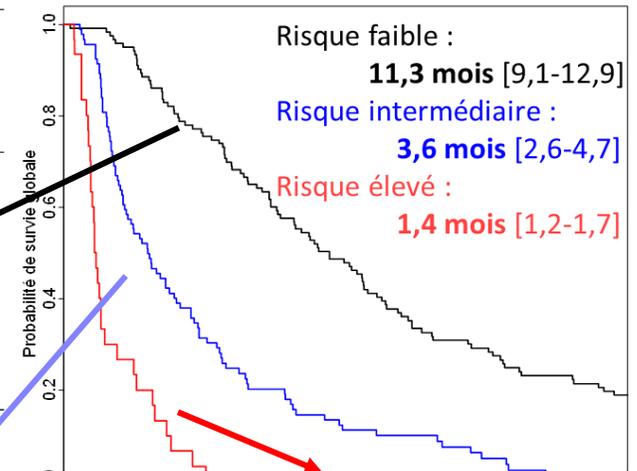
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OXFORD

JNCI J Natl Cancer Inst (2017) 109(10); doi:10.1093/jnci/djx037
First published online April 5, 2017
Article

ARTICLE
Overall Survival Prediction and Usefulness of Second-Line Chemotherapy in Advanced Pancreatic Adenocarcinoma
Angélique Vienot, Guillaume Beinse*, Christophe Louvet*, Louis de Mestier*, Aurélie Meurisse, Francine Fein, Bruno Heyd, Denis Cleau, Christelle d'Engremont, Anne-Claire Dupont-Gossart, Zaher Lakkis, Christophe Tournigand, Olivier Bouché, Benoît Rousseau, Cindy Neuzillet, Franck Bonnetain, Christophe Borg, Dewi Vernerey



— 123 116 93 74 58 39 34 27 22 — 94 51 29 18 10 8 4 1 1 — 31 7 1
— 37 11 8 6 6 5 5 4 4 — 32 4 — 8

Marqueurs biologiques



Cohorte RECAP
Base de données régionale
900 cancers du pancréas

2 marqueurs biologiques

CA19-9

Ratio
neutrophile –
lymphocyte
(NLR)

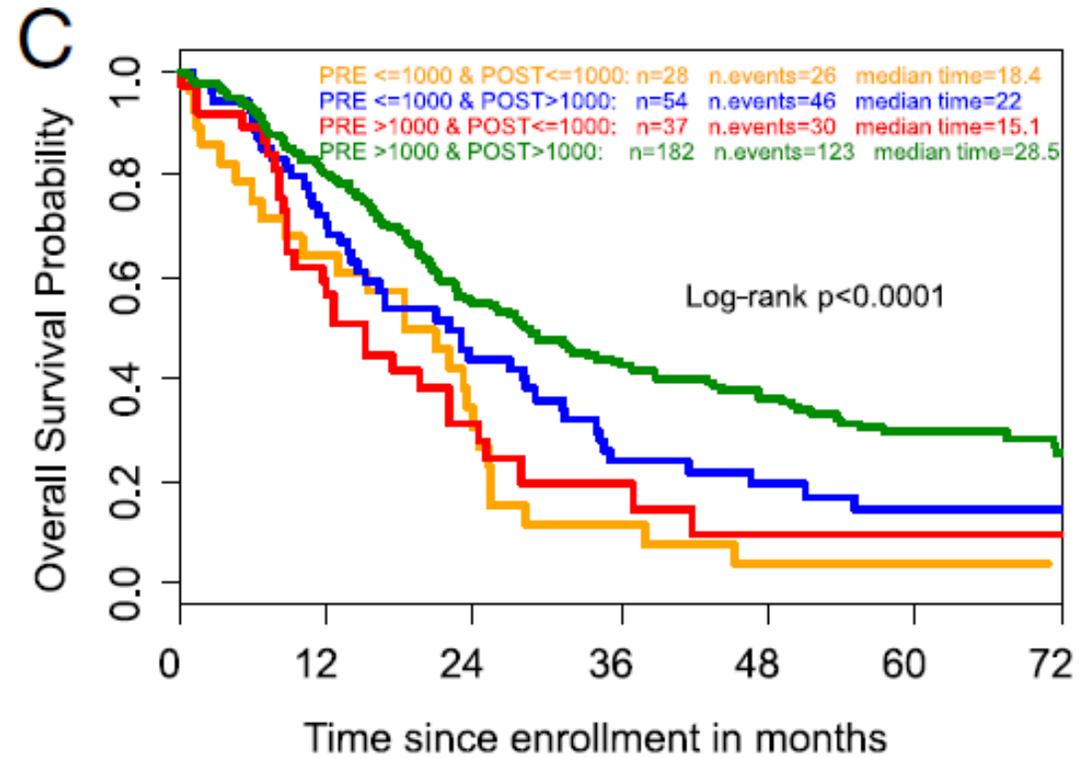
| Parameters | No. of Patients | No. of Events | HR (95% CI) | P* |
|--|-----------------|---------------|--------------------|-------|
| Demographic parameters | | | | |
| Age, years | 178 | 172 | 1.02 (1.00 - 1.04) | 0.02 |
| Smoking status | | | | |
| Never smoker or former smoker | 130 | 125 | 1.00 (Reference) | |
| Current smoker | 48 | 47 | 1.71 (1.19 - 2.46) | 0.004 |
| Tumor extension at the beginning of L2 | | | | |
| Liver metastases | | | | |
| No | 103 | 99 | 1.00 (Reference) | |
| Yes | 75 | 73 | 1.72 (1.22 - 2.42) | 0.002 |
| Clinical parameters at the beginning of L2 | | | | |
| Performance status (WHO) | | | | |
| 0 | 30 | 27 | 1.00 (Reference) | |
| 1 | 97 | 94 | 1.60 (1.00 - 2.55) | |
| ≥ 2 | 51 | 51 | 2.60 (1.49 - 4.55) | 0.003 |
| Pain† | | | | |
| No | 85 | 80 | 1.00 (Reference) | |
| Yes | 93 | 92 | 1.42 (1.00 - 2.01) | 0.05 |
| Jaundice | | | | |
| No | 152 | 146 | 1.00 (Reference) | |
| Yes | 26 | 26 | 1.79 (1.09 - 2.93) | 0.02 |
| Ascites | | | | |
| No | 141 | 135 | 1.00 (Reference) | |
| Yes | 37 | 37 | 1.57 (1.04 - 2.36) | 0.03 |
| Biological parameters at the beginning of L2 | | | | |
| Neutrophil-to-lymphocyte ratio (square root value) | 178 | 172 | 1.43 (1.15 - 1.76) | 0.001 |
| CA19-9, UI/mL (square root value) | 178 | 172 | 1.0 (1.00 - 1.01) | 0.007 |
| Treatment | | | | |
| Duration of L1 (log value), months | 178 | 172 | 0.53 (0.33 - 0.86) | 0.01 |
| Type of L2 regimen | | | | |
| 5-FU ± Oxaliplatin and/or Irinotecan | 138 | 133 | 1.00 (Reference) | |
| Gemcitabine based | 40 | 39 | 1.69 (1.15 - 2.49) | 0.008 |

Marqueurs biologiques



Tumeurs localisées

→ Lymphopénie
facteur de mauvais pronostic

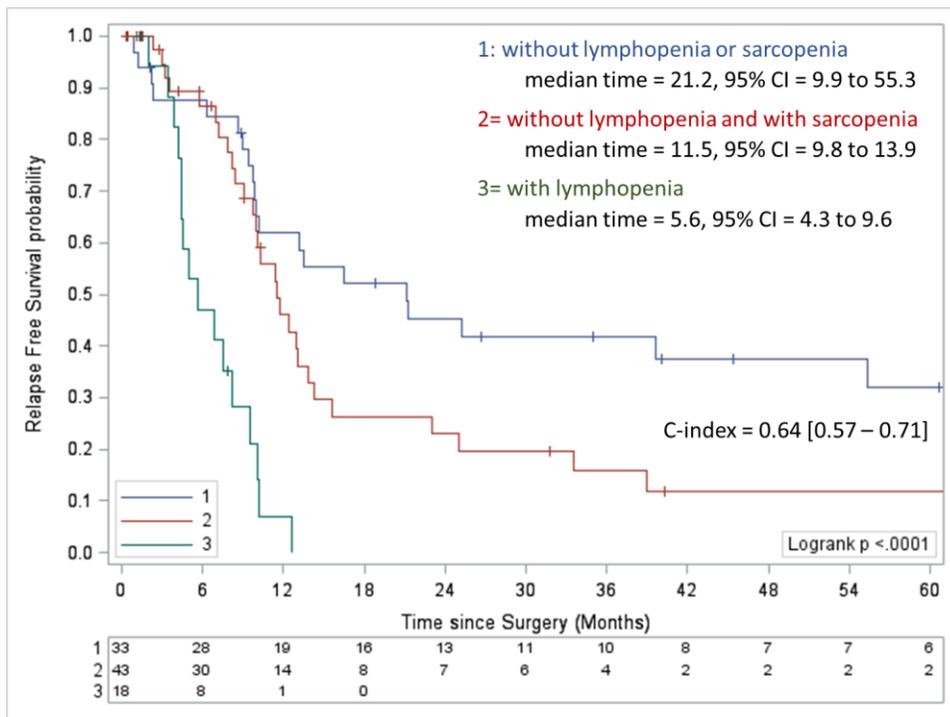


| | N at risk | | | | | | |
|----------------------------------|-----------|-----|----|----|----|----|----|
| | 0 | 12 | 24 | 36 | 48 | 60 | 72 |
| PRE ≤ 1000 & POST ≤ 1000 | 28 | 18 | 8 | 3 | 1 | 1 | 5 |
| PRE ≤ 1000 & POST >1000 | 54 | 38 | 22 | 12 | 8 | 6 | 5 |
| PRE >1000 & POST ≤ 1000 | 37 | 20 | 9 | 4 | 2 | 1 | 1 |
| PRE >1000 & POST >1000 | 182 | 143 | 91 | 68 | 46 | 31 | 18 |

Marqueurs nutritionnels



Tumeurs localisées



| Parameters | No. of patients | No. of events | HR (95% CI) | p† |
|--|-----------------|---------------|-----------------------|--------|
| Preoperative nutritional assessment | | | | |
| Body mass index, kg/m² | | | | |
| Normal weight (18.5–25) | 68 | 44 | 1.00 (Reference) | |
| Underweight (<18.5) | 4 | 3 | 0.973 (0.301 – 3.144) | |
| Overweight (25–30) and obesity (30) | 70 | 49 | 0.874 (0.581 – 1.314) | 0.8085 |
| Missing | 4 | 3 | | |
| Weight loss, % | 138 | 94 | 1.007 (0.975 – 1.039) | 0.6813 |
| Missing | 8 | 5 | | |
| Indexed muscle area (IMA), median [IQR], kg/m² | 98 | 67 | 0.963 (0.935 – 0.991) | 0.0110 |
| Missing | 48 | 32 | | |
| Sarcopenia | | | | |
| No | 40 | 26 | 1.00 (Reference) | |
| Yes | 58 | 41 | 1.773 (1.075 – 2.923) | 0.0248 |
| Missing | 48 | 32 | | |
| C-reactive protein, mg/L | | | | |
| | 109 | 76 | 1.003 (0.994 – 1.013) | 0.5061 |
| Missing | 37 | 23 | | |
| C-reactive protein, mg/L | | | | |
| <5 | 35 | 22 | 1.00 (Reference) | |
| ≥5 | 74 | 54 | 1.158 (0.705 – 1.903) | 0.5616 |
| Missing | 37 | 23 | | |
| albumin ratio | | | | |
| | 107 | 76 | 0.982 (0.940 – 1.025) | 0.3953 |
| Missing | 39 | 23 | | |
| | 92 | 64 | 1.141 (0.853 – 1.526) | 0.3751 |
| Missing | 54 | 35 | | |

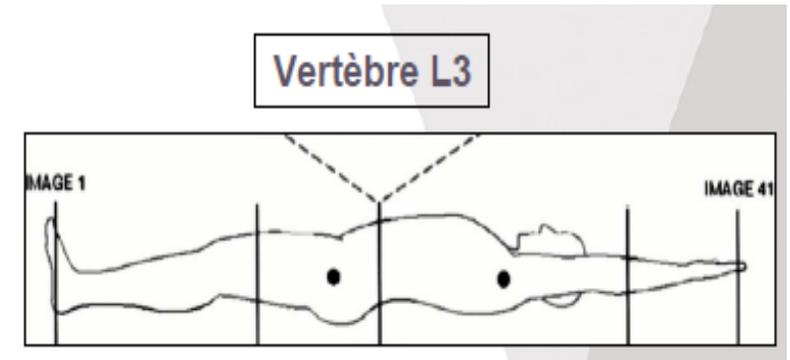
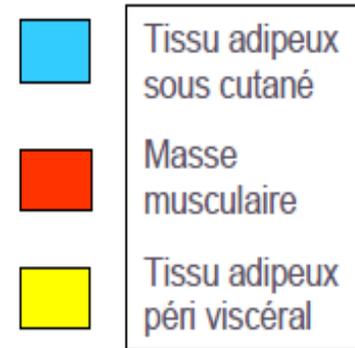
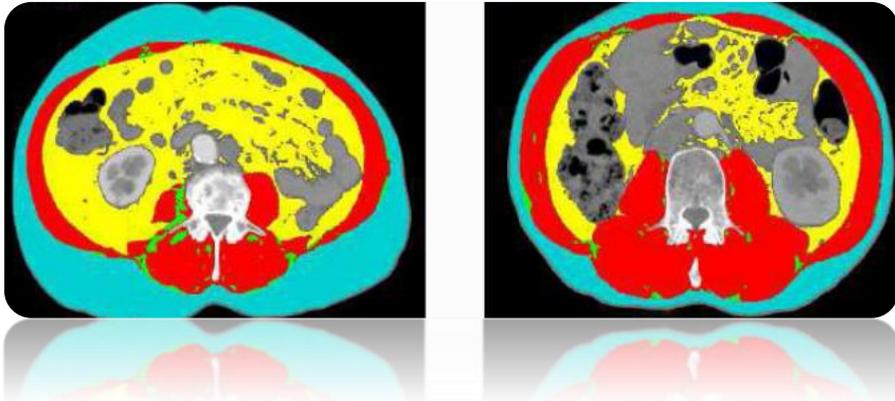
| Characteristics | Patients with lymphopenia (N = 18) | Patients without lymphopenia | | p† |
|---|------------------------------------|------------------------------|-----------------------------|--------|
| | | With sarcopenia (N = 43) | Without sarcopenia (N = 33) | |
| Postoperative biological parameters | | | | |
| Lymphopenia (<1000/mm³), | | | | 0.0029 |
| No. (%) | | | | |
| No | 9 (52.9) | 30 (81.1) | 30 (93.8) | |
| Yes | 8 (47.1) | 7 (18.9) | 2 (6.2) | |

Sarcopénie → Lymphopénie

Sarcopénie

Perte de force et de
masse musculaire

Mesure radiologique : Surface musculaire indexée sur la taille
<38,5 cm²/m² chez la femme
<52,4 cm²/m² chez l'homme



- Données disponibles
- Accord d'experts



- Difficilement utilisable routine clinique
- Chronophage
- Technique+++

Sarcopénie

Perte de force et de masse musculaire

Autres moyens d'évaluation

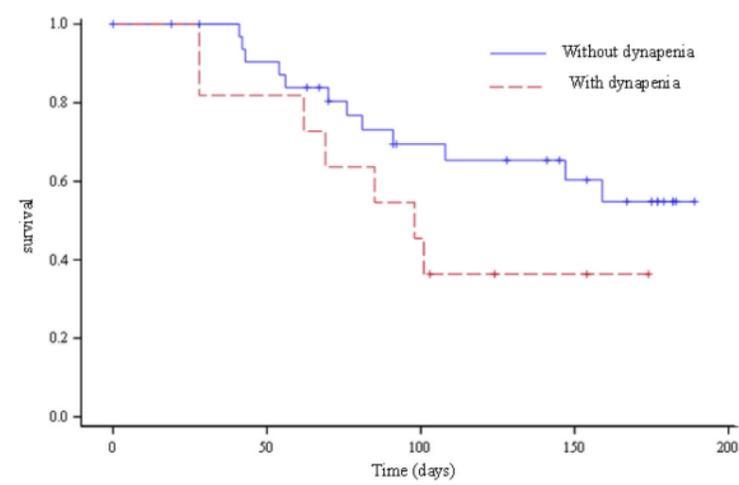
Handgrip Strength Testing
Dynamomètre



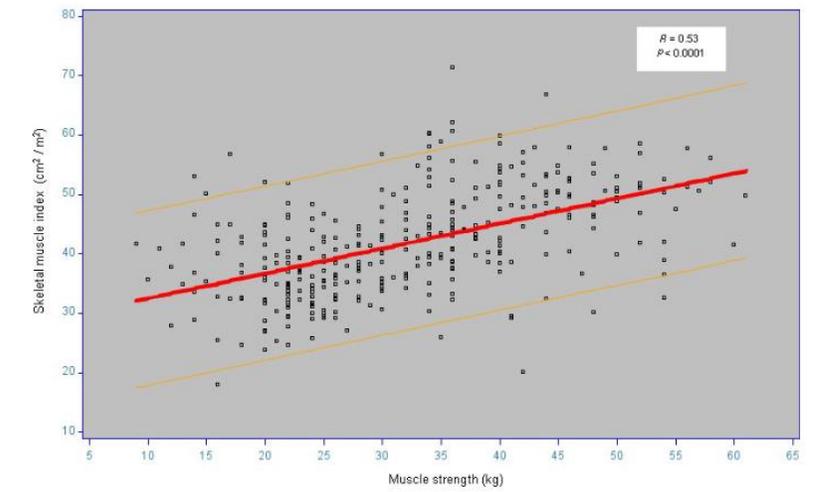
- Tests fonctionnels validés
- Rapide +++
- Outil fiable, facilement réalisable



- **Seuils bas** < 16 kg pour les femmes
< 26 kg pour les hommes



Corrélation entre handgrip et index de surface musculaire



| Toxicity (All Grade) | Overall (n = 244) | Exploratory Low HGS ¹ (n = 107) | Normal HGS ¹ (n = 137) | p Value |
|-------------------------------------|-------------------|--|-----------------------------------|---------|
| Neuropathy ² (%) | 174 (94.6) | 66 (91.7) | 108 (96.4) | 0.193 |
| Asthenia (%) | 224 (91.8) | 104 (97.2) | 120 (87.6) | 0.014 |
| Diarrhea (%) | 139 (57.0) | 56 (52.3) | 83 (60.6) | 0.214 |
| Nausea ³ (%) | 115 (56.9) | 41 (49.4) | 74 (62.2) | 0.084 |
| Vomiting ³ (%) | 51 (25.2) | 15 (18.1) | 36 (30.3) | 0.047 |
| Neutropenia (%) | 60 (24.6) | 26 (24.3) | 34 (24.8) | 1.000 |
| Anemia (%) | 165 (67.6) | 83 (77.6) | 82 (59.9) | 0.006 |
| Thrombopenia (%) | 73 (29.9) | 32 (29.9) | 41 (29.9) | 1.000 |
| Hand foot syndrome ⁴ (%) | 10 (4.8) | 5 (5.4) | 5 (4.3) | 0.629 |
| Oral mucositis ⁴ (%) | 29 (11.9) | 15 (14.0) | 14 (10.2) | 0.455 |

Moreau et al, Cancer Med 2019
Marti et al, Nutrients 2022
Botsen et al, BMC Cancer 2018

Sarcopénie

Perte de force et de masse musculaire

Autres moyens d'évaluation

Impédancemétrie



| Méthodes de mesure | Hommes | Femmes |
|--|--------|--------|
| Force de préhension (dynamomètre) en kg | < 26 | < 16 |
| Vitesse de marche (m/s) | < 0,8 | < 0,8 |
| Indice de surface musculaire en L3 en cm ² /m ² (scanner, IRM) | 52,4 | 38,5 |
| Indice de masse musculaire en kg/m ² (impédancemétrie) | 7,0 | 5,7 |
| Indice de masse non grasse (impédancemétrie ^a) en kg/m ² | < 17 | < 15 |
| Masse musculaire appendiculaire (DEXA) en kg/m ² | 7,23 | 5,67 |



- BIA multi-fréquence validée (DEXA)
- Analyse rapide
- Interprétation résultats facile
- Analyses complémentaires (hydratation, contenu protéique, etc...)



- Onéreux (1 500 à 5 000 €)

Sarcopénie

Perte de force et de
masse musculaire

Autres moyens d'évaluation

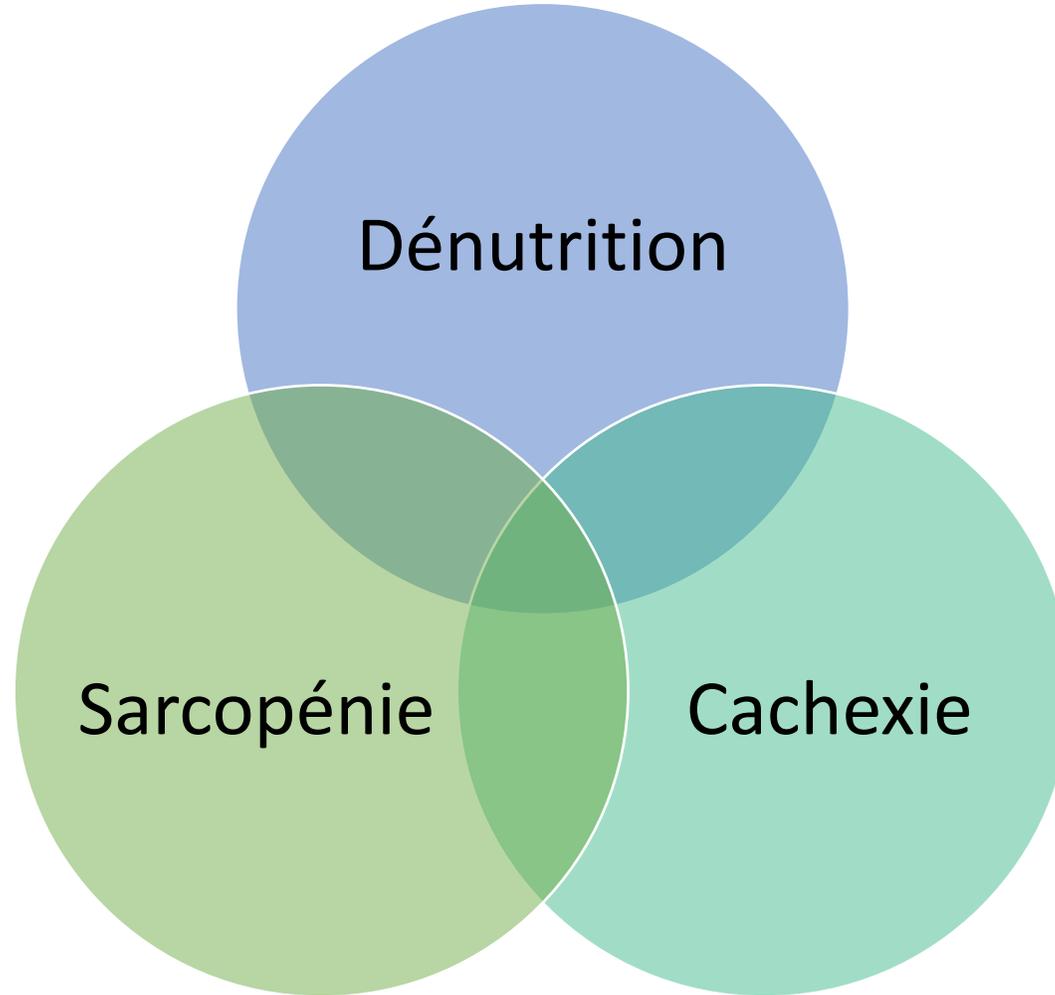
Biomarqueurs plasmatiques ?



Perte de poids, IMC bas
Perte de masse et/ou fonction musculaire

Oncologie

→ critères biologiques (albuminémie, pré-albuminémie)
ne sont plus des critères diagnostiques



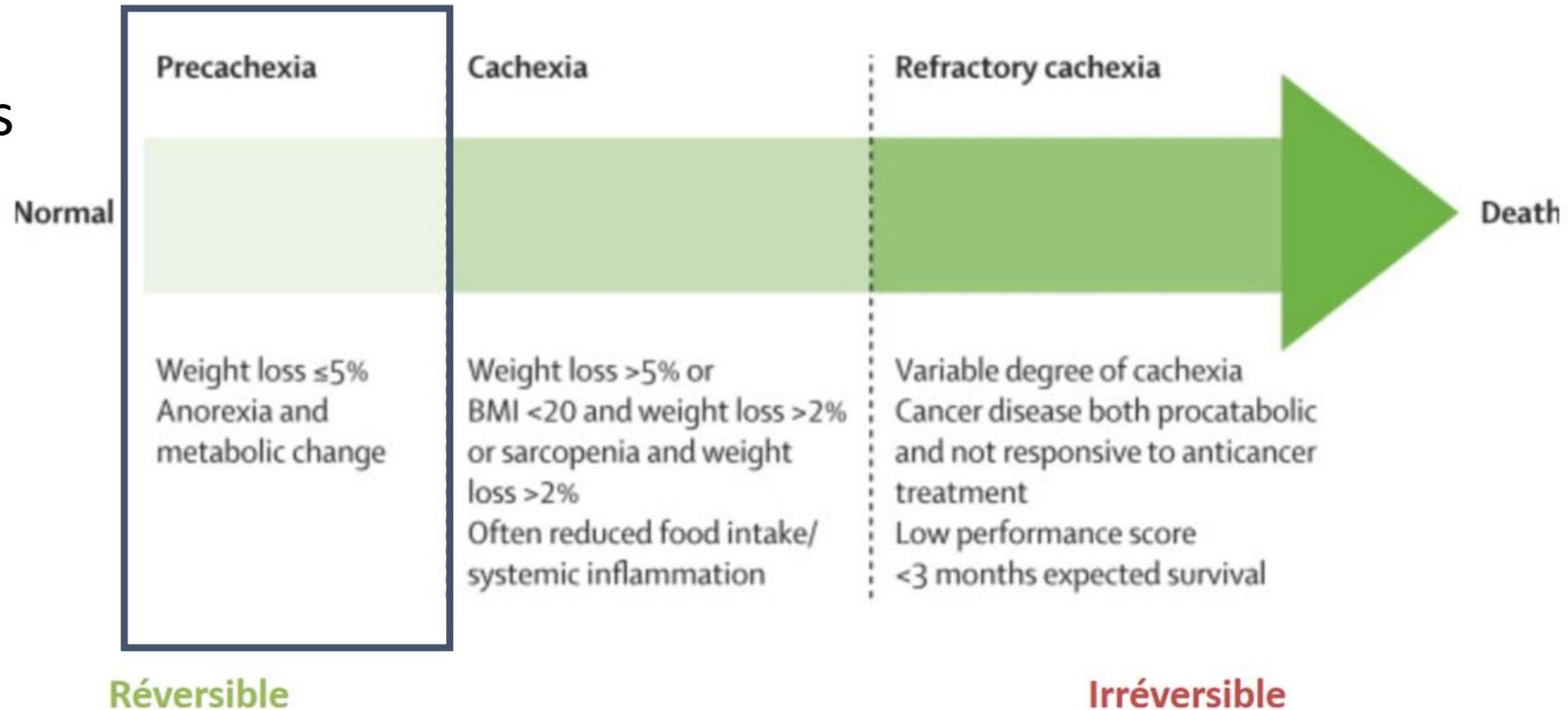
Concept initialement *gériatrique*
Perte de force et de masse
musculaire

Perte de muscle squelettique ±
Perte de masse grasse
Secondaire à un *hypercatabolisme*
en *contexte inflammatoire*

Cachexie

→ 3 stades

- ↗ complications liées au traitement (chimiothérapie, chirurgie)
- ↘ qualité de vie
- ↗ mortalité liée au cancer



Prise en charge précoce

Cachexie

Syndrome multifactoriel

Consommation alimentaire réduite

↘ apports énergétiques



Balance énergétique

Modifications métaboliques

- Dépense énergétique élevée
- Catabolisme excessif
- Inflammation

↗ dépenses
énergétiques au repos

Cachexie

Syndrome multifactoriel

Consommation alimentaire réduite

↘ apports énergétiques



↗ dépenses
énergétiques au repos

Modifications métaboliques

- Dépense énergétique élevée
- Catabolisme excessif
- Inflammation

Balance énergétique

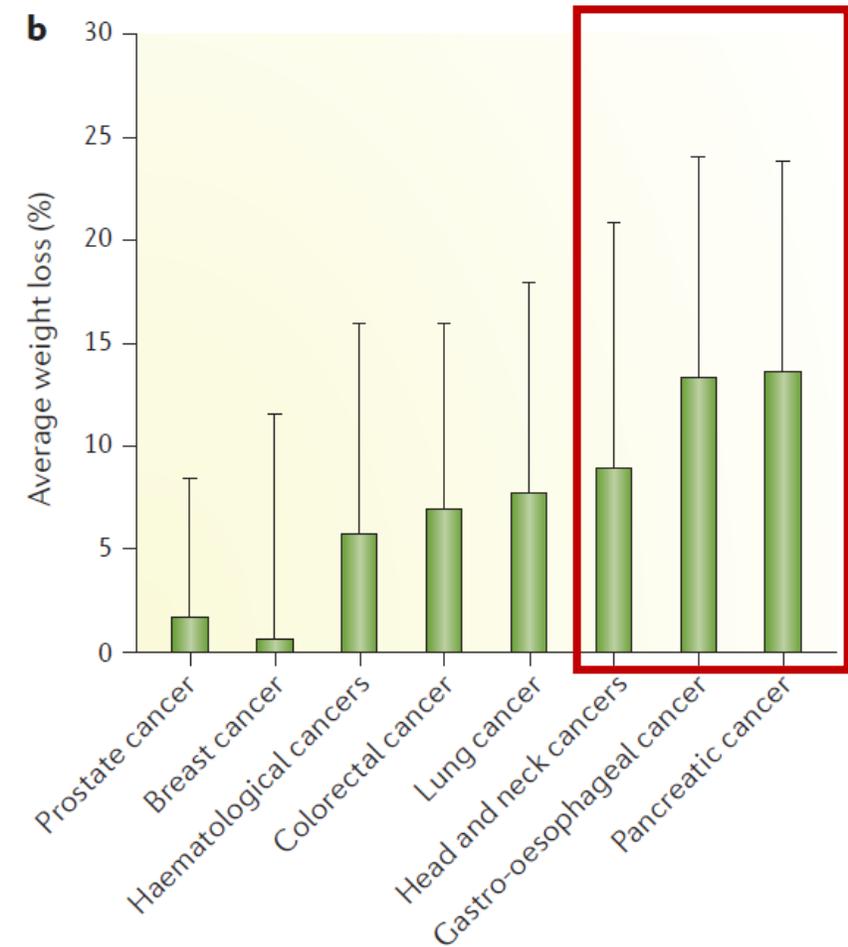
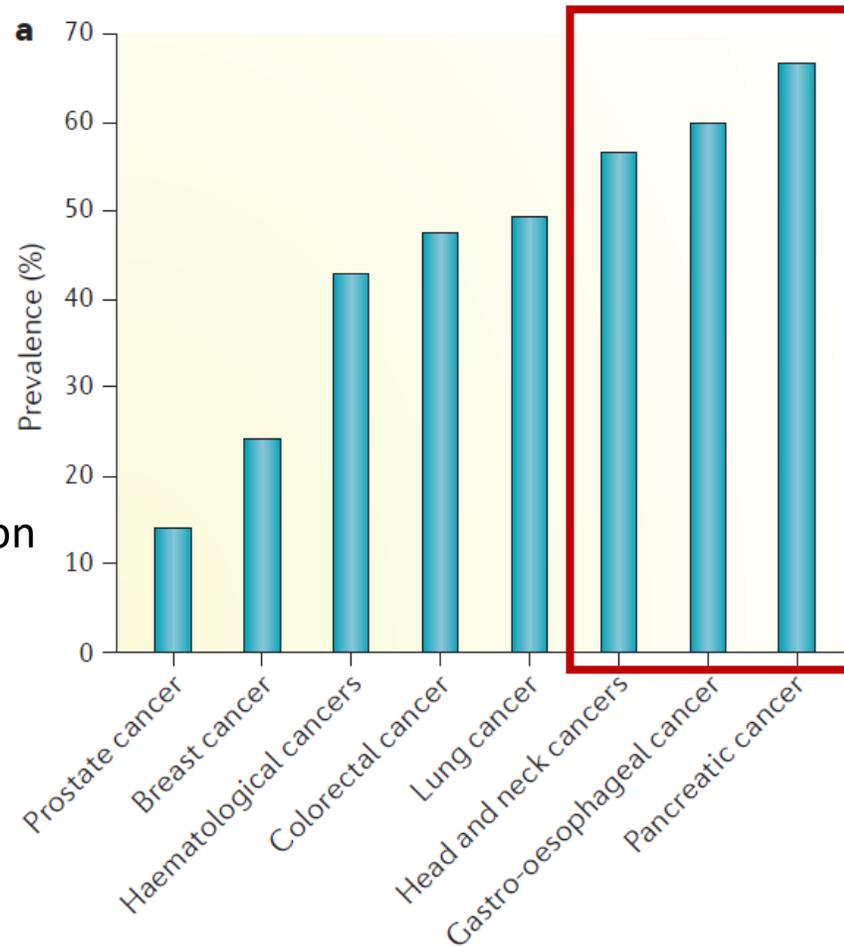
Cachexie

Cancers digestifs et ORL

Diagnostic à un stade avancé

Effets directs sur ingestion/digestion/absorption des aliments

Variable selon le type de cancers



Cachexie

Syndrome multifactoriel

Consommation alimentaire réduite

↘ apports énergétiques



↗ dépenses
énergétiques au repos

Modifications métaboliques

- **Dépense énergétique élevée**
- Catabolisme excessif
- Inflammation

Balance énergétique

Cachexie

Dépense énergétique élevée

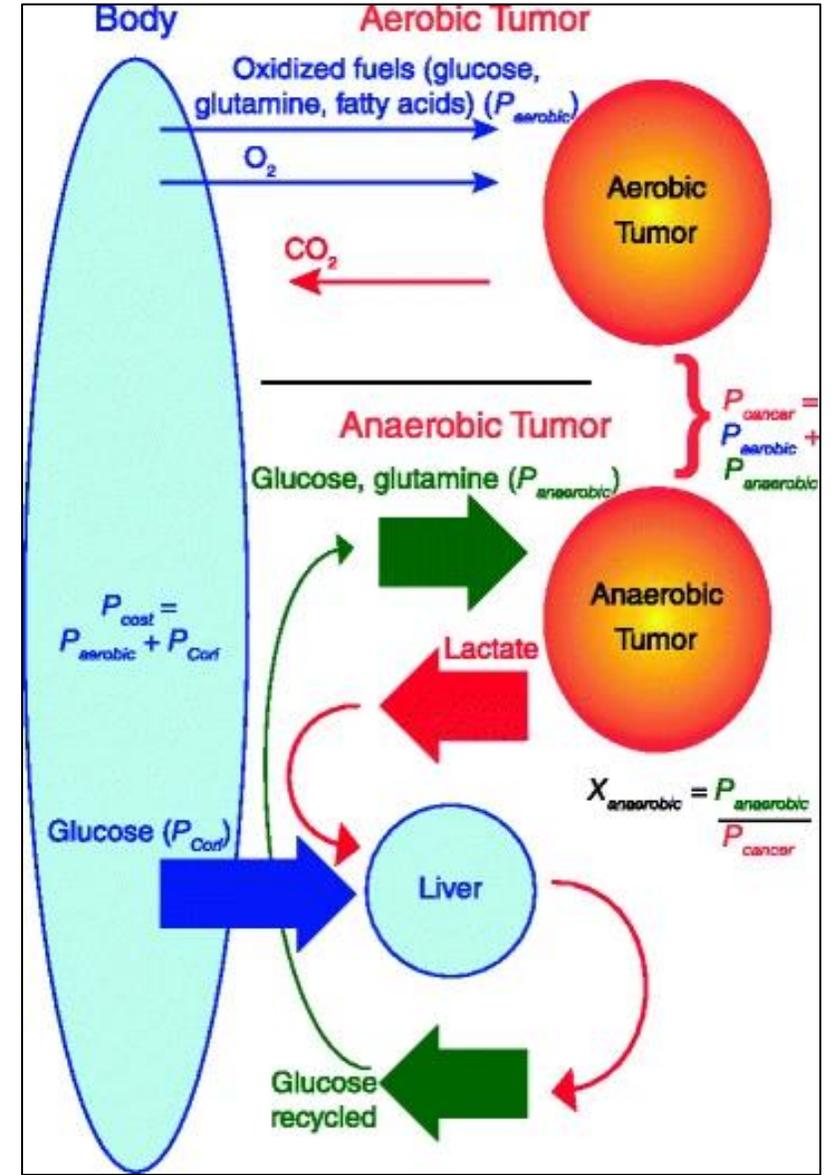
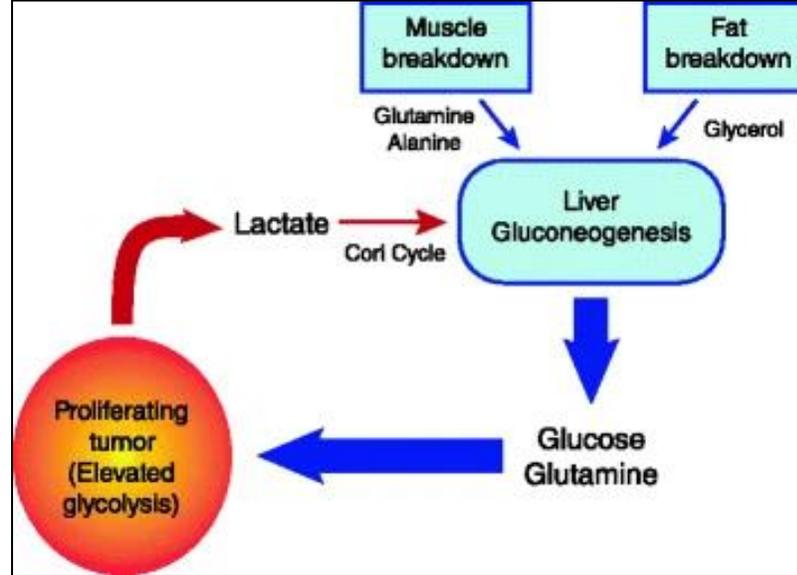
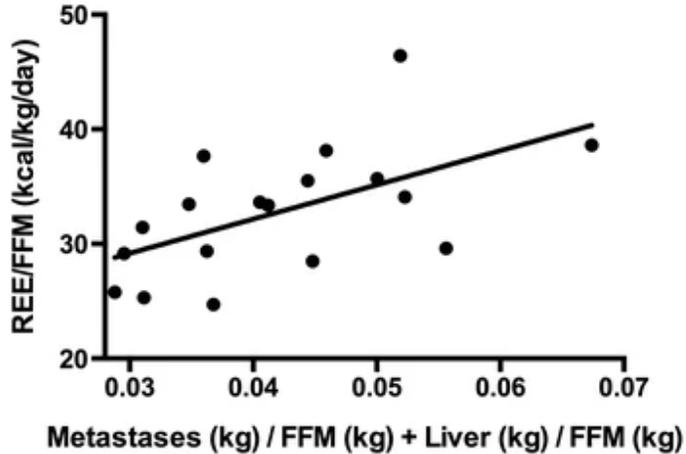
Métabolisme tumoral élevé

→ ↗ dépenses énergétiques au repos

Taux métabolique intrinsèque à la tumeur
→ lié à la masse tumorale

→ lié au degré de métabolisme
énergétique anaérobie

REE/FFM vs (Metastases/FFM + Liver/FFM)

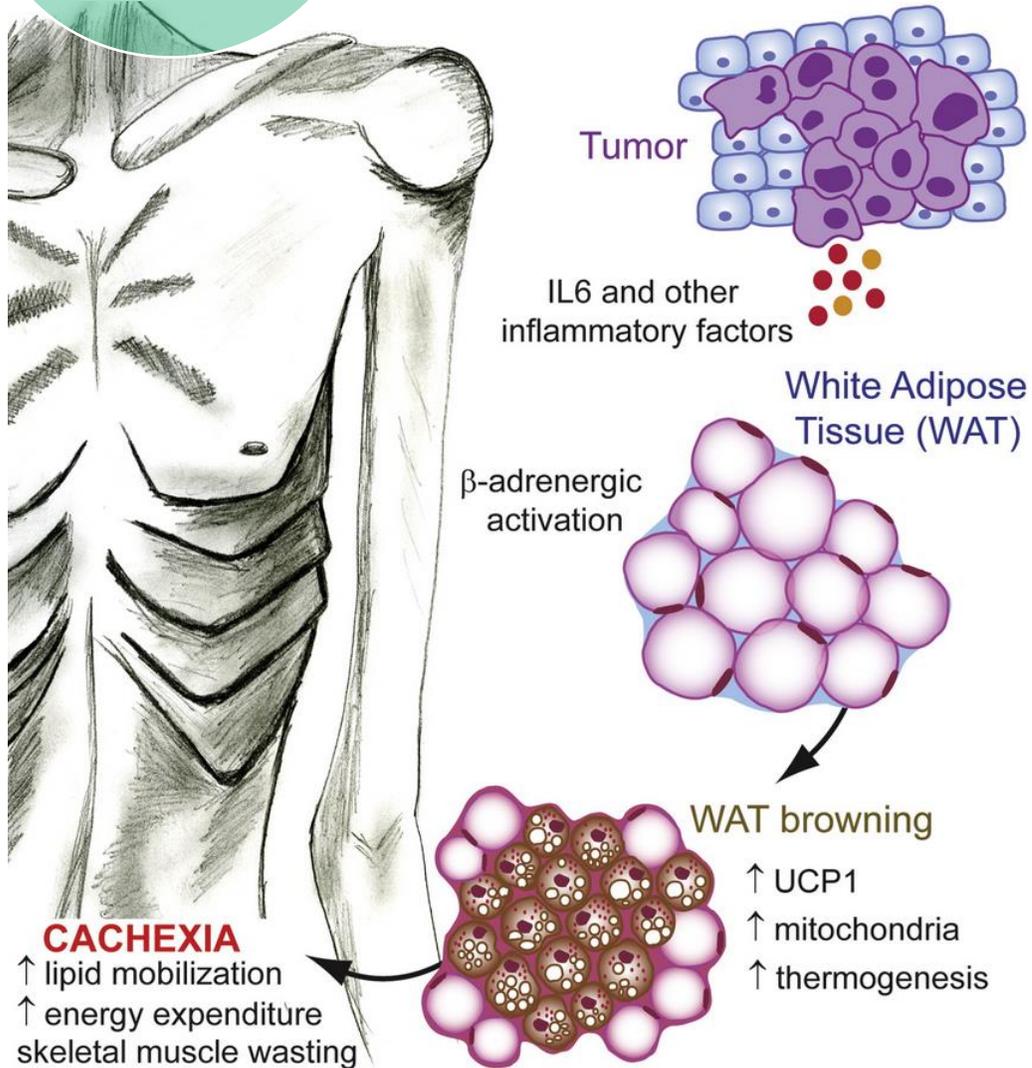


→ Le métabolisme anaérobie coûte 3 fois plus d'énergie en raison du coût de recyclage du lactate perdu par le tumeur

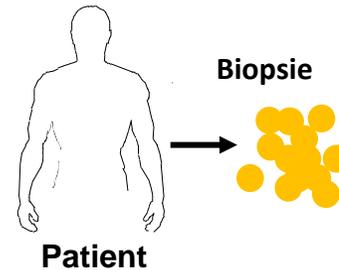
Cachexie

Dépense énergétique élevée

Thermogénèse (graisse brune) → ↗ dépenses énergétiques au repos

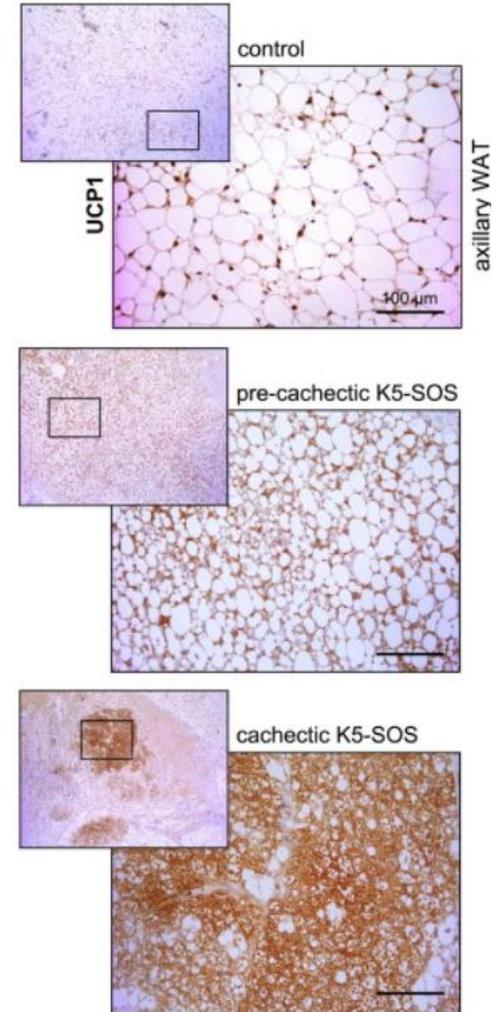


Altération de la thermogénèse via le «brunissement» des cellules adipeuses blanches



Thermogénèse régulée par **UCP1**

UCP1 ↗ dans tissu adipeux blanc chez les patients atteints de cachexie



Cachexie

Syndrome multifactoriel

Consommation alimentaire réduite

↘ apports énergétiques



↗ dépenses
énergétiques au repos

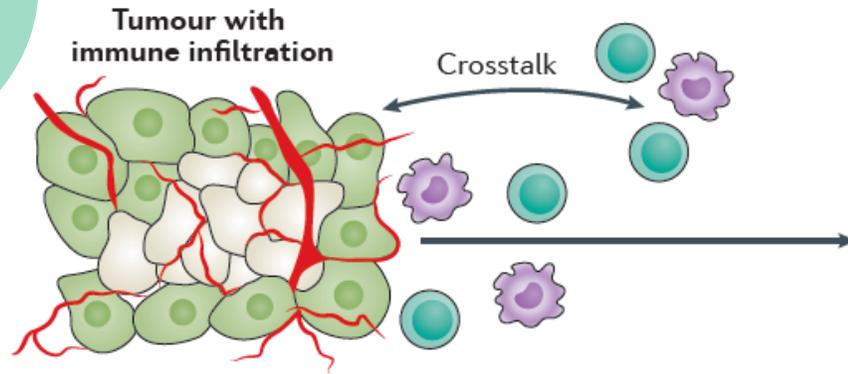
Modifications métaboliques

- Dépense énergétique élevée
- **Catabolisme excessif**
- **Inflammation**

Balance énergétique

Cachexie

Facteurs pro-cachexie



Facteurs sécrétés par la tumeur et le microenvironnement

Tumour-derived catabolic factors

- Activins
- Myostatin
- TGF β
- Serotonin
- Parathyroid hormone-related protein
- Adrenomedullin, miR-21, HSP70 and HSP90 (exported in exosomes)

Catabolisme

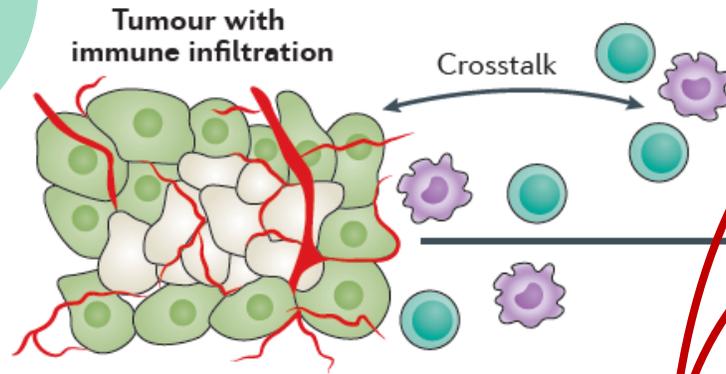
Pro-inflammatory mediators arising from tumour-immune system crosstalk

- IL-1 α
- IL-1 β
- IL-6
- IFN γ
- TNF
- IL-11
- IL-17
- LIF
- GDF15
- TWEAK
- TRAF6
- Oncostatin M
- TNFRSF12A
- PGE $_2$

Inflammation

Cachexie

Facteurs pro-cachexie



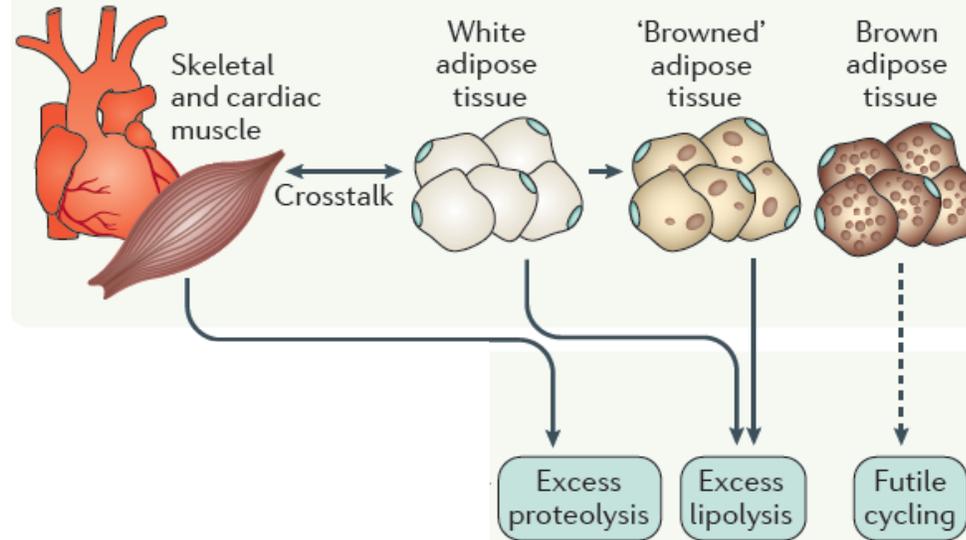
Facteurs sécrétés par la tumeur et le microenvironnement

- Tumour-derived catabolic factors
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 - **TGF β**
 - Serotonin
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 - TWEAK
 - TRAF6
 - Oncostatin M
 - TNFRSF12A
 - PGE₂

Catabolisme

Inflammation

Target organs



➔ Action sur les organes cibles

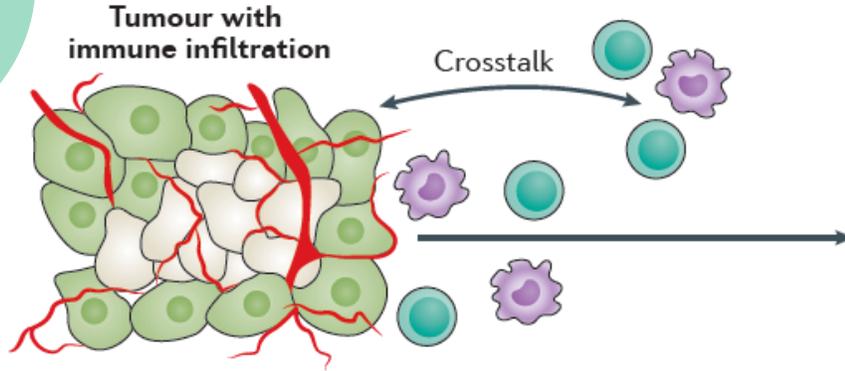
↗ Protéolyse

↗ Lipolyse

Cachexie

Facteurs pro-cachexie

Facteurs sécrétés par la tumeur et le microenvironnement

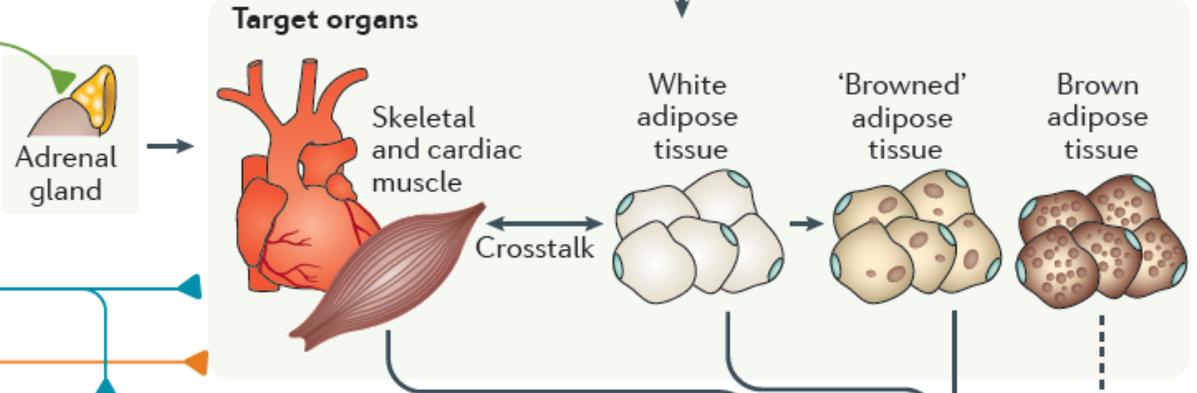
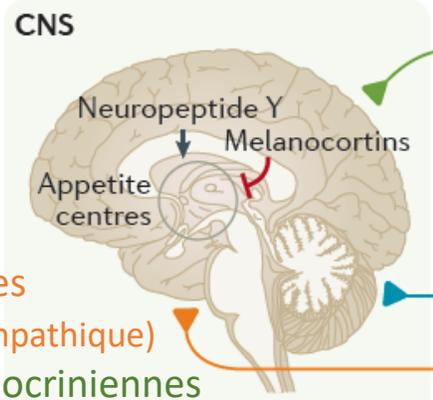


- Tumour-derived catabolic factors
 - Activins
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 - IL-11
 - IL-17
 - LIF
 - GDF15
 - TWEAK
 - TRAF6
 - Oncostatin M
 - TNFRSF12A
 - PGE₂

Catabolisme

Inflammation

Altération des contrôles du SNC

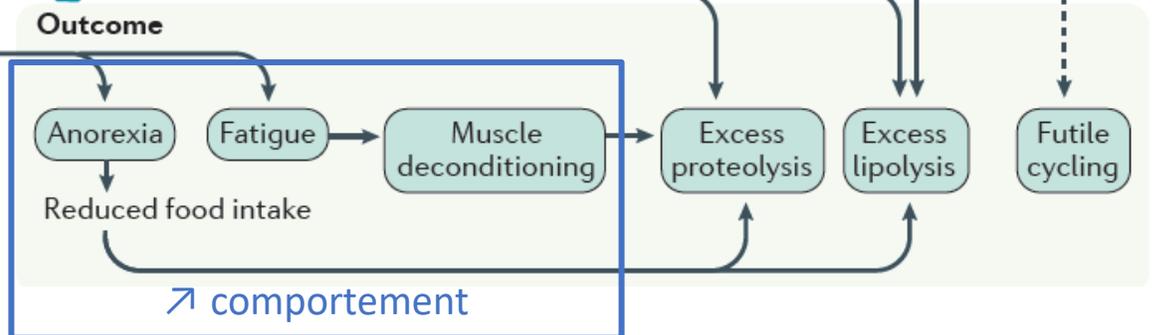


➔ Action sur les organes cibles

➤ sorties neuronales cataboliques (SN sympathique)

➤ sorties neuroendocriniennes (libération de corticostéroïdes surrénaliens)

- Catabolic sympathoadrenal outputs
- Catabolic behavioural outputs
- Catabolic sympathetic outputs

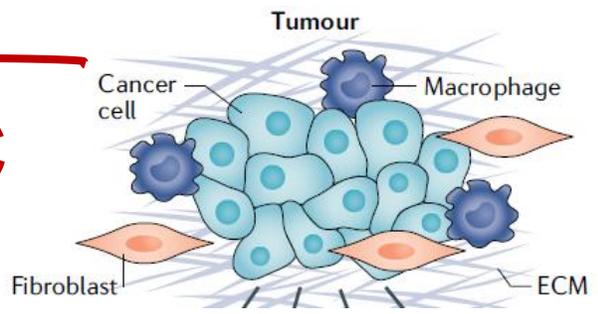
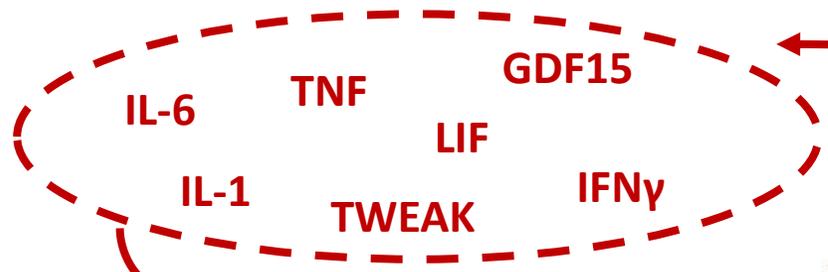


➤ Protéolyse

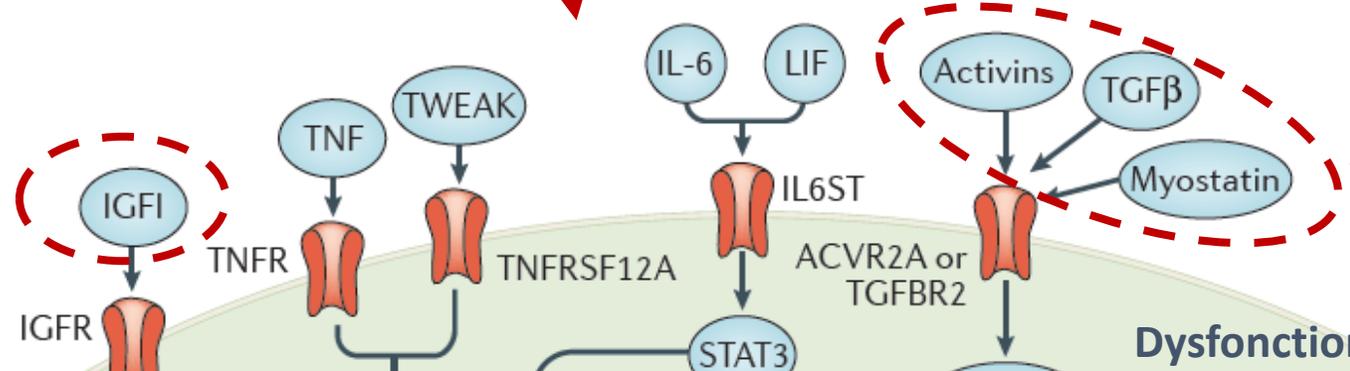
➤ Lipolyse

Cachexie

Facteurs pro-cachexie



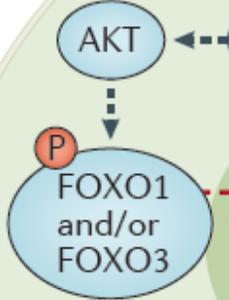
↘ Facteur de croissance analogue à l'insuline



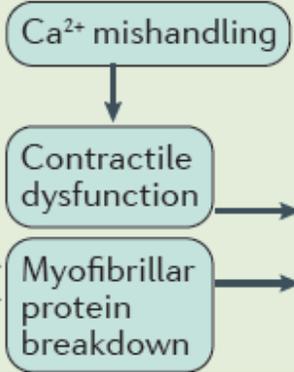
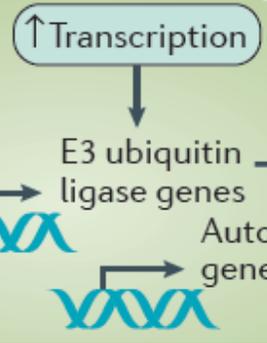
Dysfonctionnement du sarcomère

→ Atrophie et faiblesse musculaires

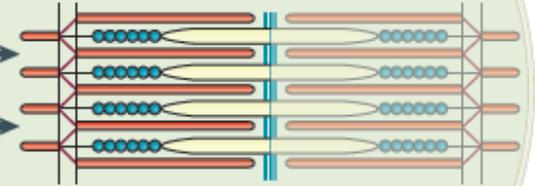
Favorisent la transcription de composants du système ubiquitine-protéasome et de l'autophagie



Inhibition of nuclear import



Disrupted sarcomere, muscle atrophy and weakness



Destruction sélective des protéines myofibrillaires qui forment les sarcomères et assurent la fonction contractile des muscles squelettiques

Cachexie

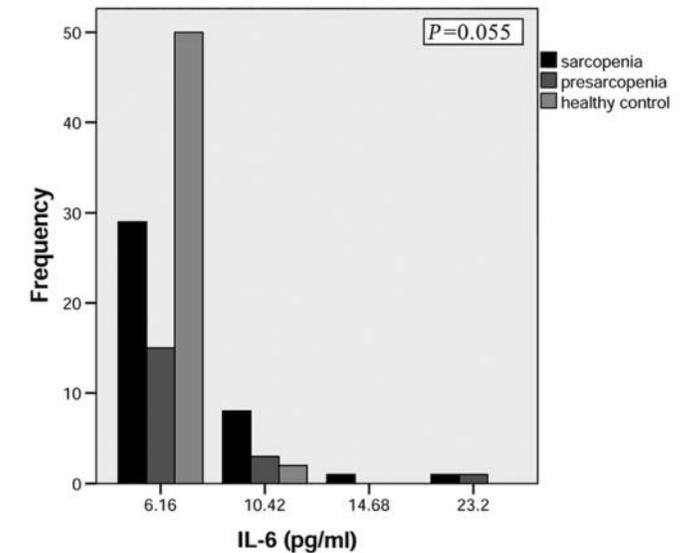
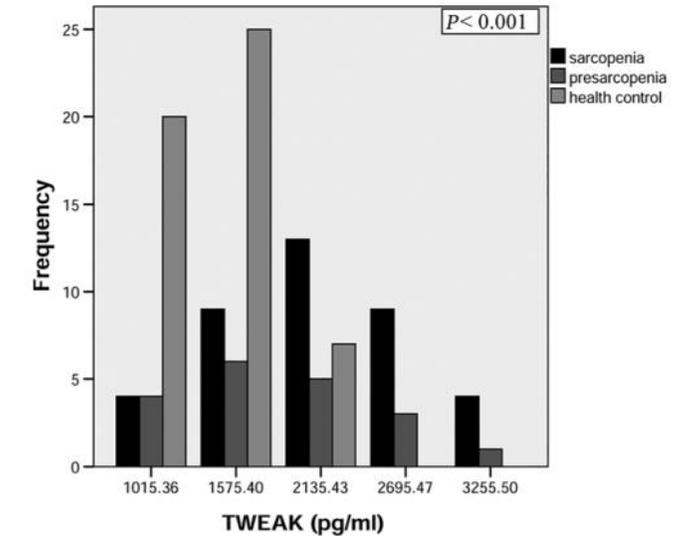
Facteurs pro-cachexie

Biomarqueurs plasmatiques ?



Circulating factors associated with sarcopenia during ageing and after intensive lifestyle intervention

| Characteristics | Sarcopenic subjects | Non-sarcopenic subjects | P value |
|--------------------|---------------------------|---------------------------|-------------------|
| N | 56 | 56 | — |
| IL-6, pg/mL | 2.8 (2.0–6.1) | 2(2.0–2.8) | 0.006 |
| IL-18, pg/mL | 893.61 ± 833.29 | 403.62 ± 250.89 | <0.001 |
| TNF-α, pg/mL | 29.11 ± 22.67 | 11.87 ± 10.56 | <0.001 |
| TWEAK, pg/mL | 1794.06 ± 639.13 | 1107.86 ± 303.65 | <0.001* |
| HsCRP, mg/L | 0.95(0.36–1.56) | 1.19(0.54–2.45) | 0.067 |
| Adiponectin, µg/mL | 3.53(1.63–7.39) | 7.26(3.11–13.47) | <0.001 |
| Leptin, ng/mL | 11.62(6.23–25.49) | 4.66(2.71–8.46) | <0.001 |
| IGF1, ng/mL | 62.13 ± 22.52 | 82.86 ± 32.84 | <0.001* |
| Insulin, pmol/L | 22.19 ± 17.36 | 31.26 ± 24.31 | 0.027* |
| FGF21, pg/ml | 49.99 (46.4, 61.2) | 58.00 (50.1, 68.9) | 0.150 |



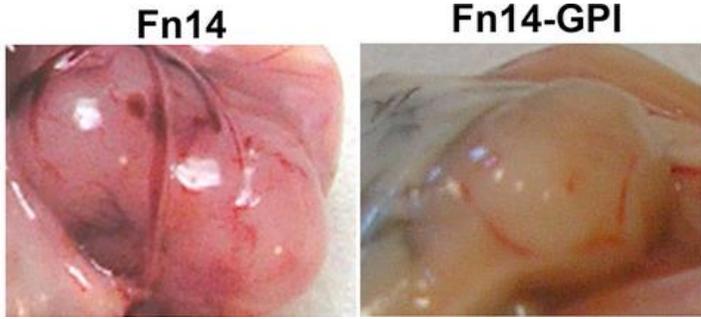
Cachexie

Facteurs pro-cachexie

TWEAK

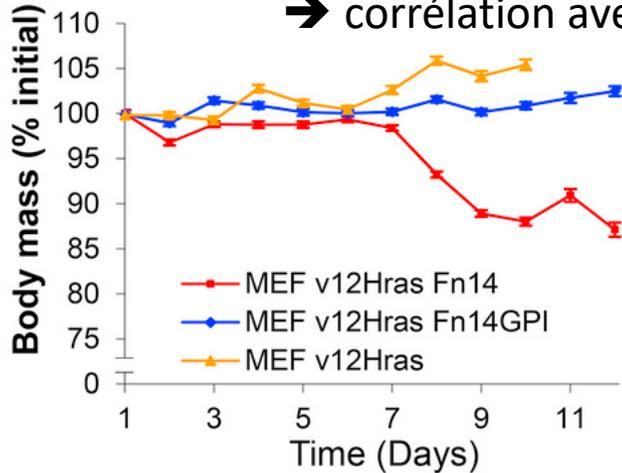
TNFSF12: TNF Superfamily Member 12

Action par son récepteur Fn14 (TNFRSF12A)

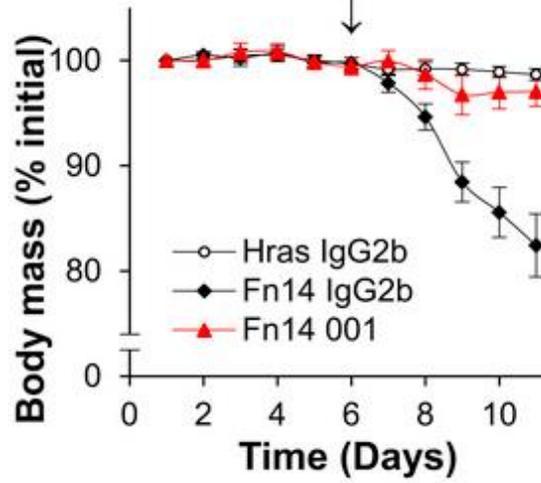


Fn14 surexprimé dans les tumeurs

→ corrélation avec la cachexie

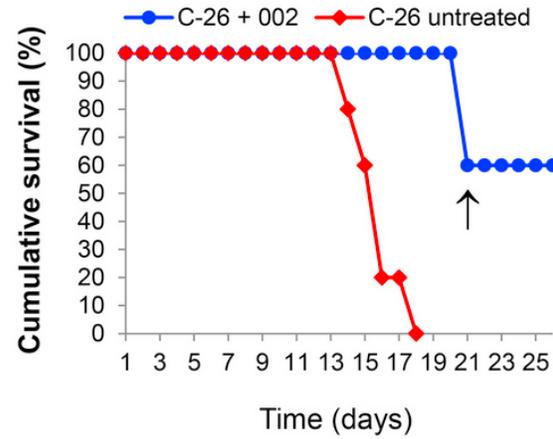
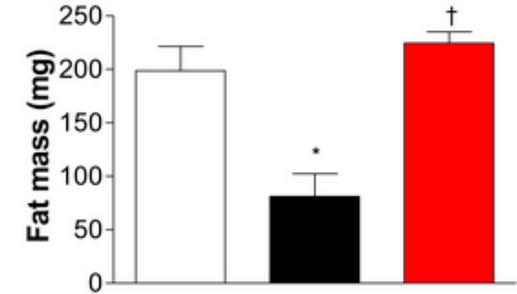
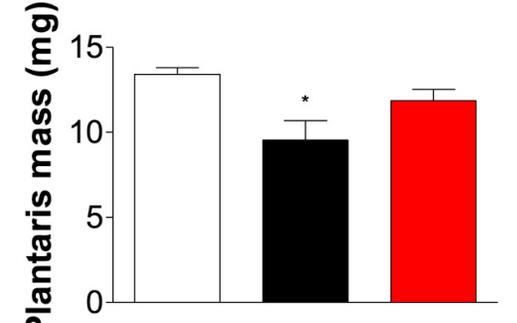
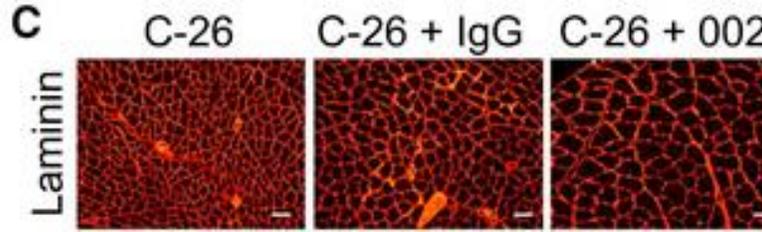


Neutralisation avec anticorps anti-Fn14



→ ↘ perte de poids

→ ↗ masse musculaire et masse grasse

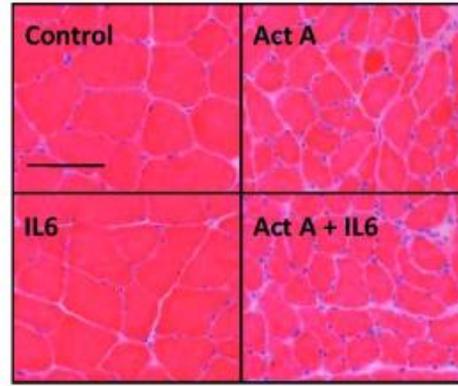


→ ↗ durée de vie

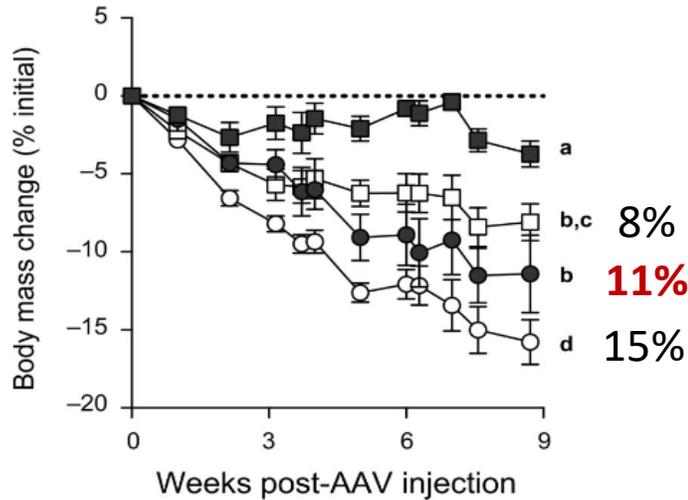
Cachexie

Facteurs pro-cachexie

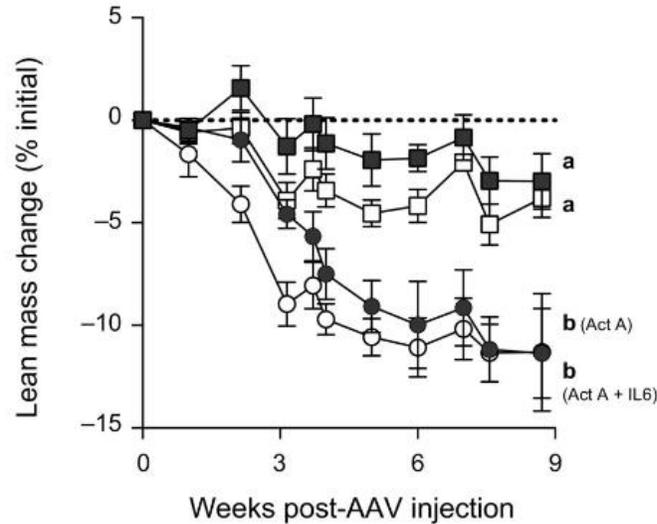
Activine A > IL-6



Control IL6
 Act A Act A + IL6



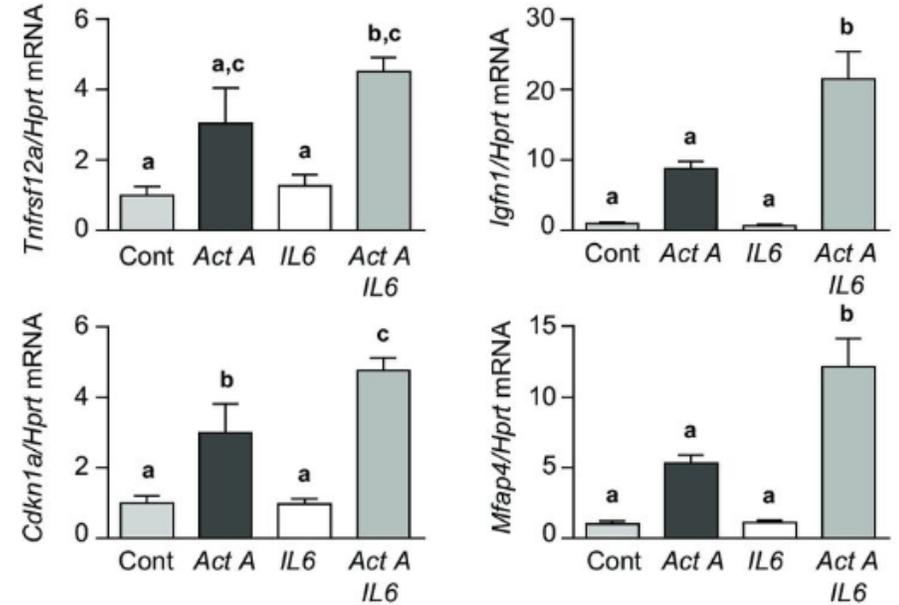
C



Activine A ↔ IL-6

Interactions entre les voies de signalisation de l'activine A et de l'IL-6

IL-6 ↗ l'expression des gènes associés à l'atrophie et la fibrose régulés par l'activine A
 → Tnfrsf12a, Igfn1, Zmynd17, Cdkn1a, Mfap4, Comp



➔ Perte de poids et perte de muscle squelettique induite par l'activine A avec une puissance plus élevée que l'IL-6

➔ IL-6 ↗ les effets délétères de l'activine A dans le muscle squelettique

Cachexie

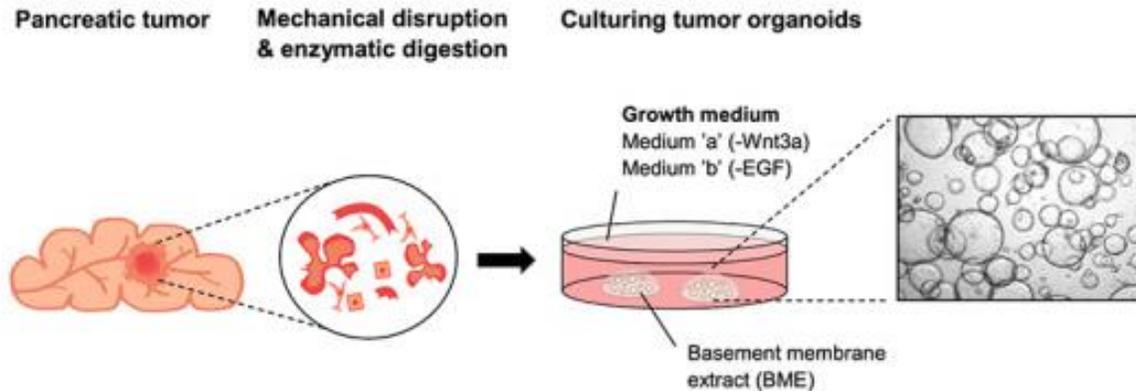
Facteurs pro-cachexie

Biomarqueurs plasmatiques ?



Cancers du pancréas

C-Establishment pancreatic tumor organoids



D-Characterization pancreatic tumor organoids

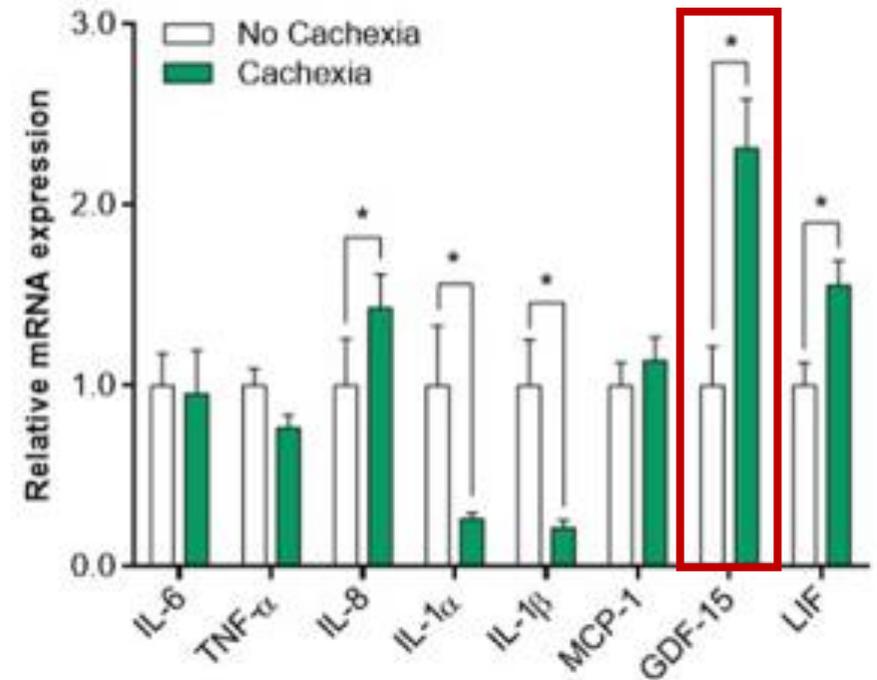


E-Expression of factors involved

Organoid-released factors

| | |
|---------------|-------------|
| IL-1 | MCP-1 |
| IL-6 | MIC-1/GDF15 |
| IL-8 | LIF |
| TNF- α | |

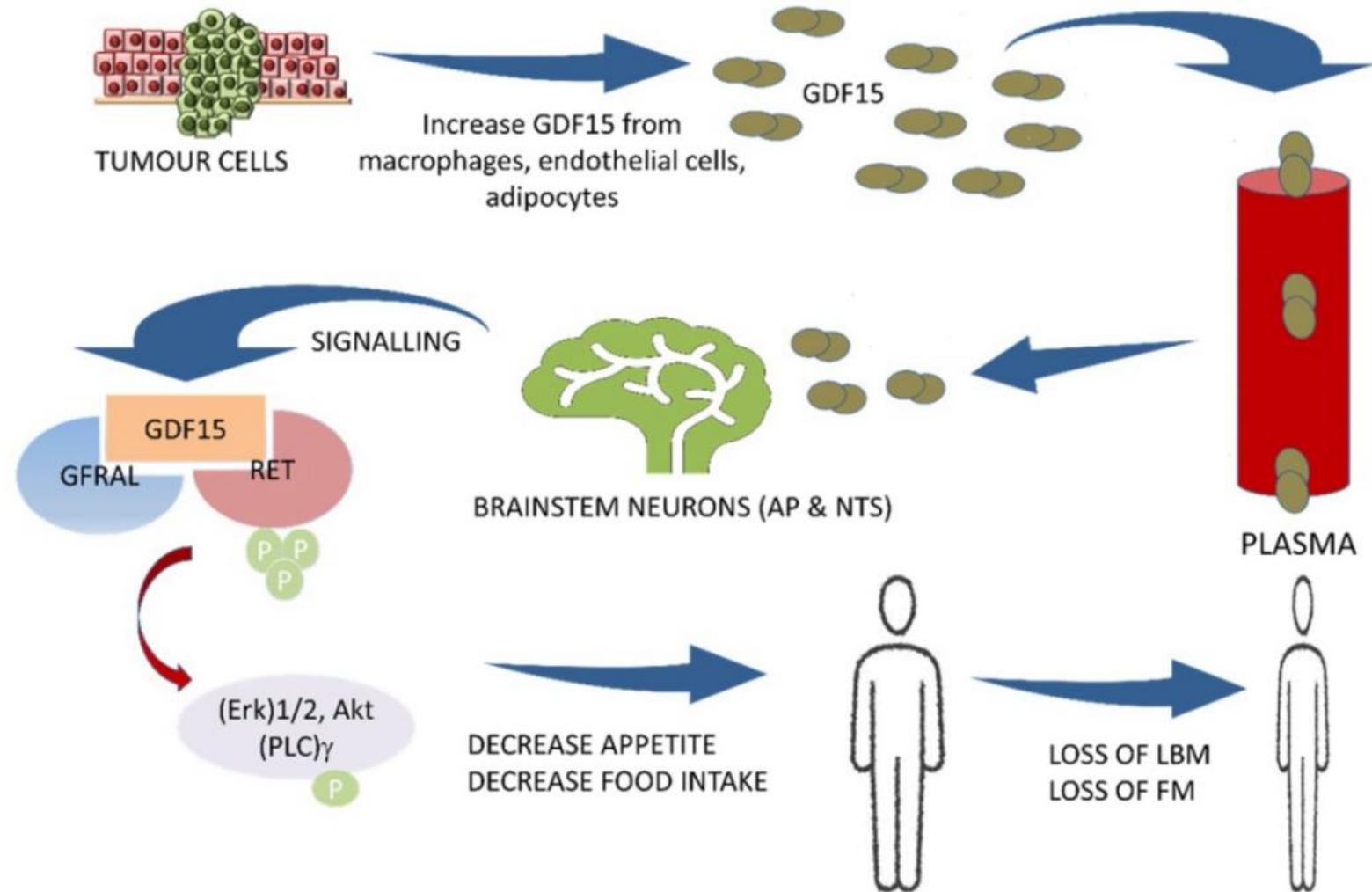
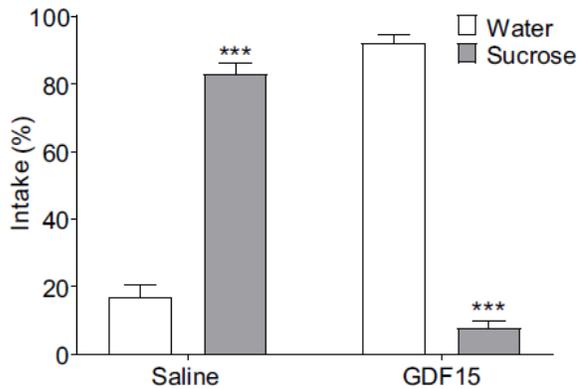
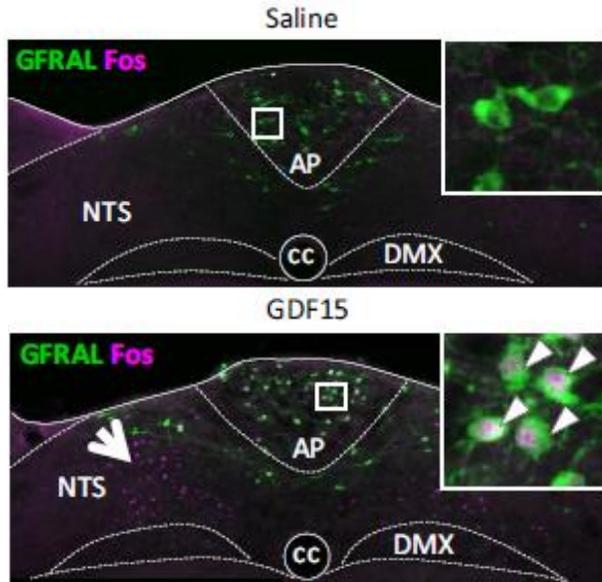
GDF15



Cachexie

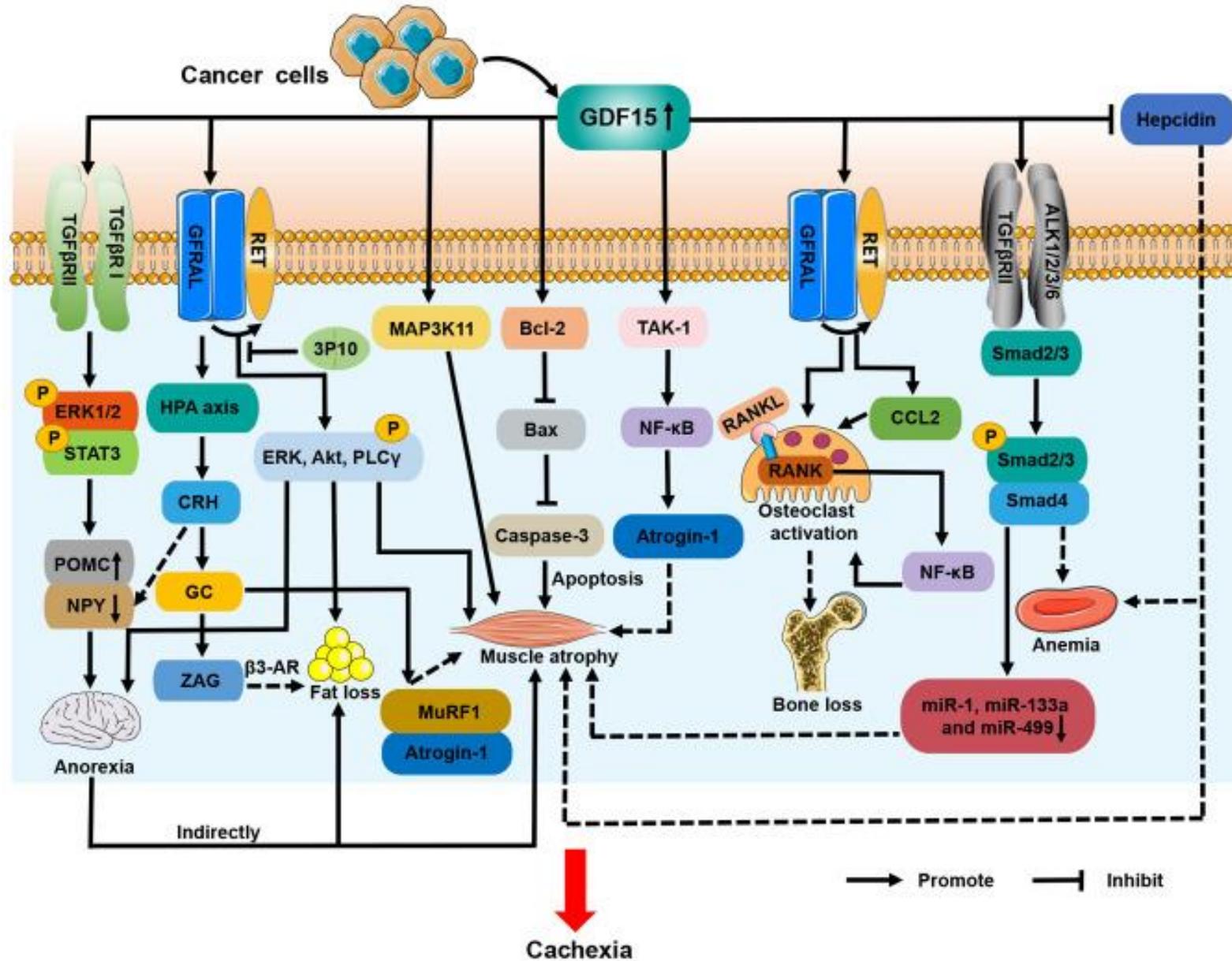
GDF15

member of the TGF- β cytokine family, also known as MIC-1 and NAG-1
 GDF15 receptor, GFRAL (GDNF-family receptor α -like)



Cachexie

GDF15



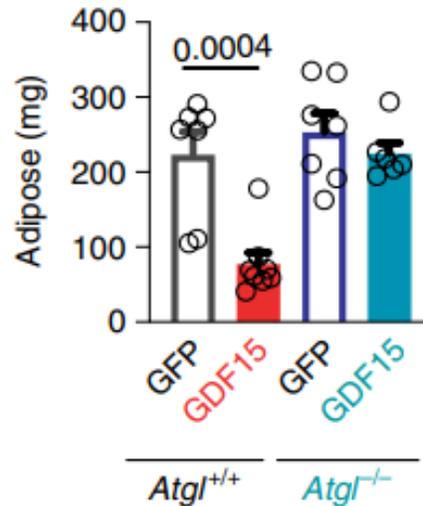
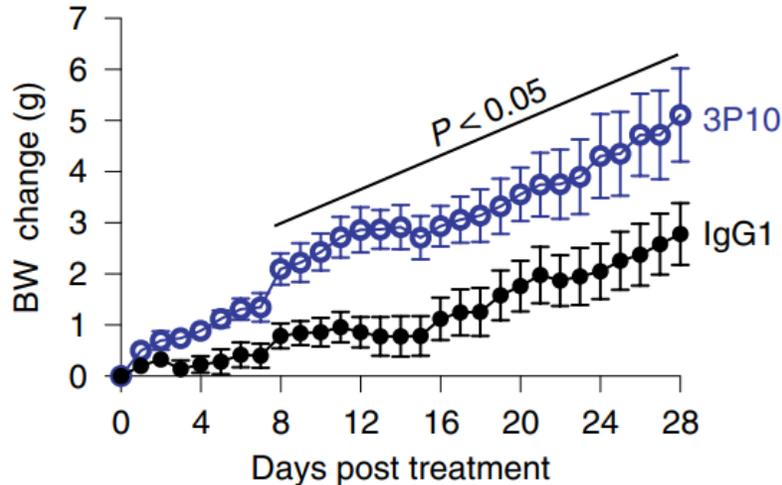
Cachexie

GDF15

Ciblage thérapeutique

Therapeutic antagonistic monoclonal antibody (3P10)

→ targets GFRAL and inhibits RET signaling



reverses excessive lipid oxidation and prevents cancer cachexia

GDF15 neutralization restores muscle function and physical performance in a mouse model of cancer cachexia

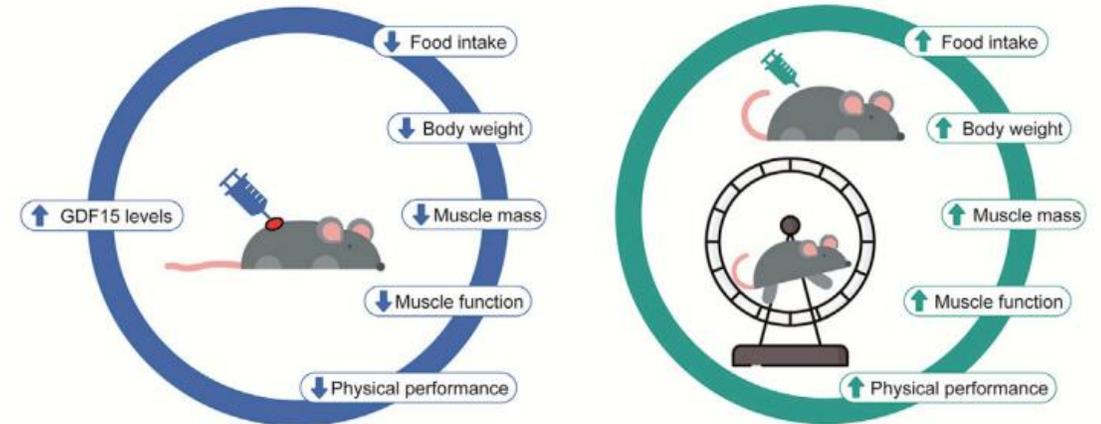
Mouse model of cancer-induced cachexia

The role of GDF15 in the cancer cachexia model

Subcutaneous implantation of TOV21G ovarian cancer cells

Treatment with an anti-GDF15 monoclonal antibody improves outcomes

mAB2

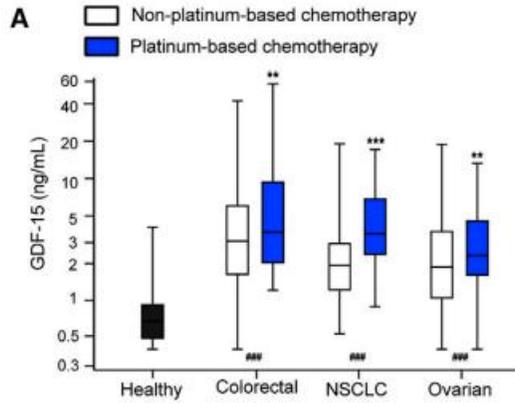


Treatment with a GDF15 neutralizing monoclonal antibody alleviates weight loss and improves muscle function and performance

Cachexie

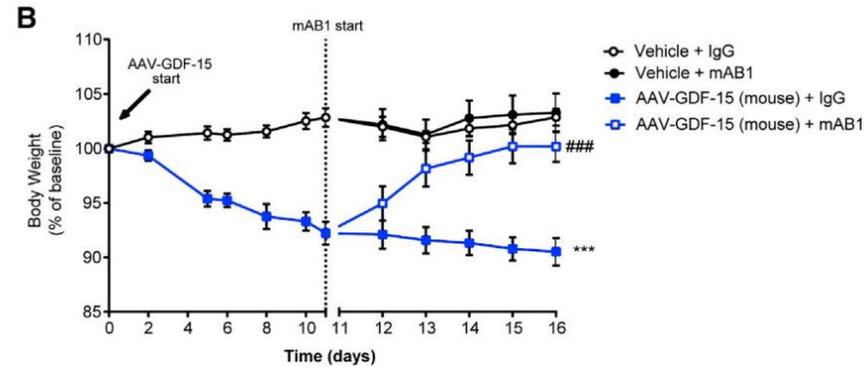
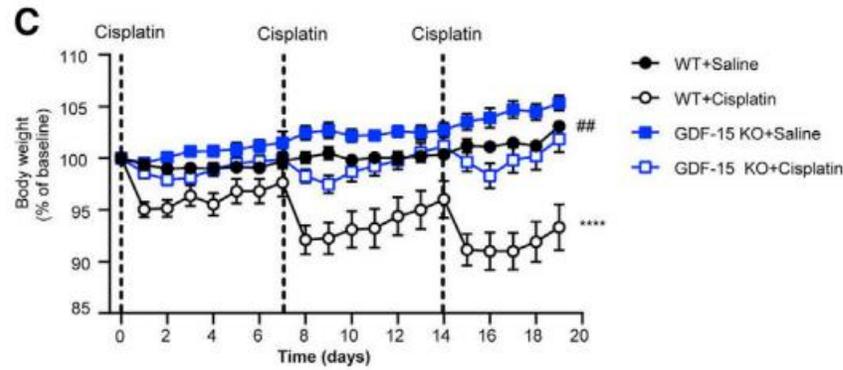
GDF15

Ciblage thérapeutique

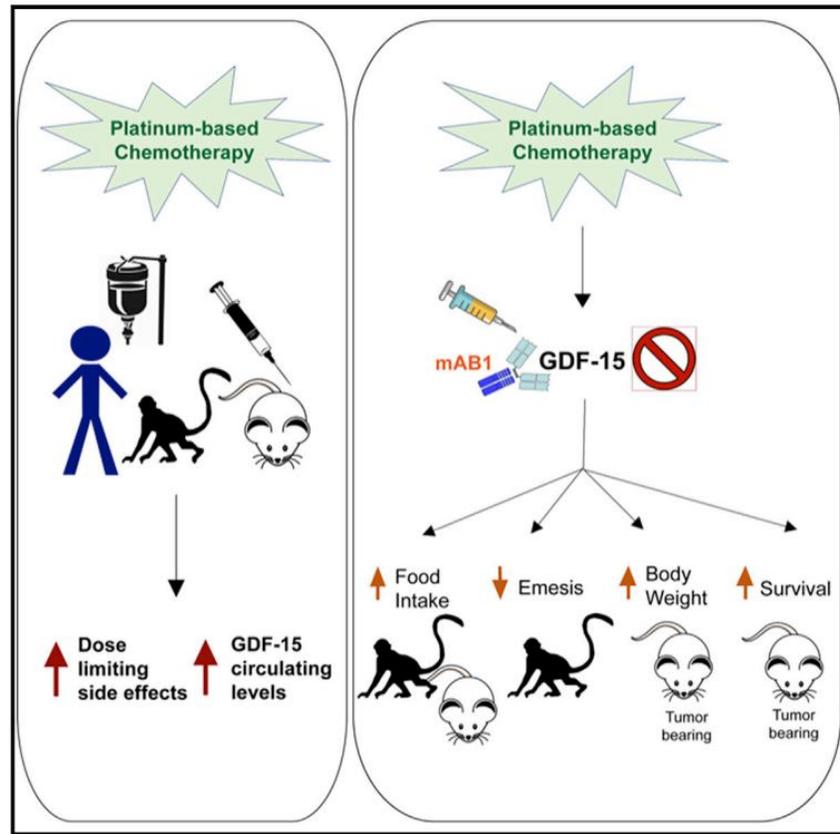
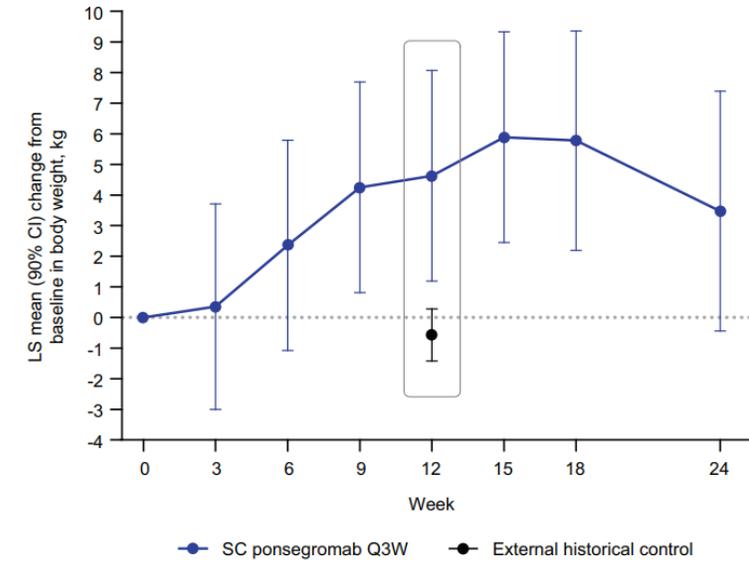


A Phase 1b First-In-Patient Study Assessing the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Ponegromab in Participants with Cancer and Cachexia

Jeffrey Crawford ; Roberto A. Calle ; Susie M. Collins ; Yan Weng ; Shannon L. Lubaczewski ; Clare Buckeridge ; Ellen Q. Wang ; Magdalena A. Harrington ; Anil Tarachandani ; Michelle I. Rossulek ; James H. Revkin



No treatment-related adverse events

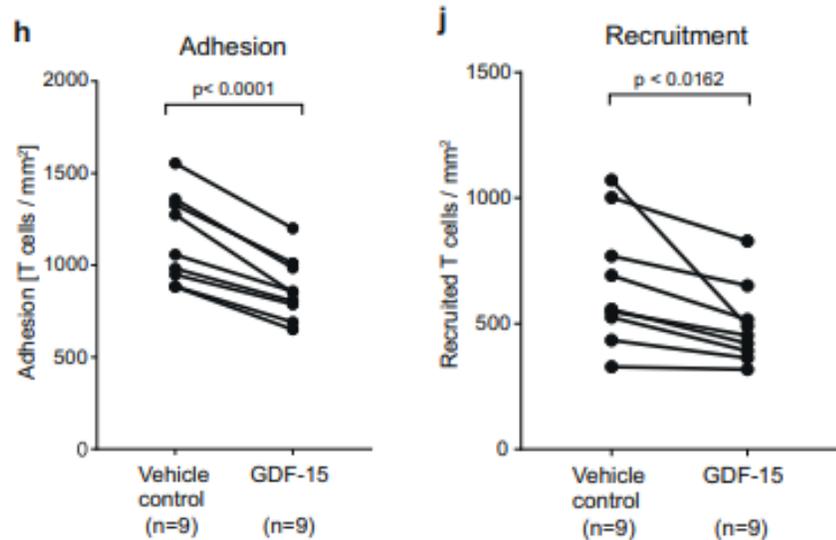


Cachexie

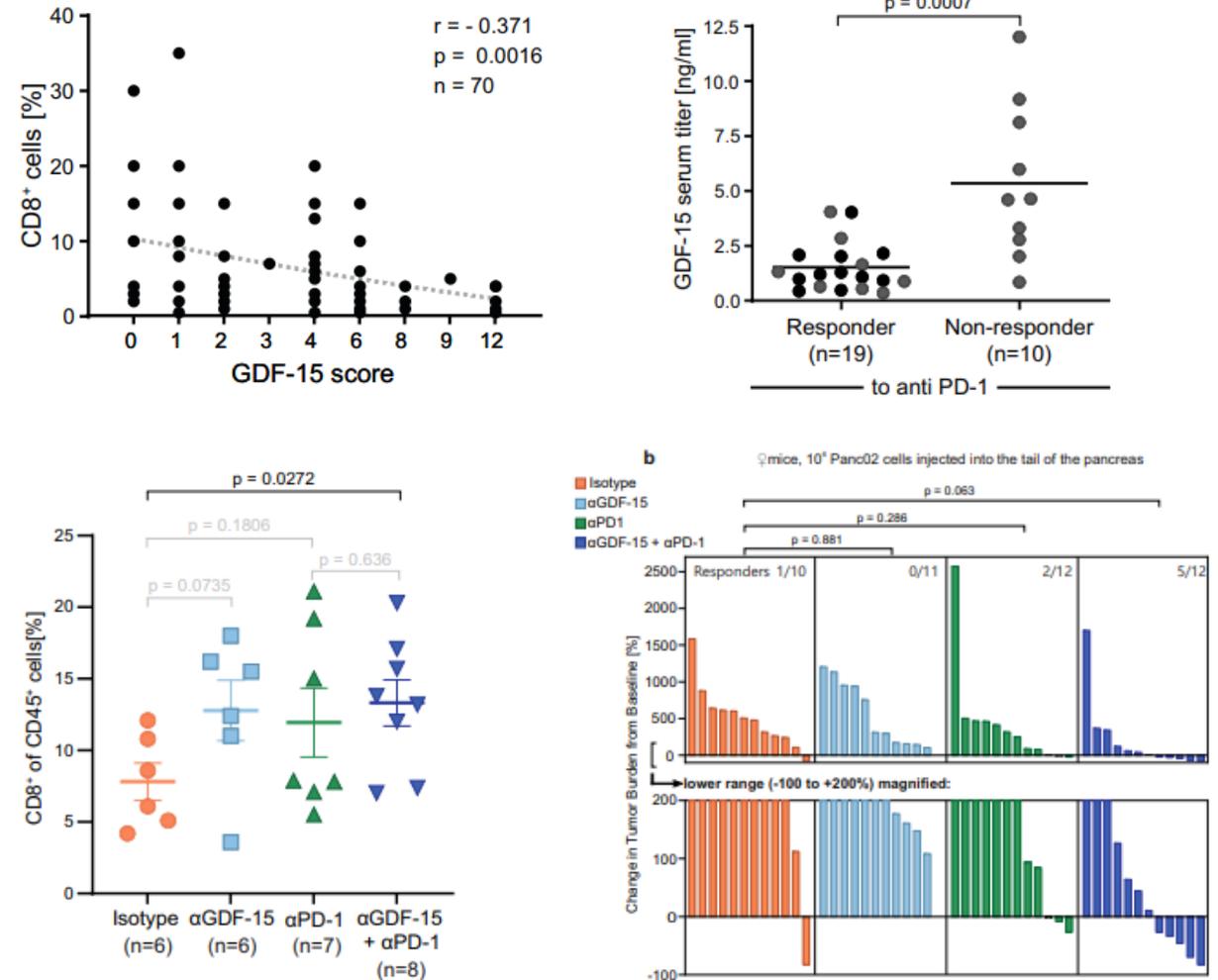
GDF15

Regulator of T cell extravasation into the tumor microenvironment

GDF-15 impairs LFA-1/ β 2-integrin-mediated adhesion of T cells to activated endothelial cells, which is a pre-requisite of T cell extravasation



GDF-15 serum levels strongly correlate with failure of anti-PD1



IRFC – Oncologie médicale

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Olivier Adotevi
Julien Viot
Emeline Orillard
Laura Mansi
Elodie Klajer
Stefano Kim

Tumorotheque

Frédéric Bibeau
Franck Monnier
Chloé Molimard



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Service de hépatologie

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Thierry Thevenot

Inserm CIC 1431 Biothérapies

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ARC et administrative**

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| Adeline Bouard | Marie Perchaud |
| Virginie Mougey | Ugo Chartral |
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Irwin Davidson
Christelle Thibault-Carpentier
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CIT – Ligue contre le Cancer

Aurélien de Reynies



GERCOR

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Anthony Turpin

