Caractérisation du profil d'expression des rétrovirus endogènes dans les cancers colorectaux métastatiques

Doctorat de Cancérologie, Génétique, Hématologie, Immunologie

Université Bourgogne Franche-comté

Ecole doctorale n°554: Environnement-Santé

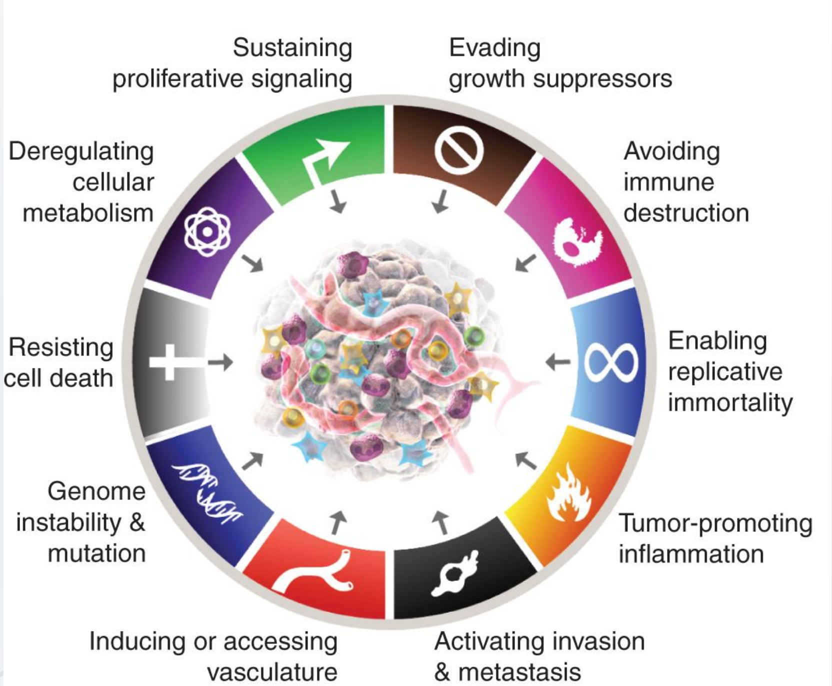
Par Dr Viot Julien

Direction : Pr Christophe Borg et Pr Daniel Gautheret

01

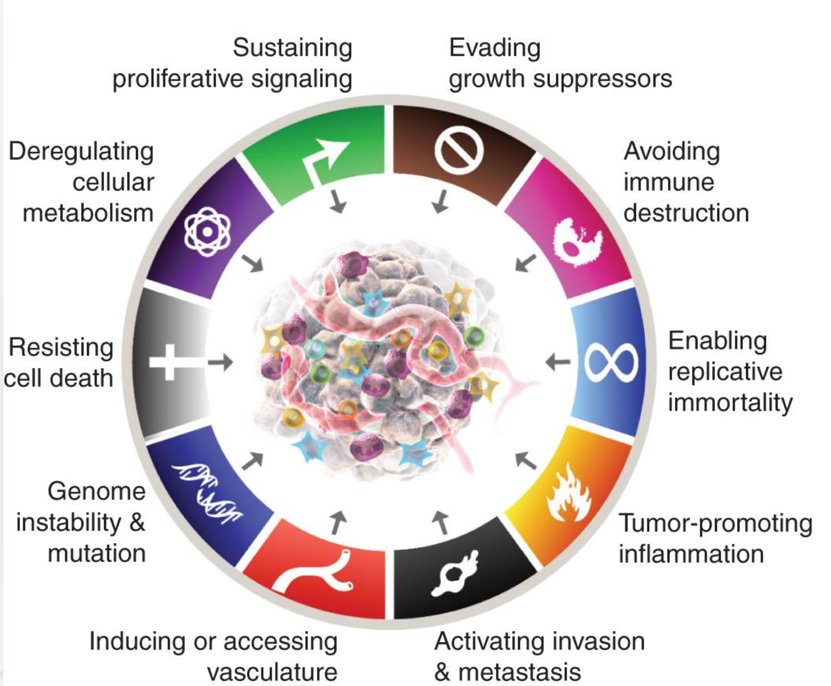
Contexte Scientifique

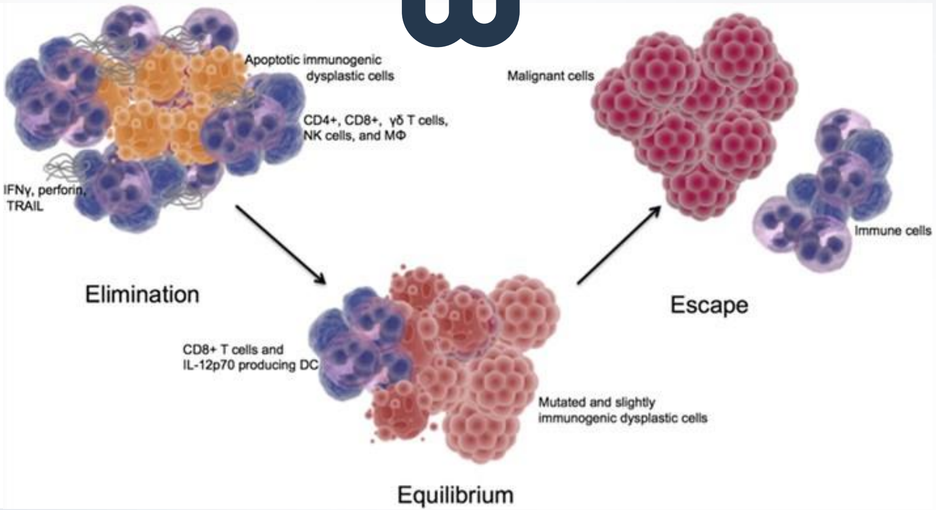
Le Cancer



Douglas Hanahan. *Cancer Discov* January 2022
Raja, J. *et al*. *Journal for immunotherapy of cancer*. 2018

Le Cancer





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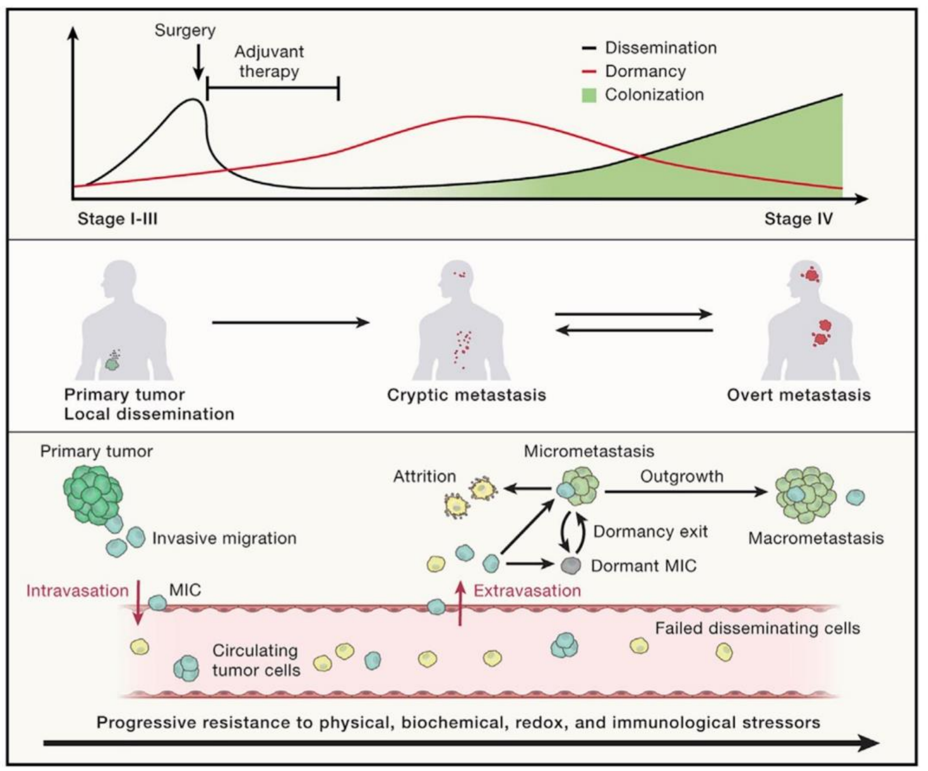
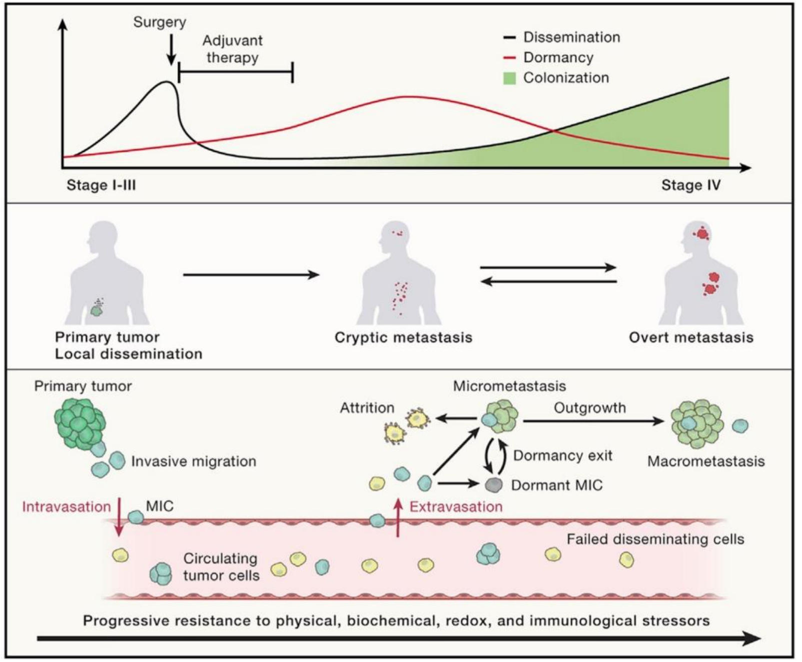
Les Métastases



Gerstberger S et al.Cell. 2023

Les Métastases



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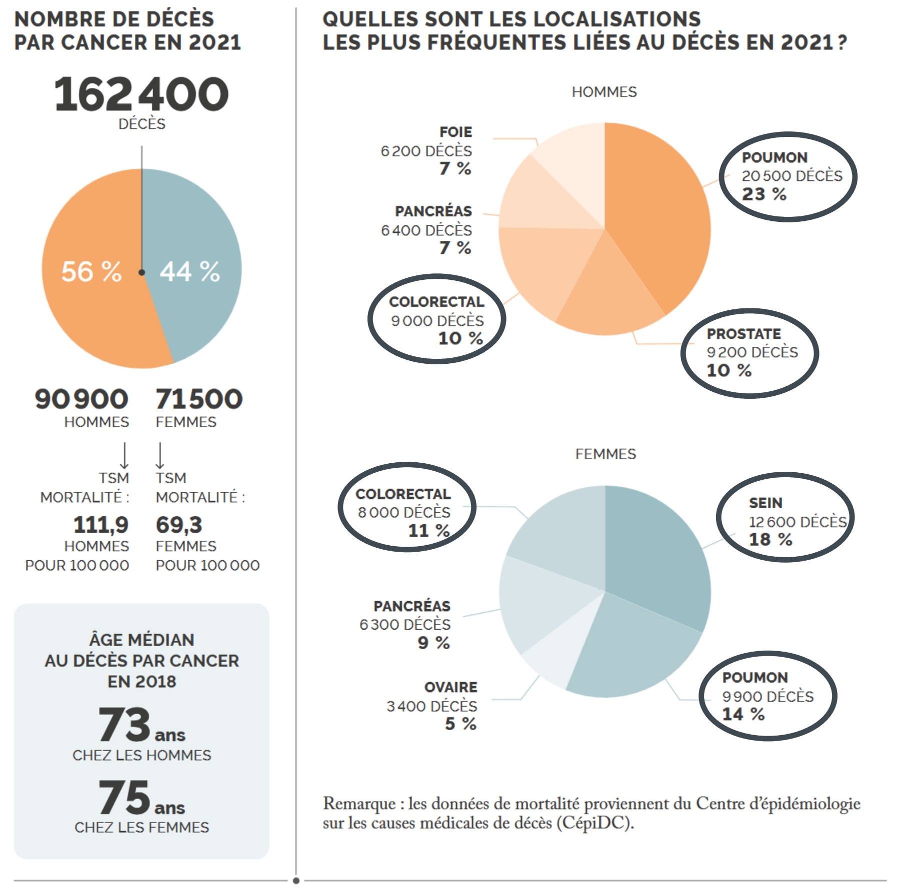
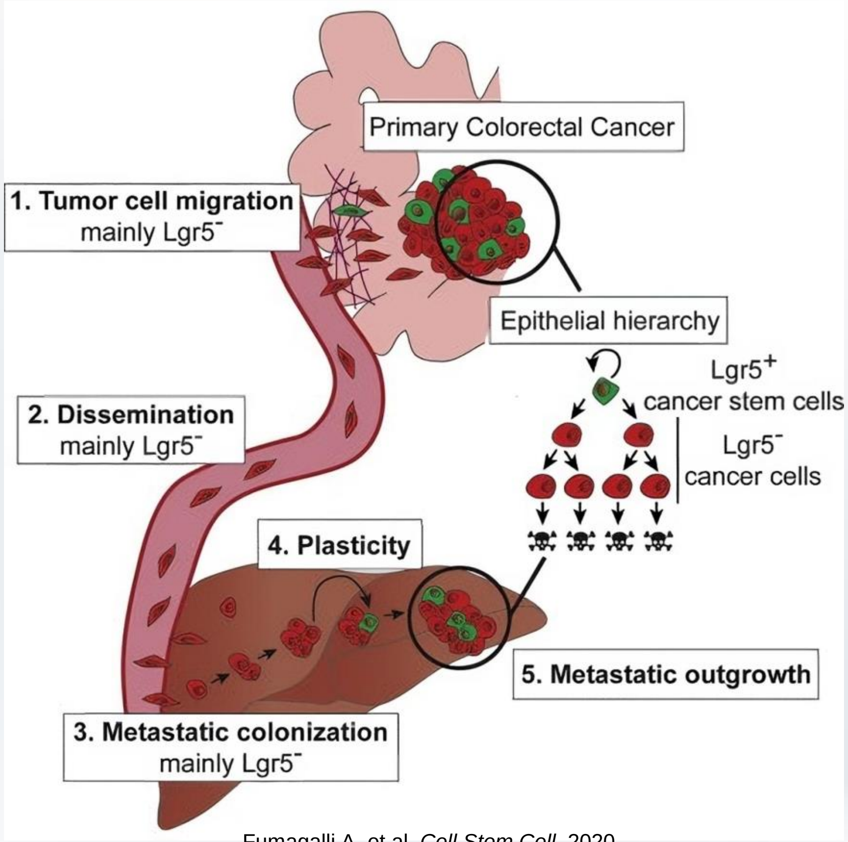


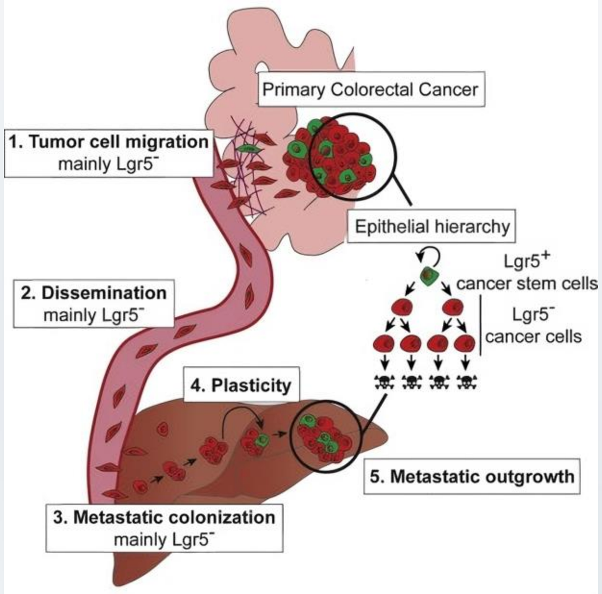
INCA données 2023

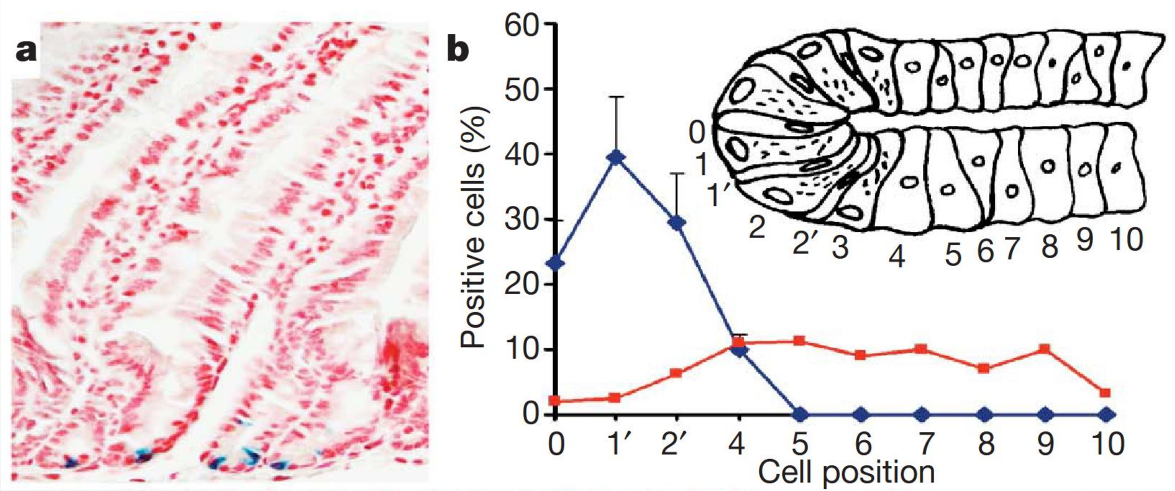
Marqueurs de propagation tumorale



Fumagalli A, et al. *Cell Stem Cell.* 2020

Marqueurs de propagation tumorale





Barker N et al.*Nature*. 2007

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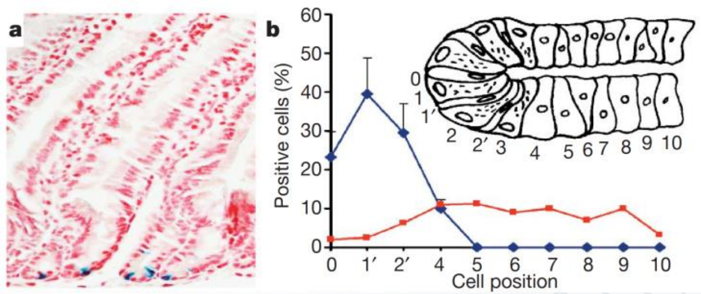
Marqueurs de propagation tumorale



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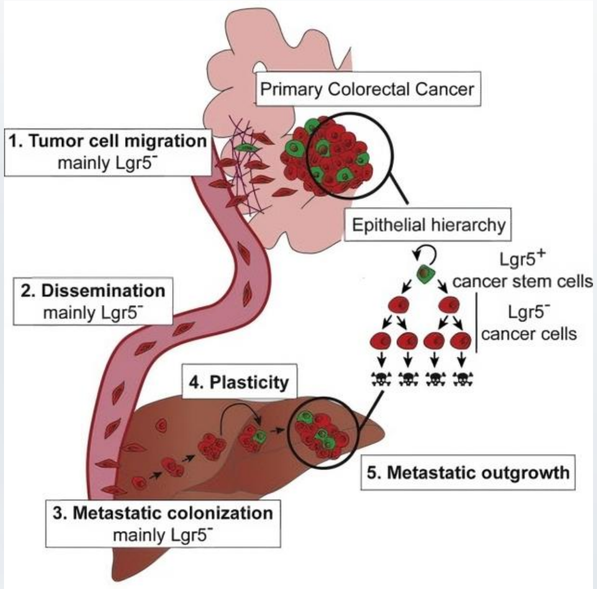

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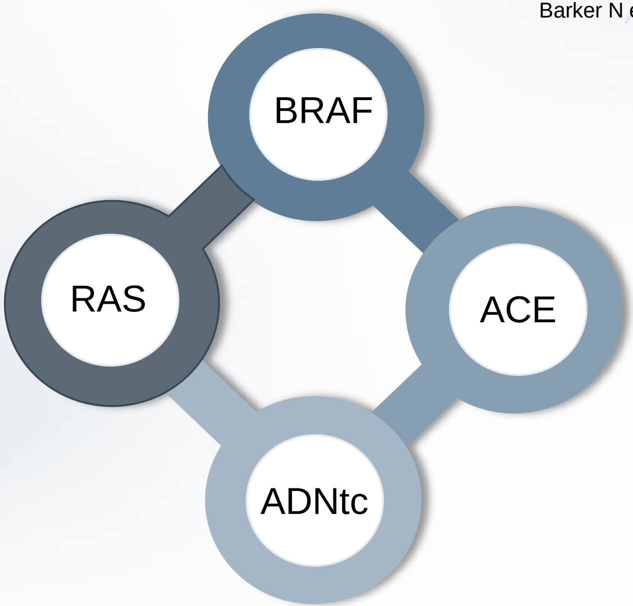

Diversité biologique des cancers colorectaux

CMS1 MSI Immune	CMS2 Canonical	CMS3 Metabolic	CMS4 Mesenchymal
14%	37%	13%	23%
MSI, CIMP high, hypermutation	SCNA high	Mixed MSI status, SCNA low, CIMP low	SCNA high
BRAF mutations		*KRAS* mutations	
Immune infiltration and activation	WNT and MYC activation	Metabolic deregulation	Stromal infiltration, TGFβ activation, angiogenesis
Worse survival after relapse			Worse relapse-free and overall survival

Guinney J, et al. *Nat Med*. 2015

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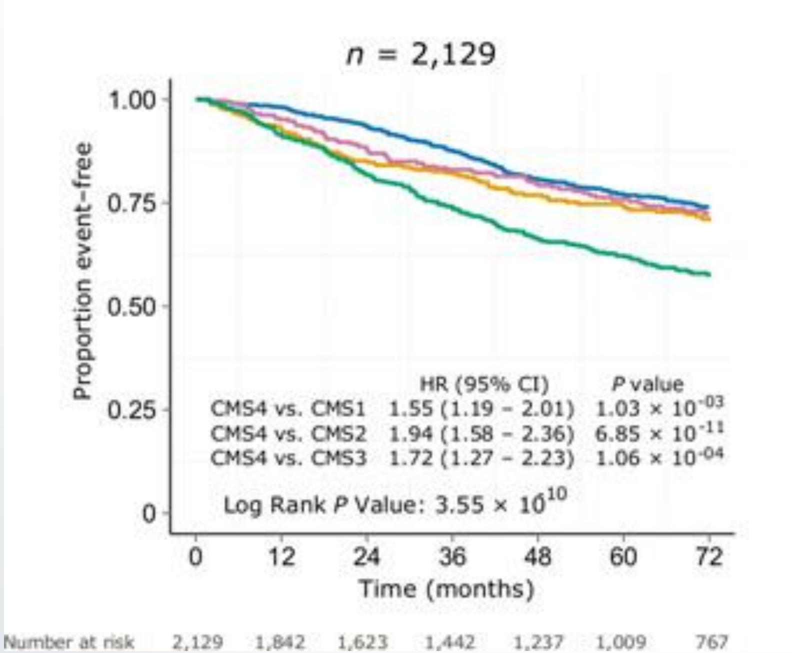
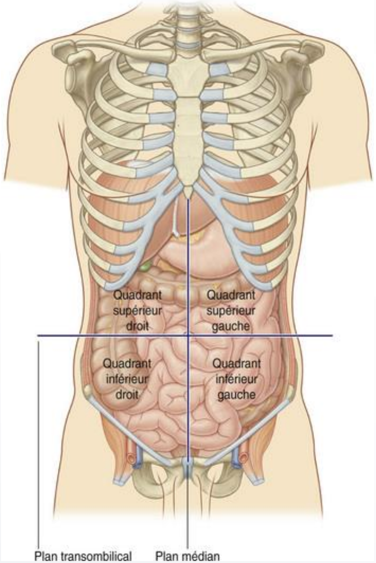
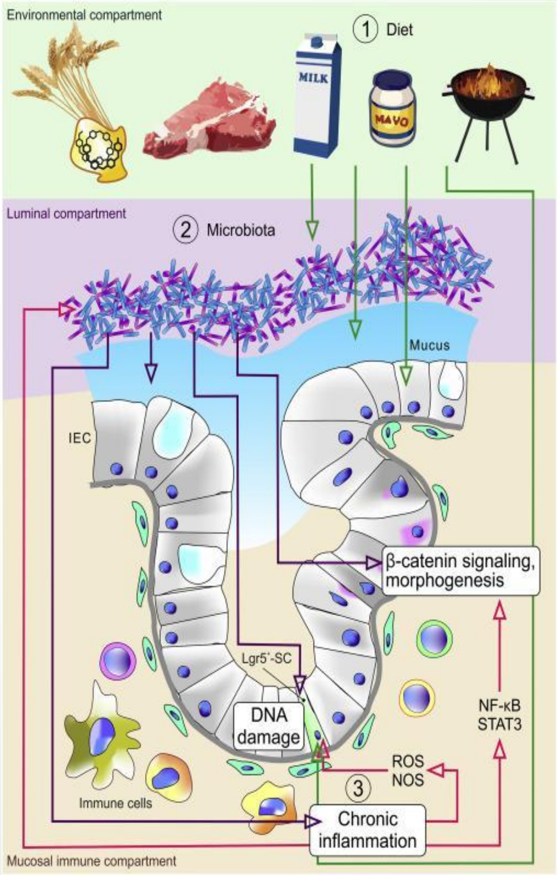


Guinney J, et al. *Nat Med*. 2015

Les cancers du colon et du rectum





Tilg H, et al. *Cancer Cell*. 2018

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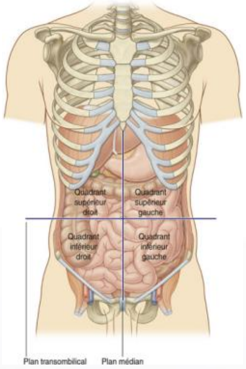

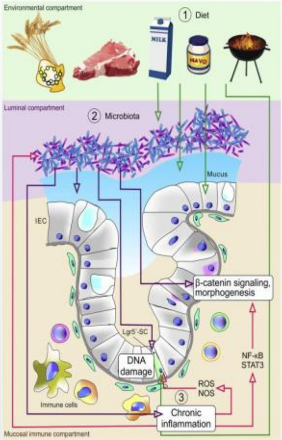

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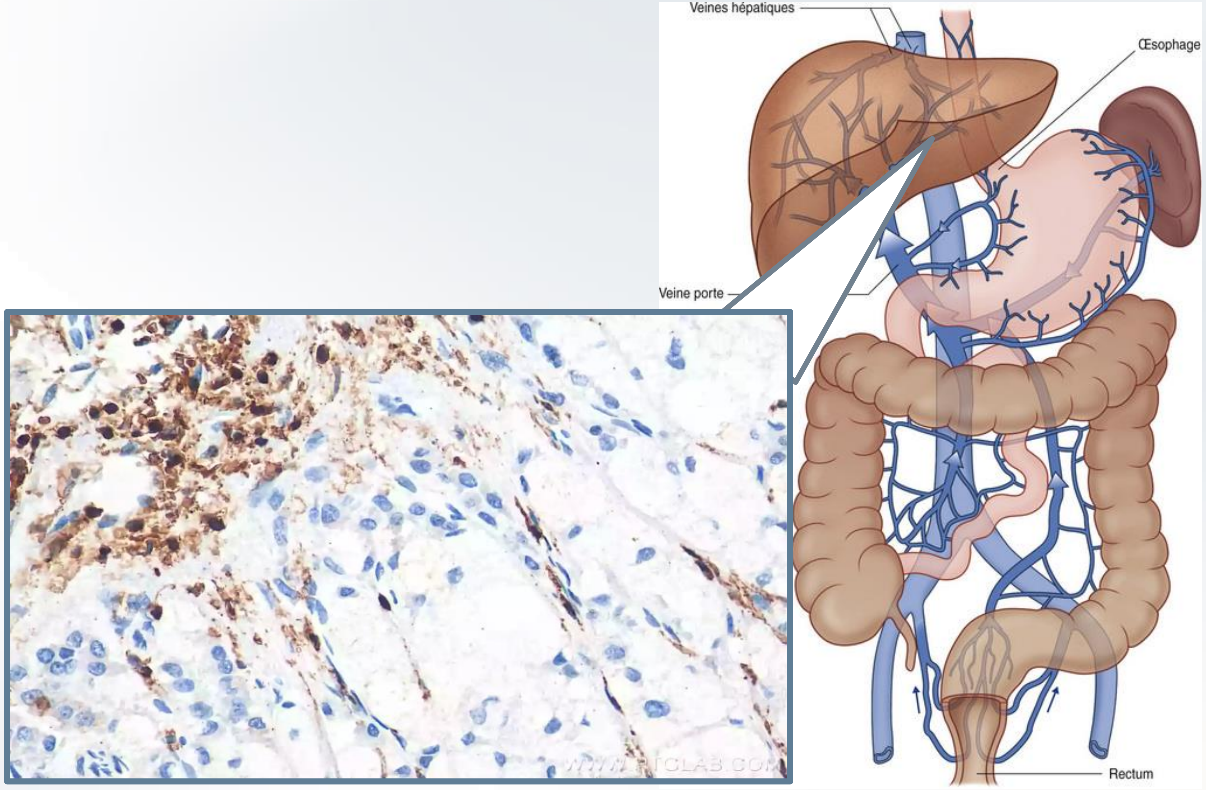
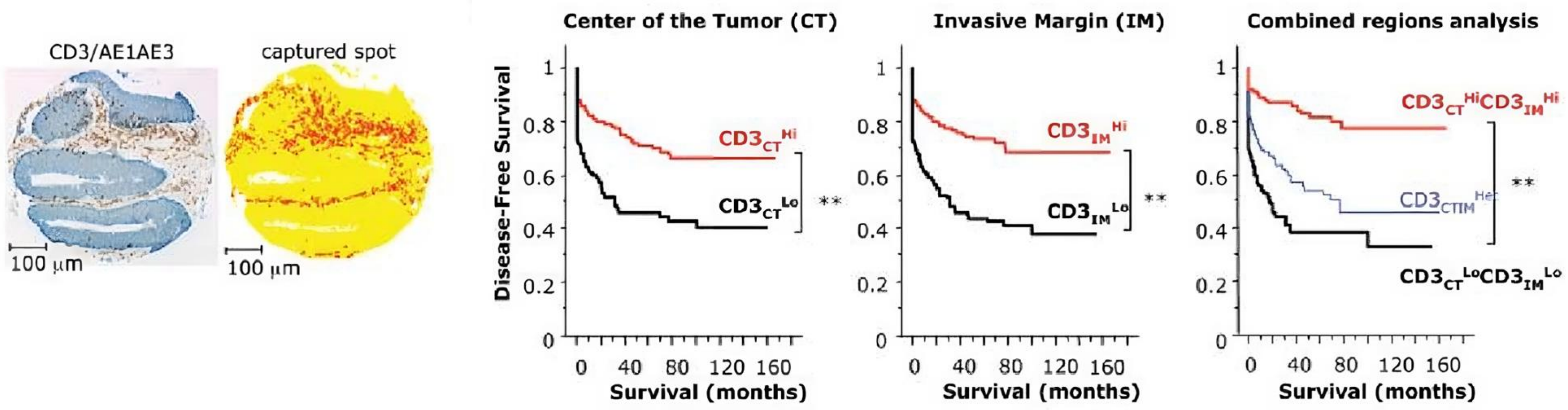
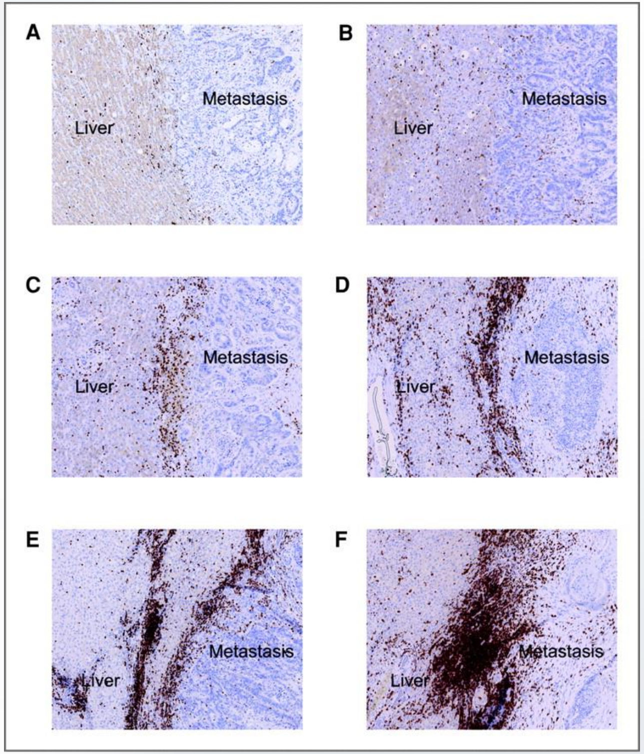


Infiltrat immunitaire péri-tumoral



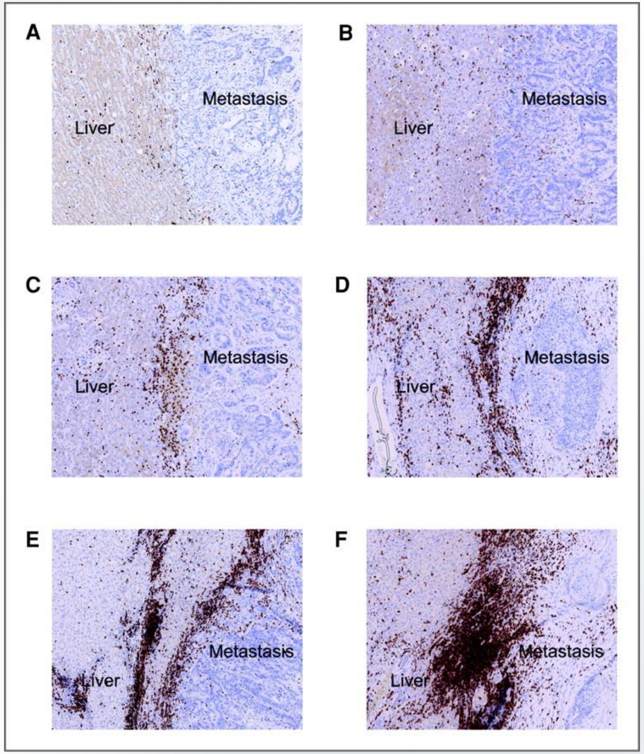
Galon J. *Science* 2006.

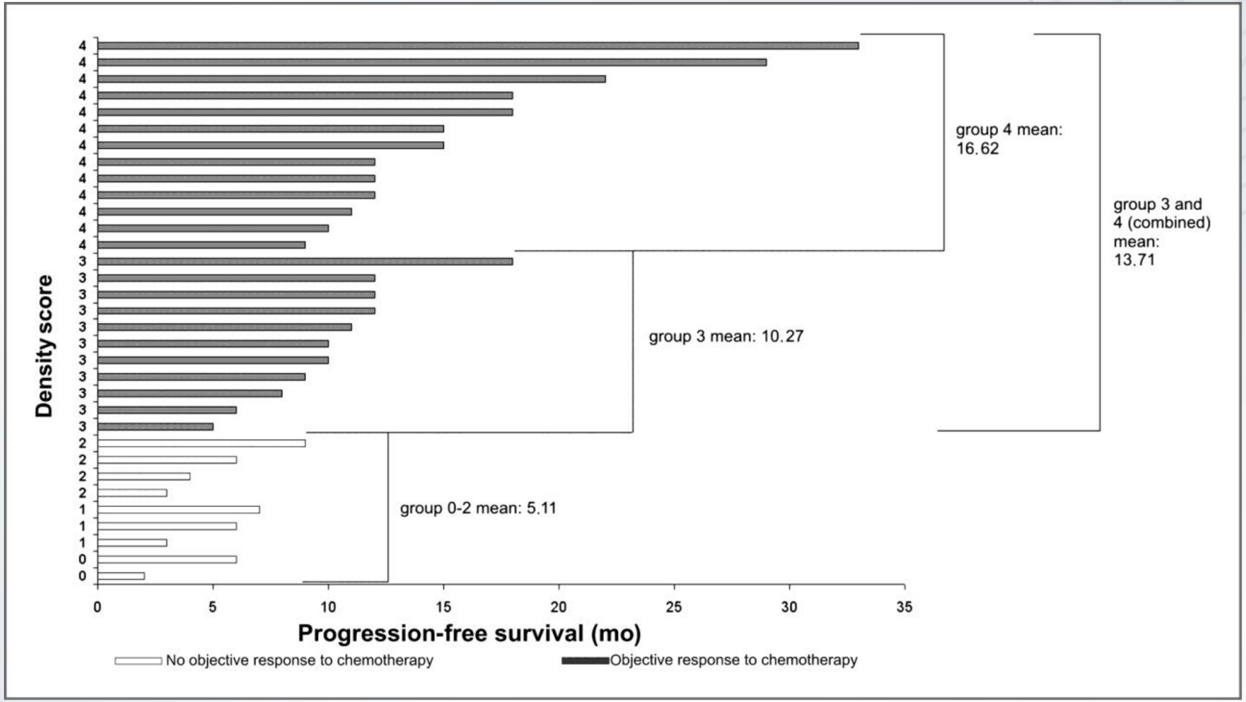
Métastases hépatiques



Halama N, et al. *Cancer Res.* 2011

Métastases hépatiques





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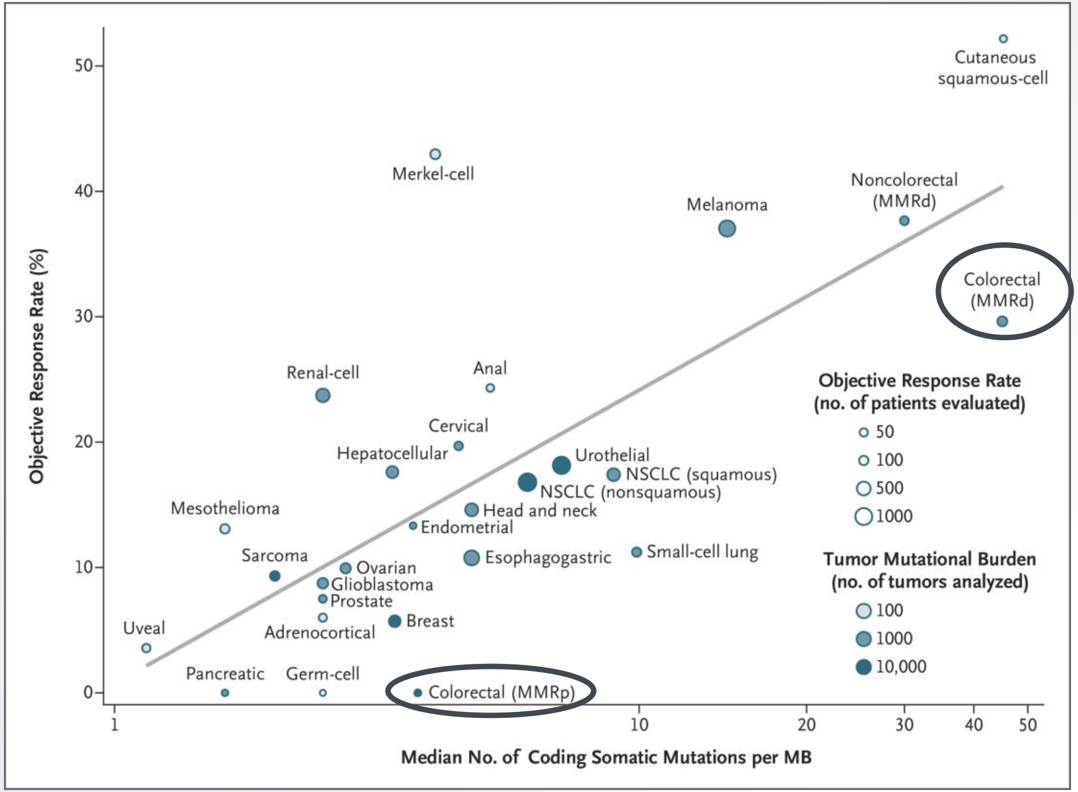
Immunothérapie dans les CRC



Yarchoan et al. *NEJM* 2017

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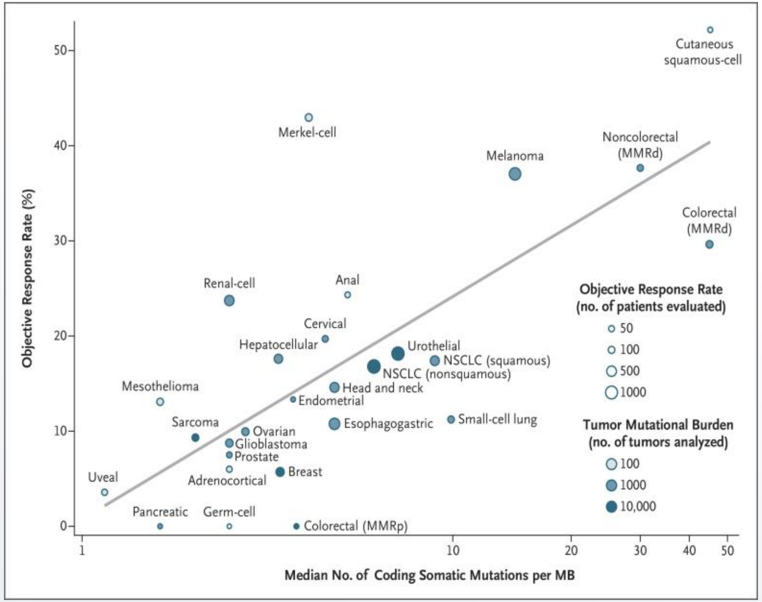

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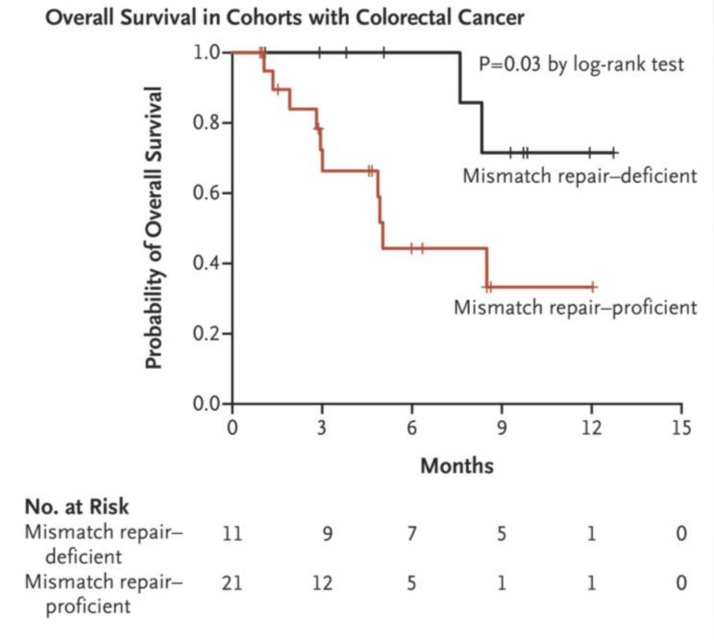

Le DT, et al. *N Engl J Med*. 2015

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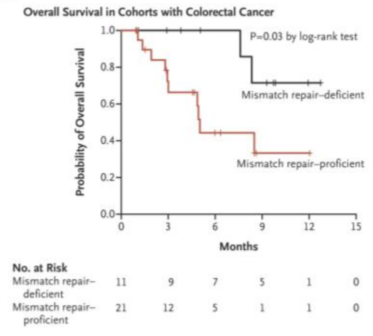

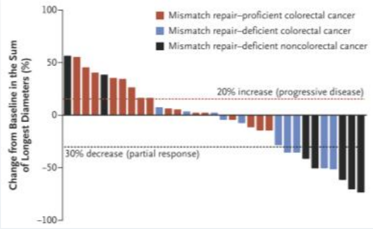

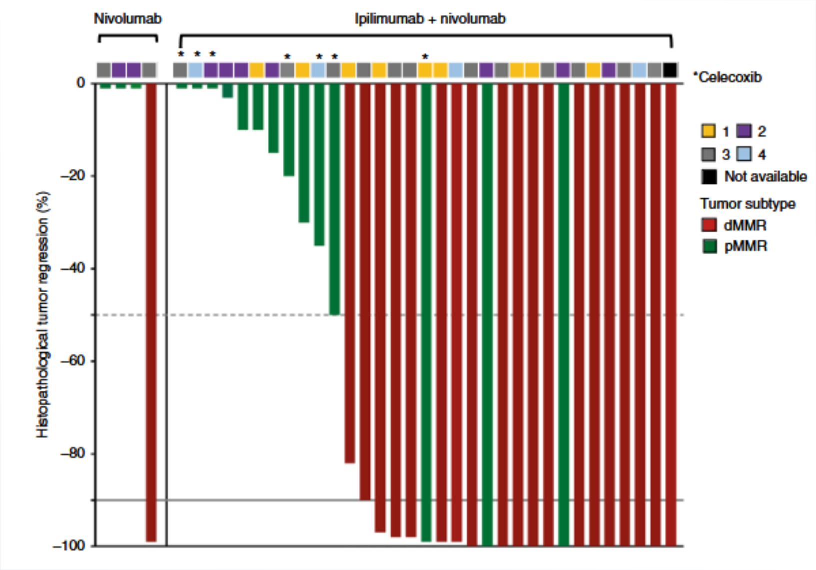

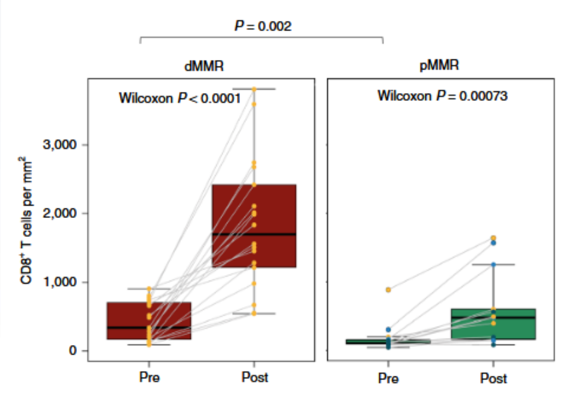

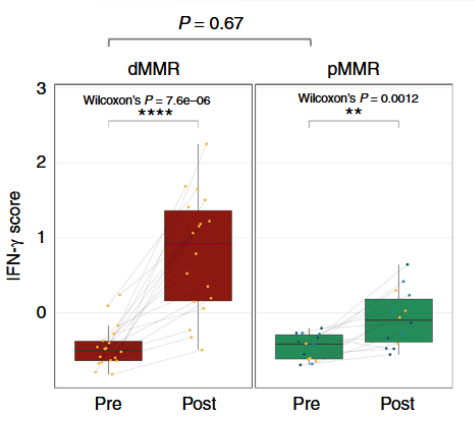

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Chalabi M, et al. *Nat Med*. 2020

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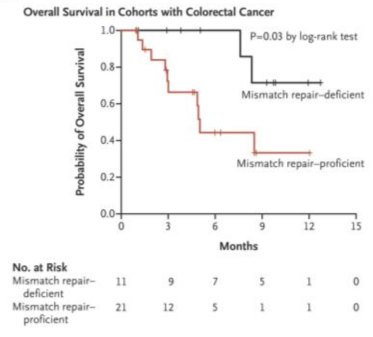

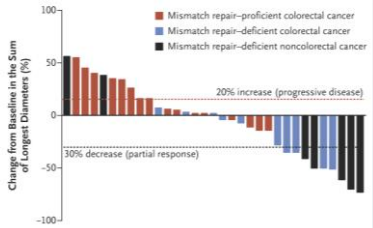

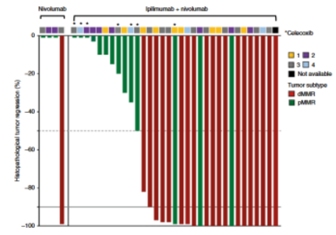

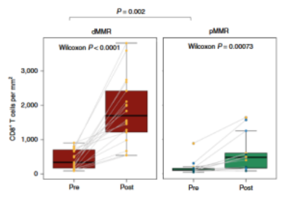

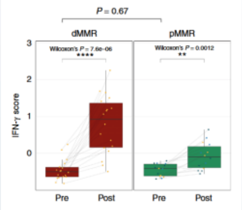

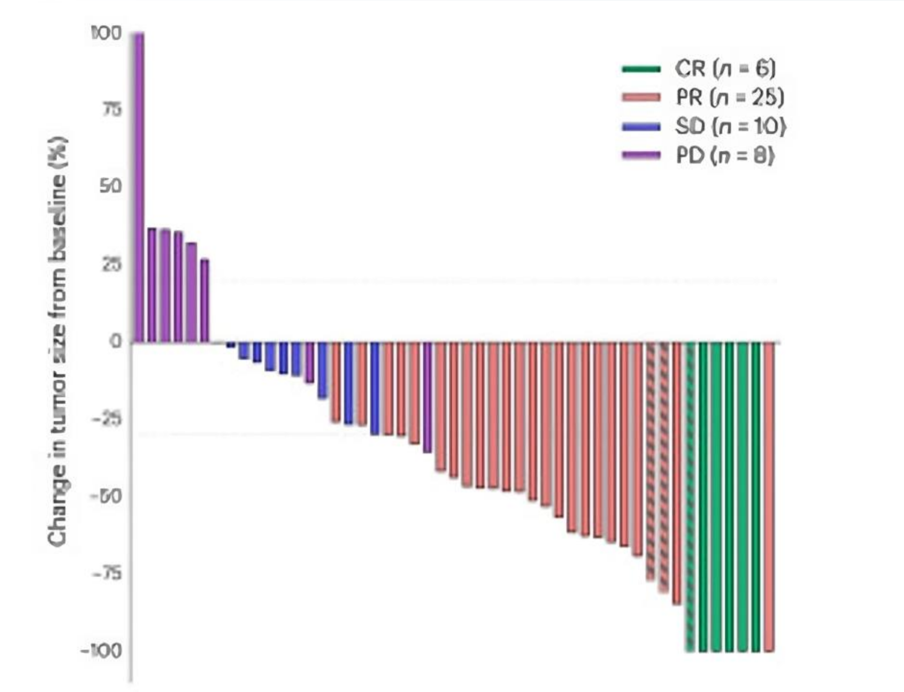

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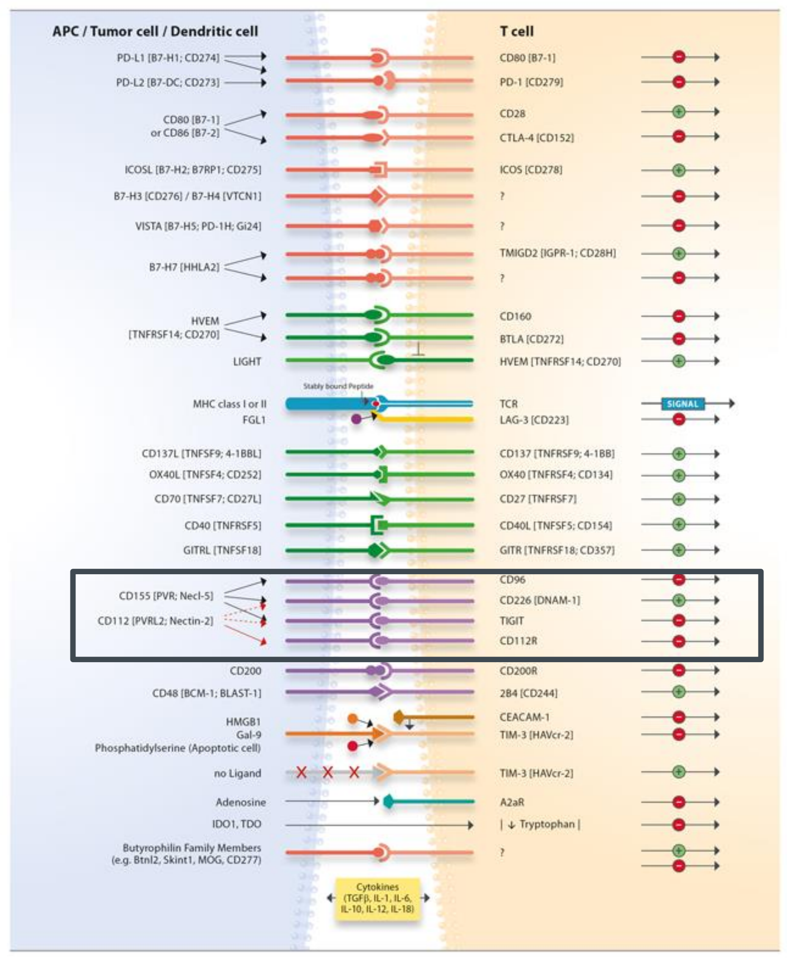
Chalabi M, et al. *Nat Med*. 2020

Thibaudin M, et al. *Nat Med.* 2023

Immune checkpoints



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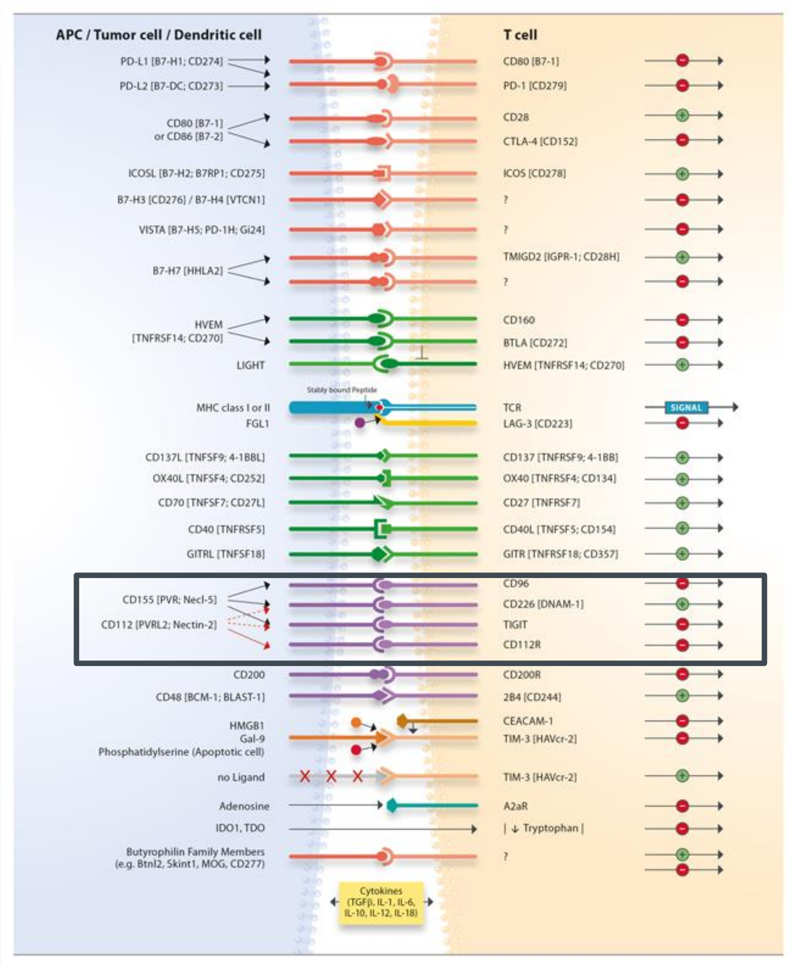

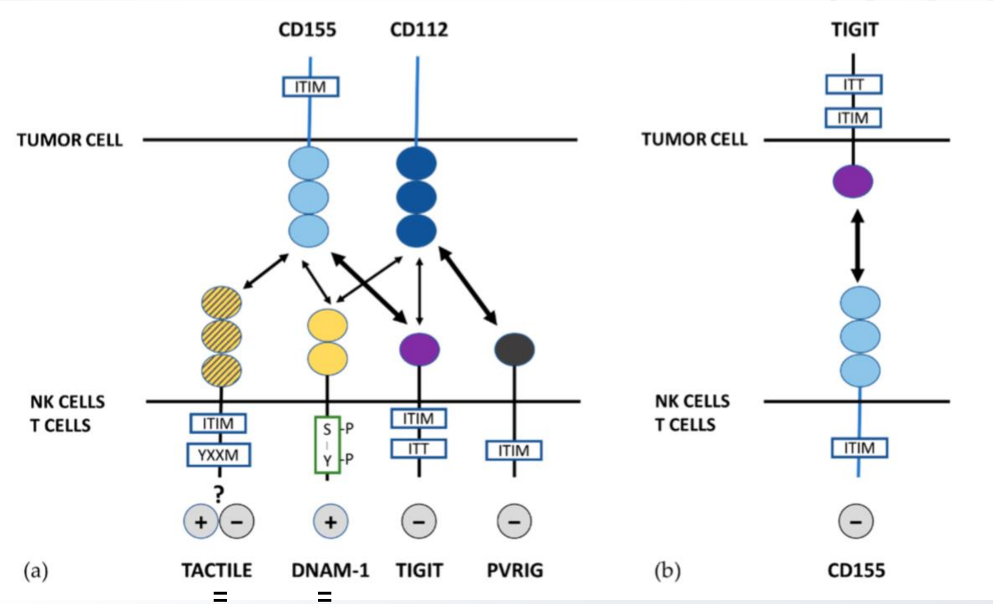

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CD96

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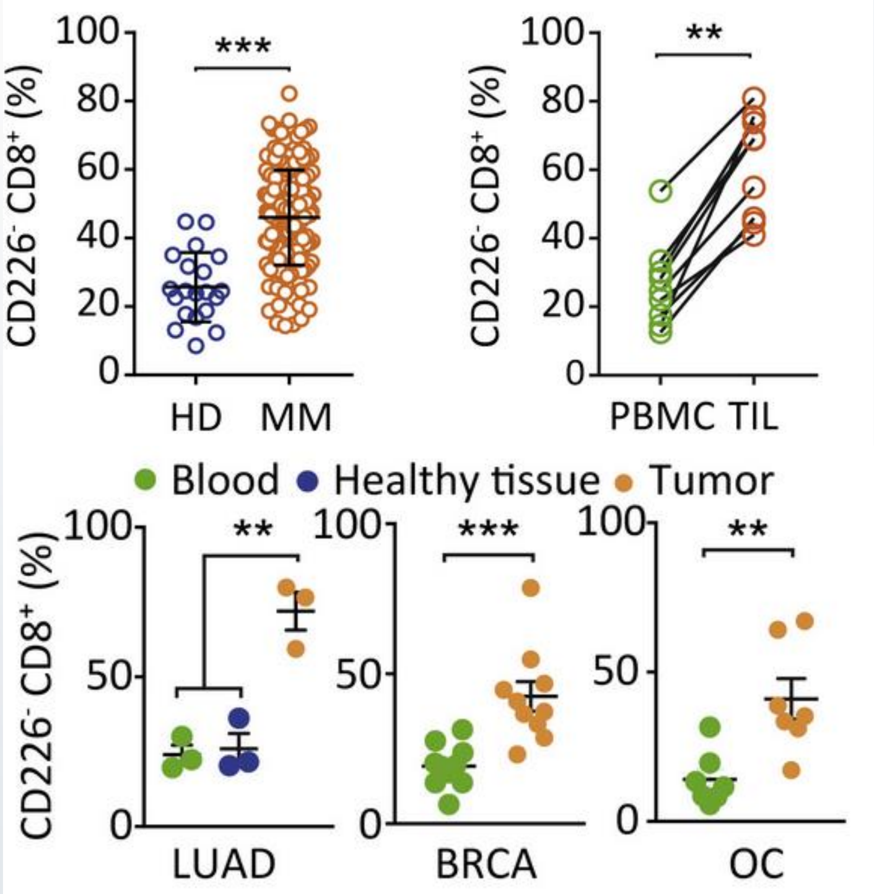
CD226

Raquel Tarazona, et al. *Cancers* 2019

L'absence de CD226 identifie des lymphocytes T CD8+ infiltrants la tumeur dysfonctionnels



Weulersse M, et al. *Immunity*. 2020
Banta KL, et al. *Immunity*. 2022

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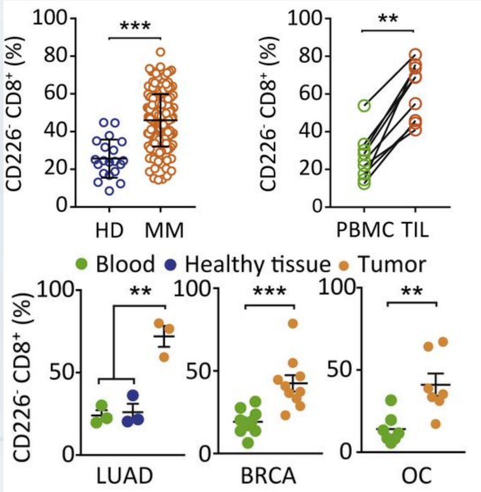

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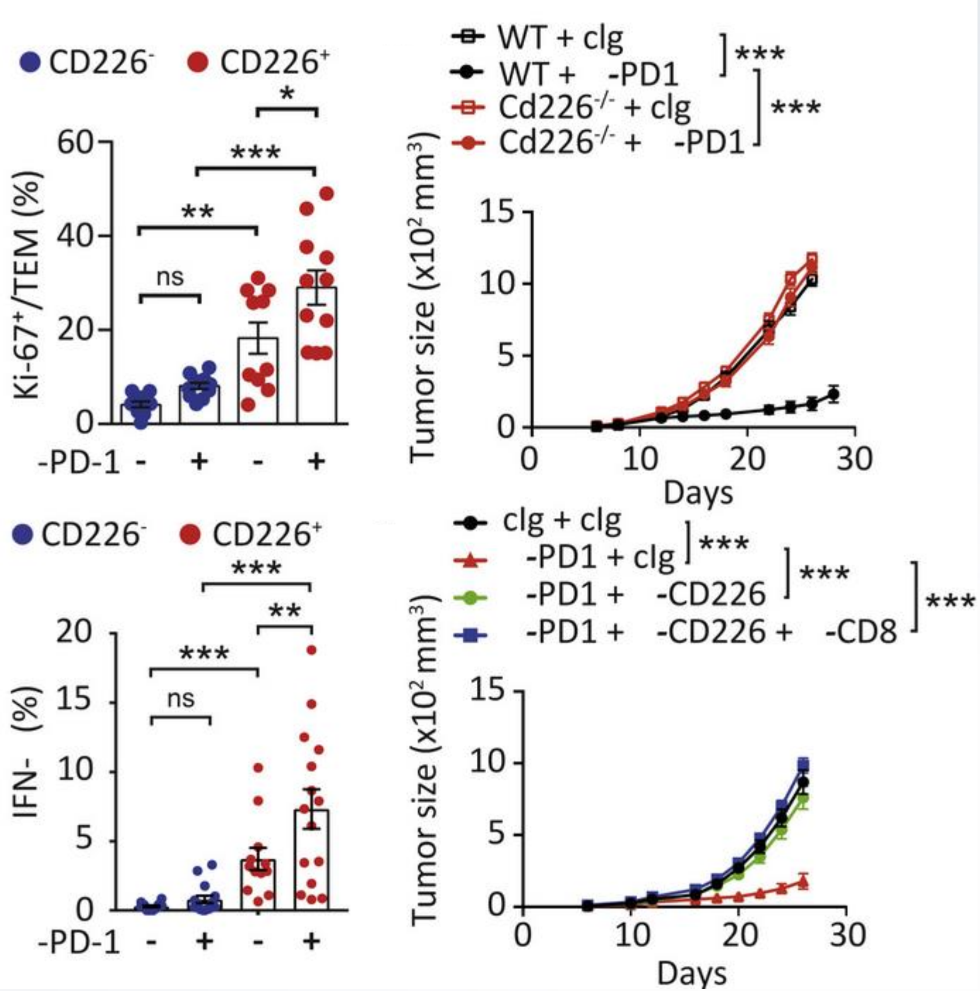
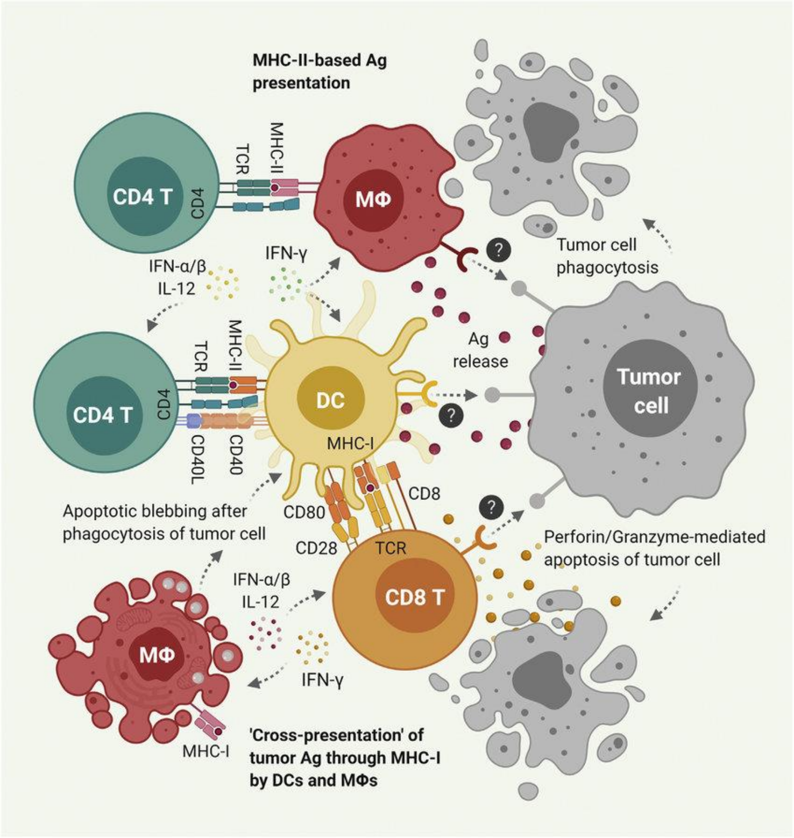


Nouvelles sources d'activation lymphocytaire



Poorebrahim M, et al. *Pharmacol Ther*. 2020

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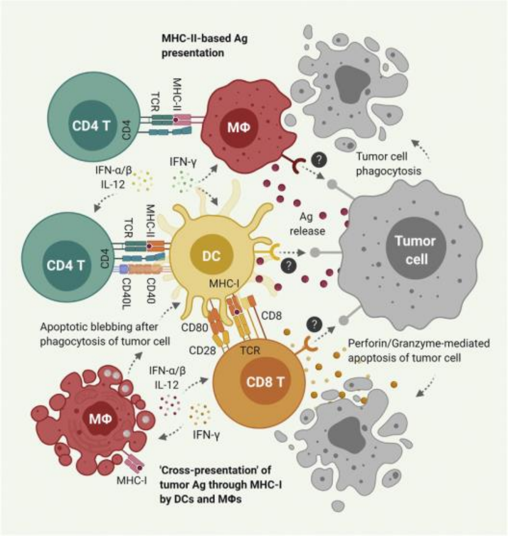

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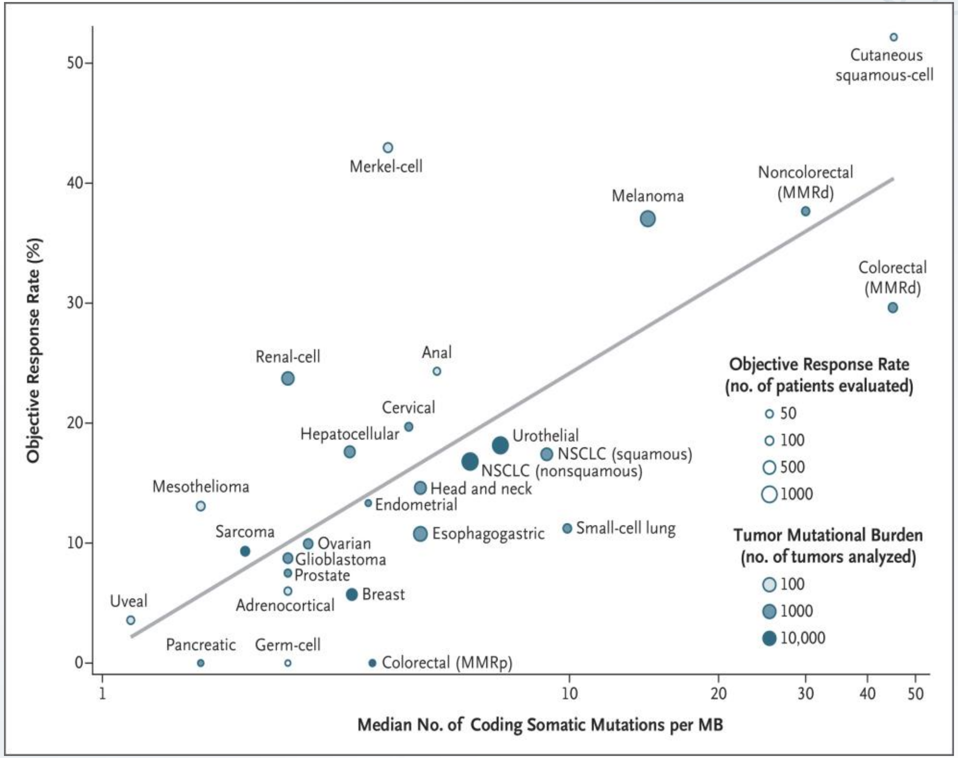
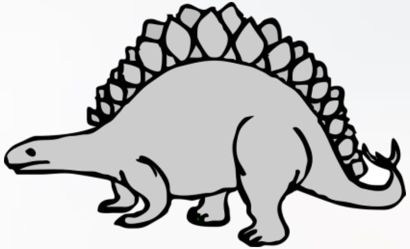
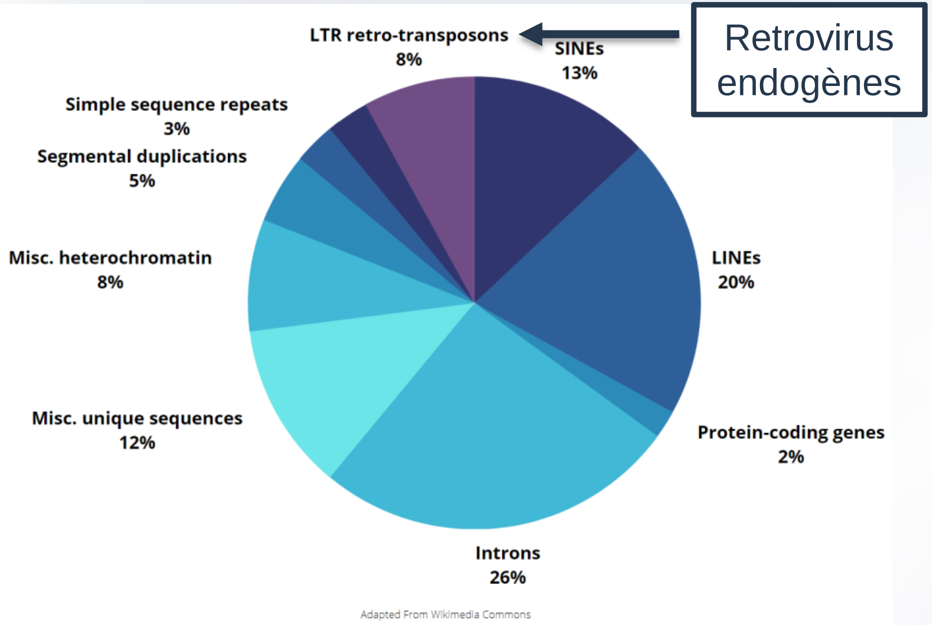


Yarchoan et al. *NEJM* 2017

Elements transposables et rétrovirus endogènes





HERV = Rétrovirus Endogène Humain

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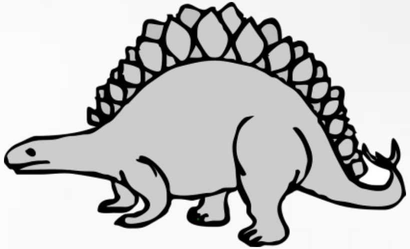
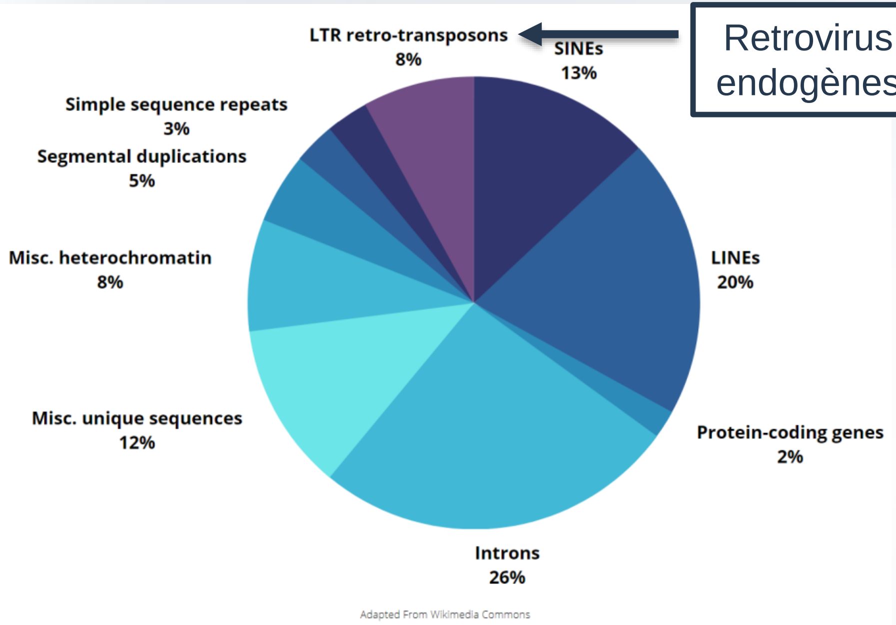
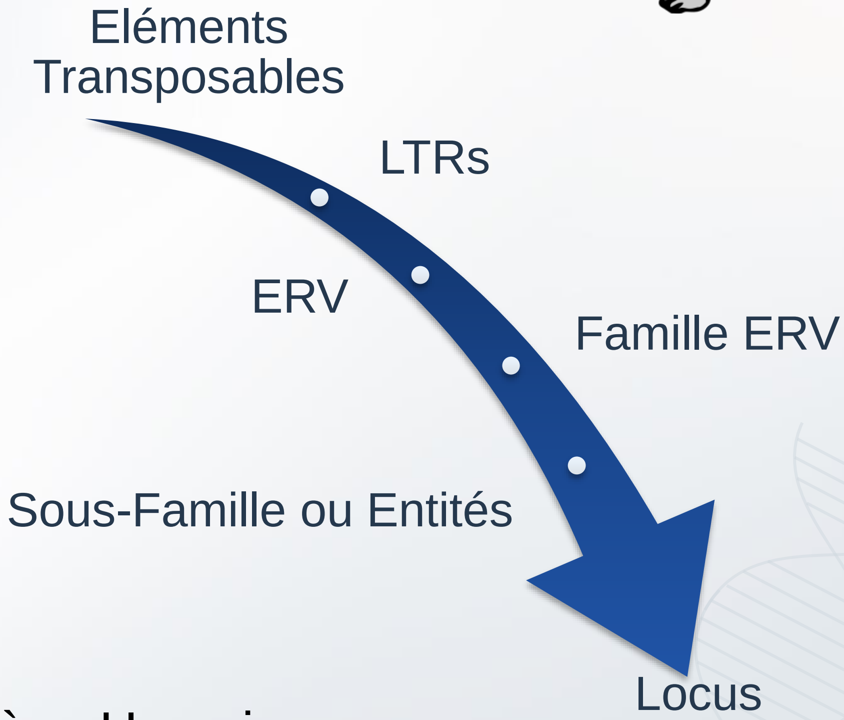


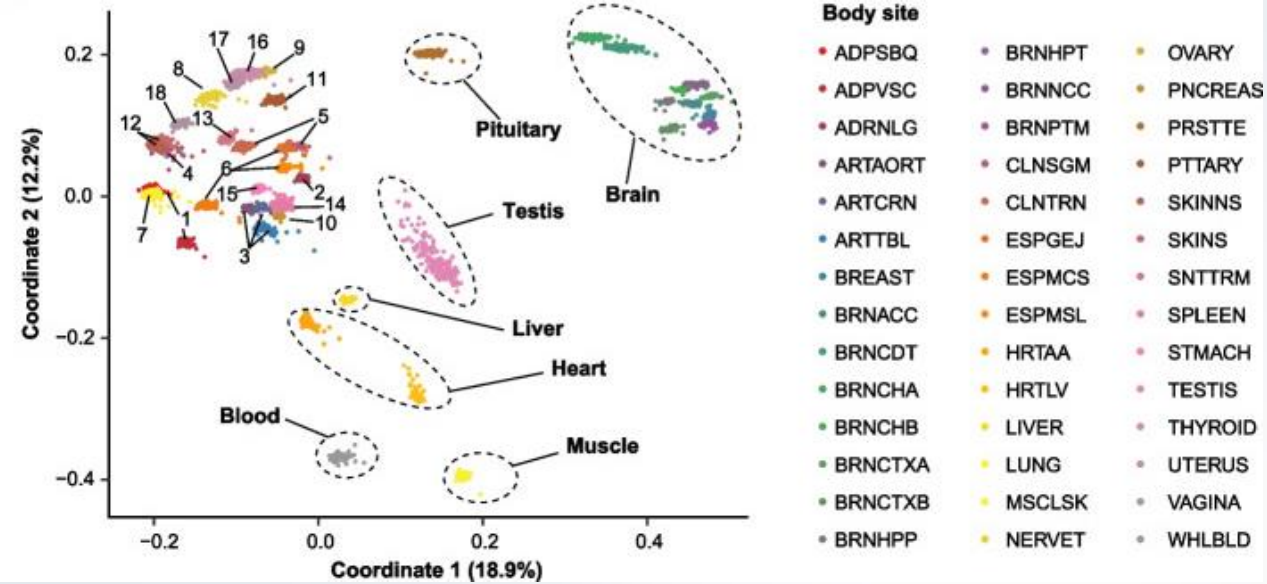


Retrovirus endogènes



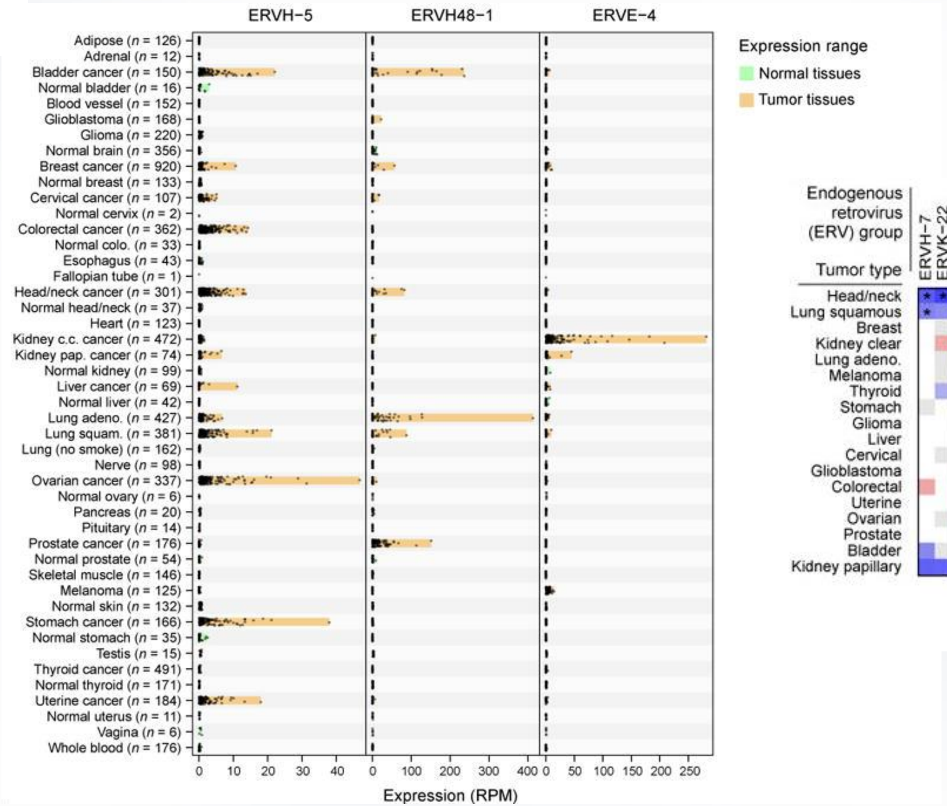
HERV = Rétrovirus Endogène Humain

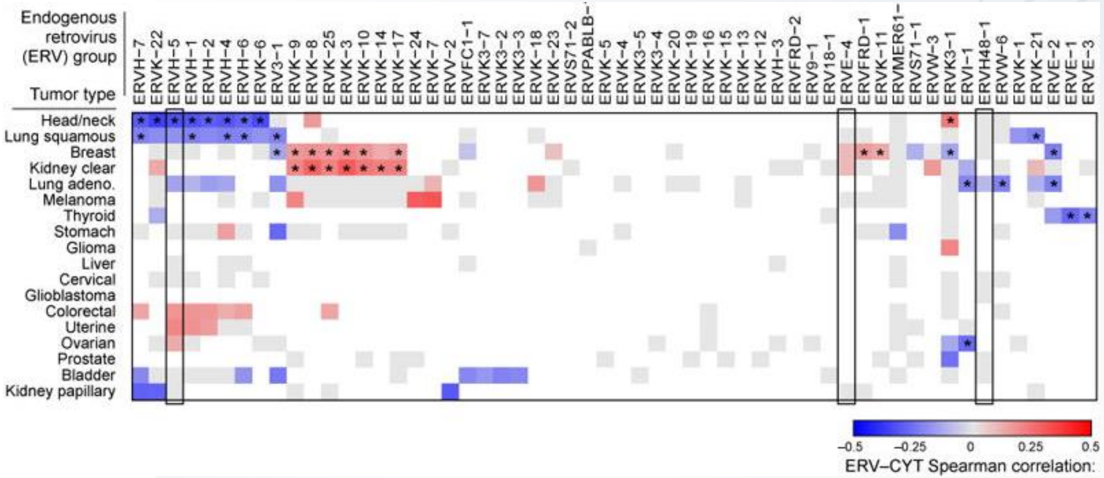
Dérégulation de l'expression d'HERV



She J,et al. *Genome Biol.* 2022

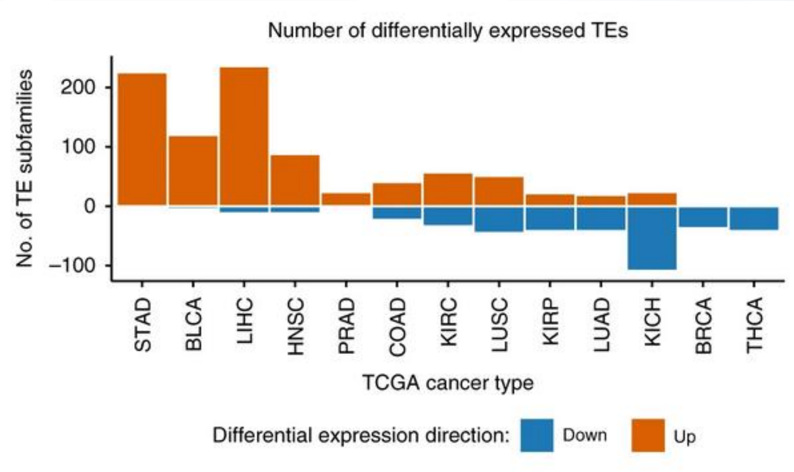
Dérégulation de l’expression d’HERV





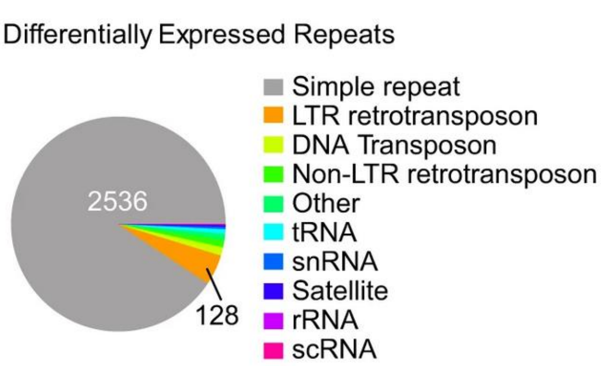
Rooney MS, et al. *Cell*. 2015

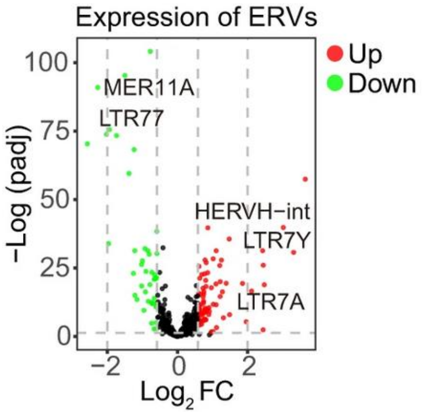
Dérégulation des TE dans les CRC

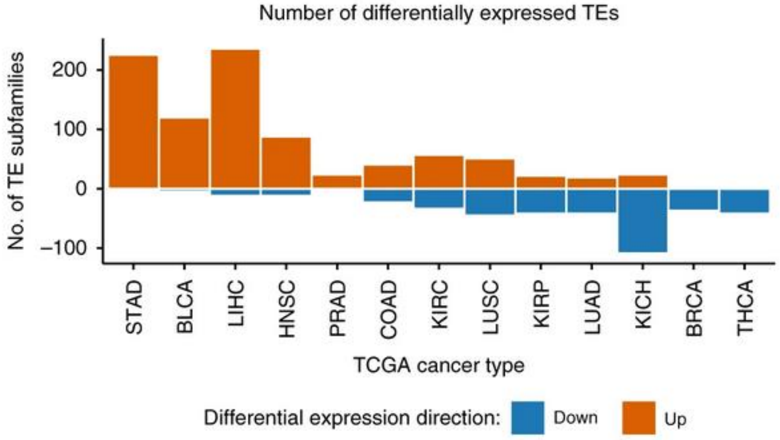


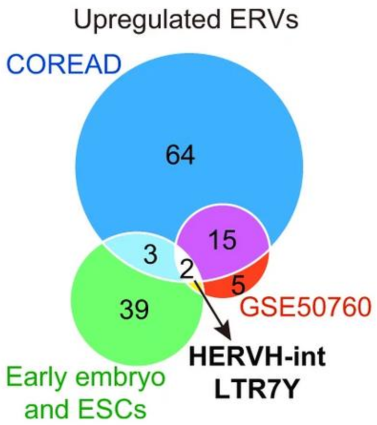
Kong et al. *Nature Com* 2019
Yu et al. *Nature Com* 2022

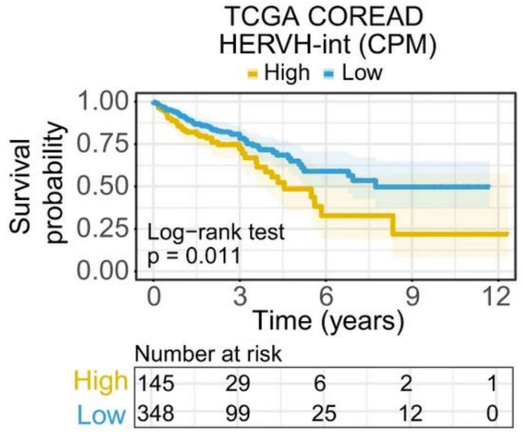
Dérégulation des TE dans les CRC





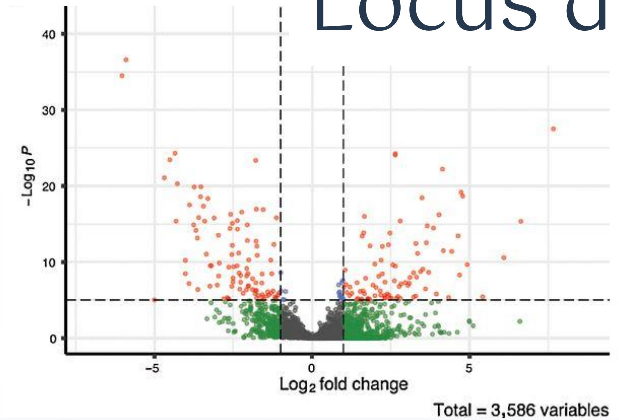


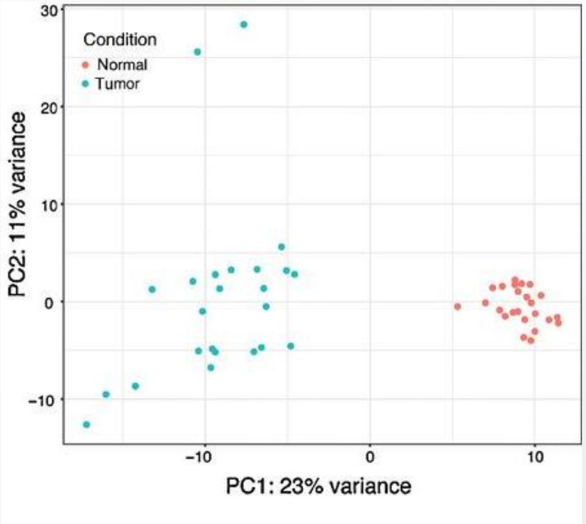


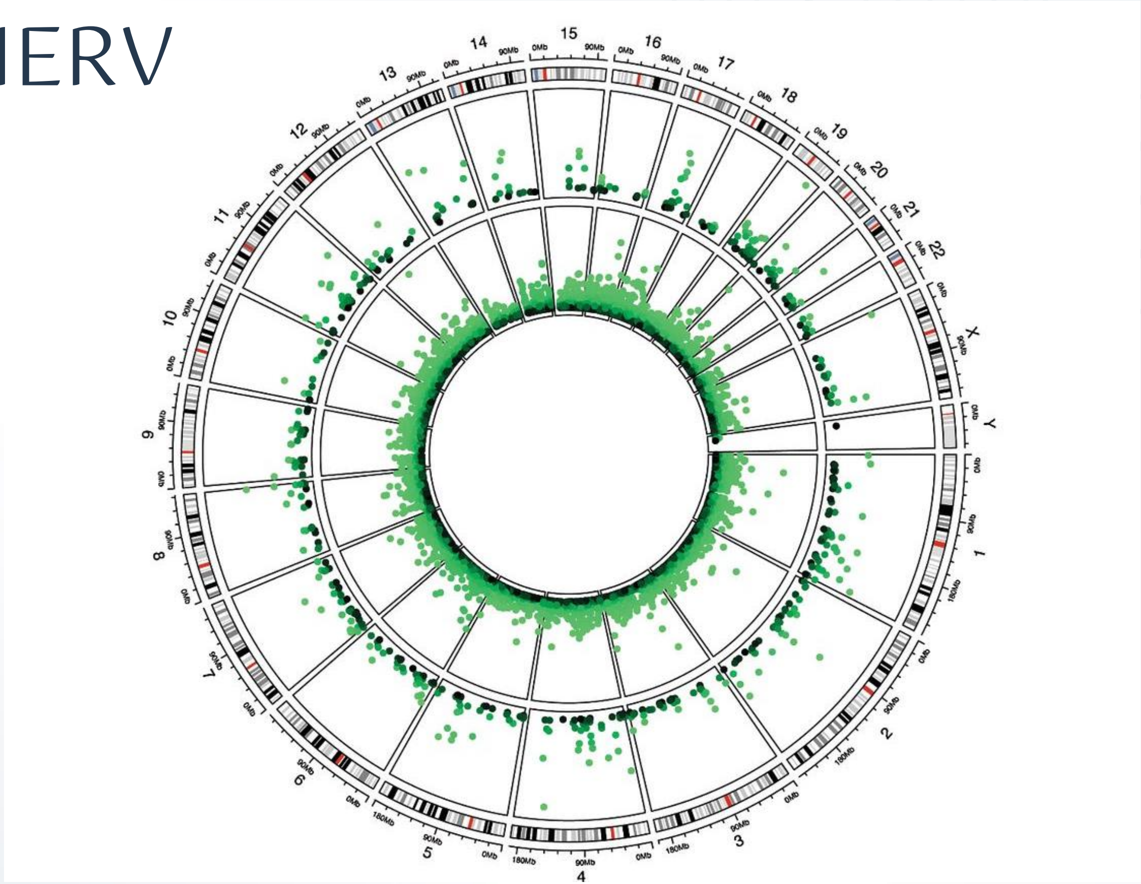


Kong et al. *Nature Com* 2019
Yu et al. *Nature Com* 2022

Locus d'HERV

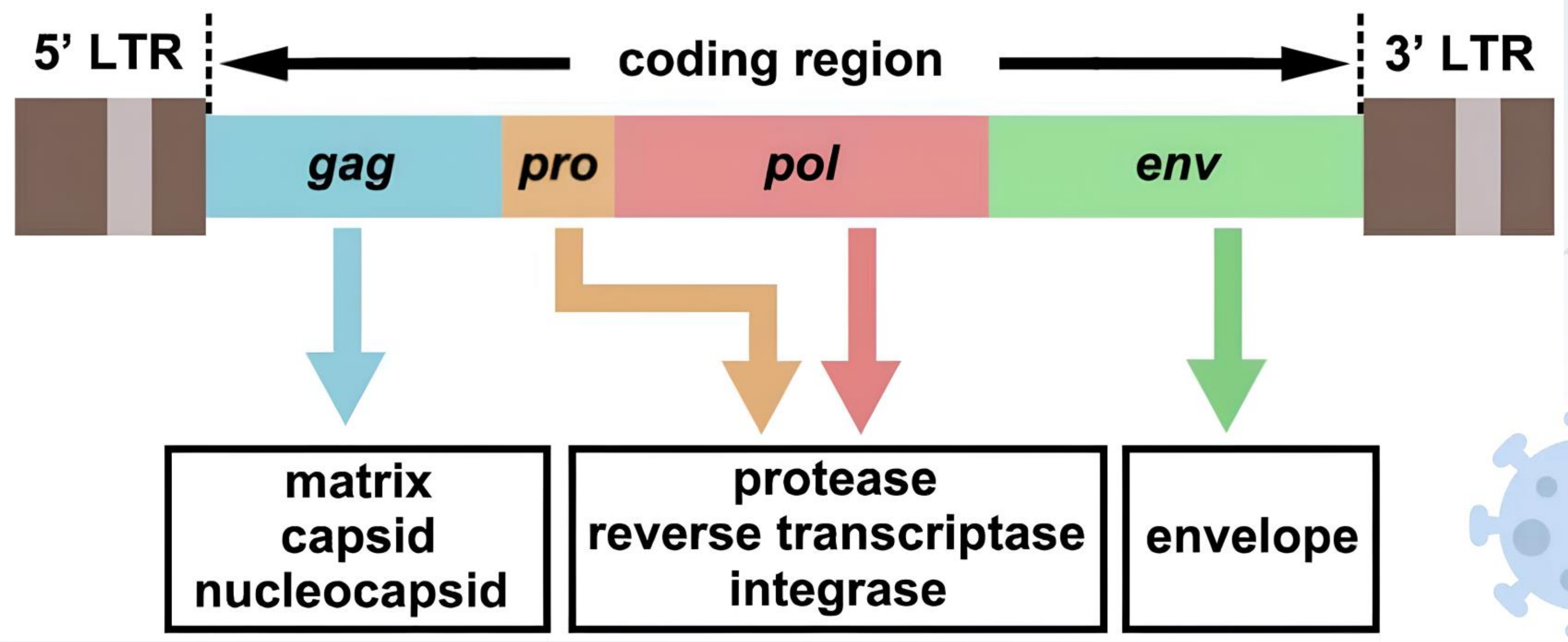


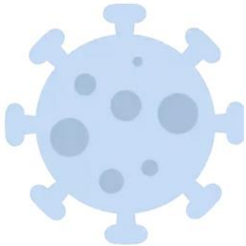




Steiner MC, et al. *Cancer Res*. 2021

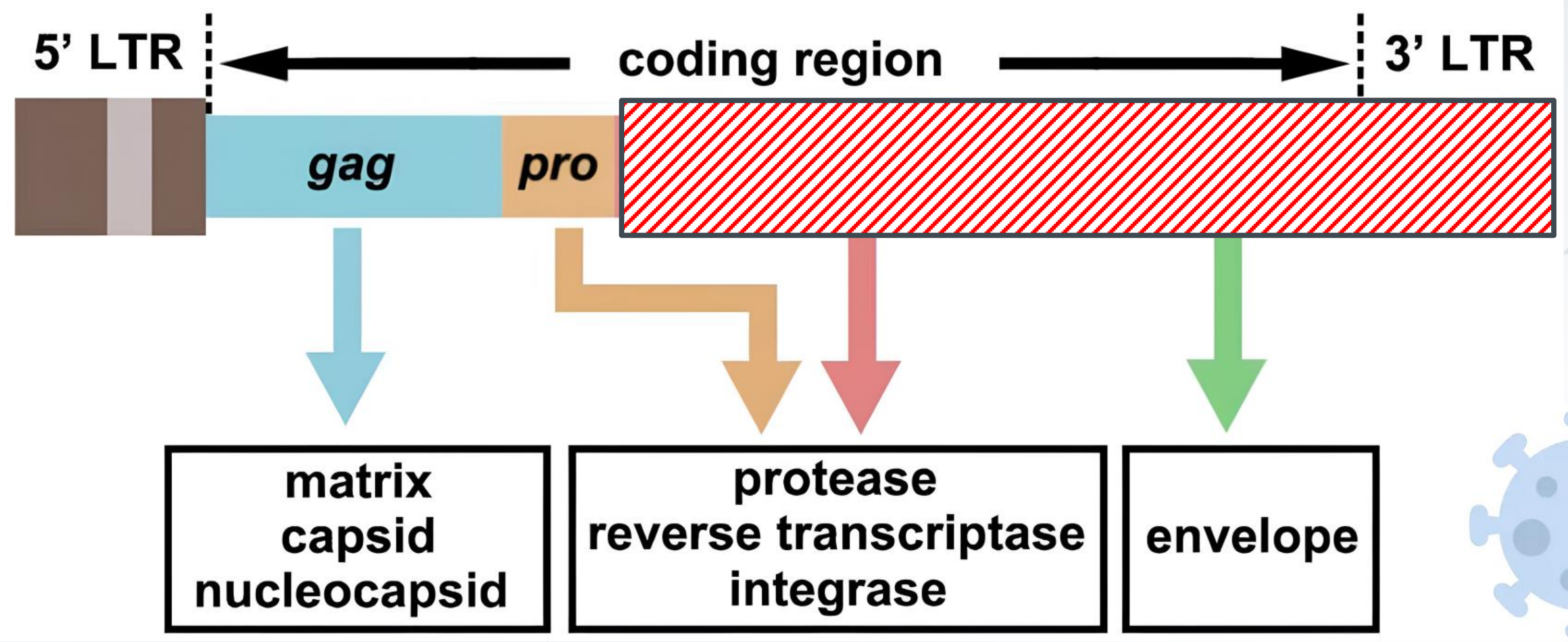
Structure d’un rétrovirus

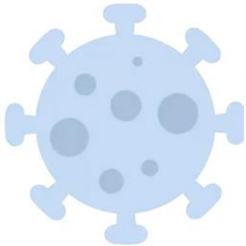




Mao J, et al. *Comput Struct Biotechnol J*. 2021

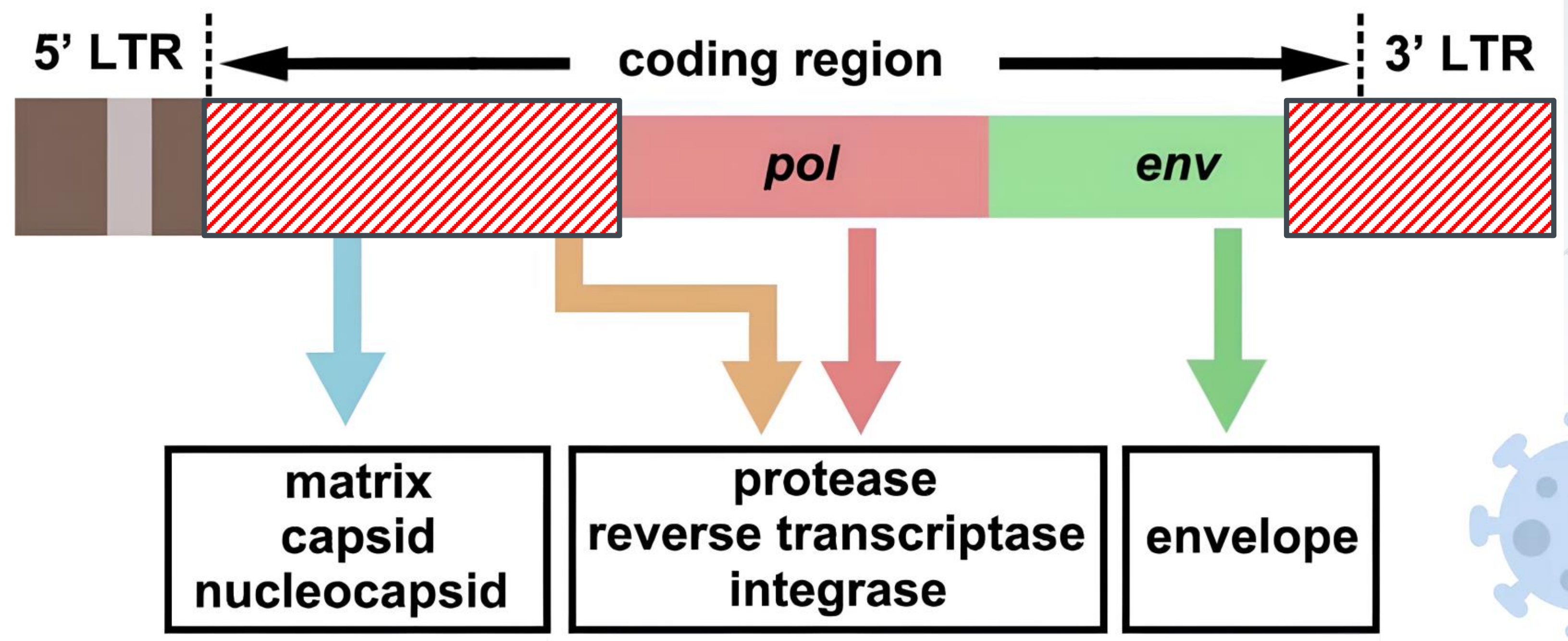
Structure d’un rétrovirus





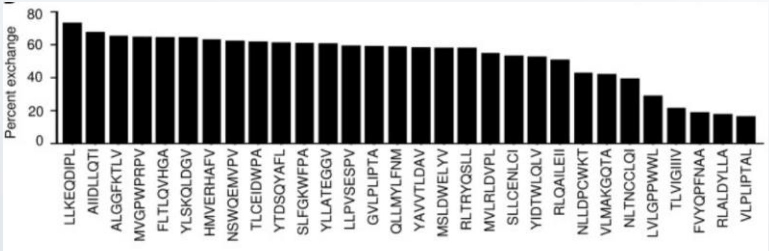
Mao J, et al. *Comput Struct Biotechnol J*. 2021

Structure d’un rétrovirus



Mao J, et al. *Comput Struct Biotechnol J*. 2021

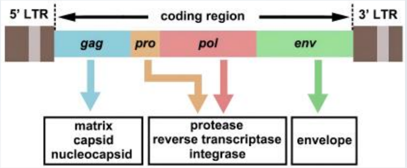
Structure d’un rétrovirus



Smith CC, et al. *J Clin Invest.* 2018

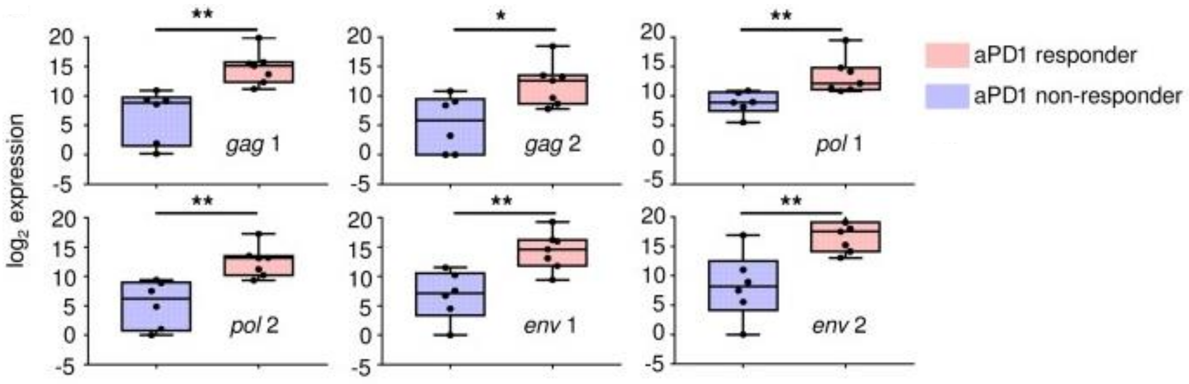
Sequence	MHCflurry score	Affinity (nM)	Rank (%)	Protein
FLQFKTWWI	0.79	9.62	0.04	Gag
RLIPYDWEI	0.81	7.78	0.03	Gag
KLIDCYTFL	0.84	5.72	0.01	Pol
YSLFIKILL	0.75	14.22	0.08	Gag
AMIPKDWPL	0.73	17.79	0.11	Pol
YAMSNLFSI	0.77	11.87	0.06	Pol

Bonaventura P et al. *Sci Adv*. 2022

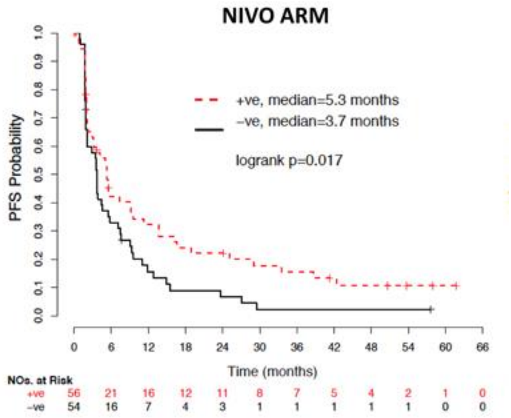


Mao J, et al. *Comput Struct Biotechnol J*. 2021

Activation lymphocytaire par les HERV

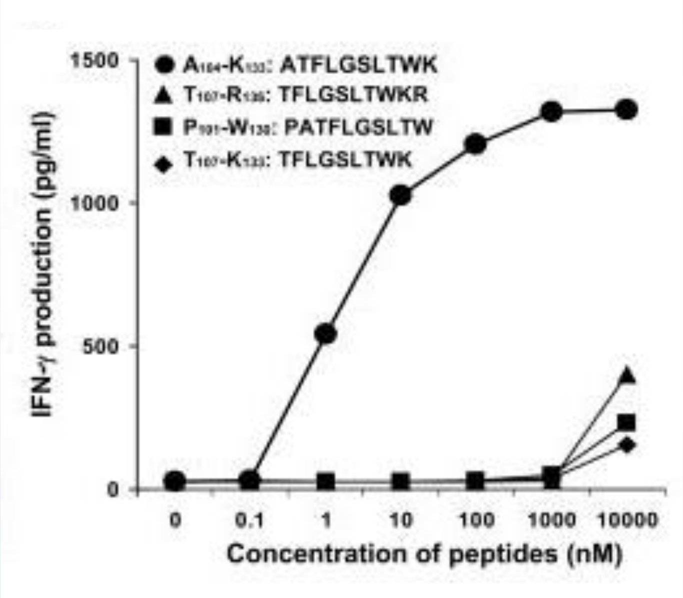


Smith CC, et al. *J Clin Invest.* 2018



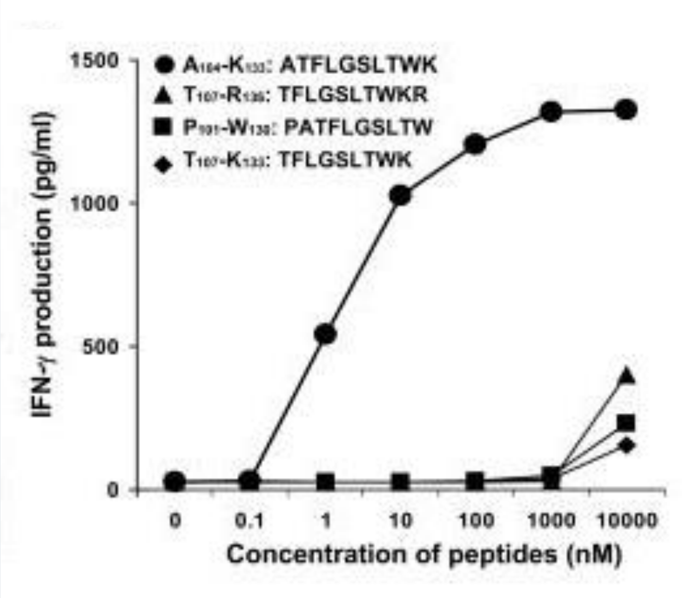
Ficial M, et al. *Clin Cancer Res*. 2021.

Activation lymphocytaire par les HERV

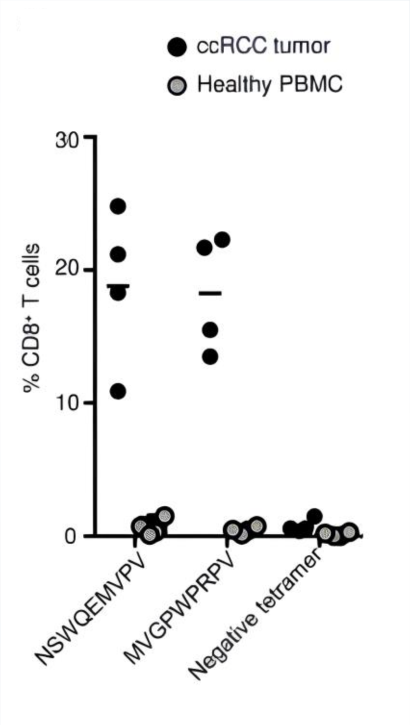


Takahashi Y, et al. *J Clin Invest*. 2008

Activation lymphocytaire par les HERV

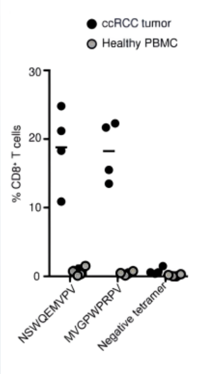


Takahashi Y, et al. *J Clin Invest*. 2008

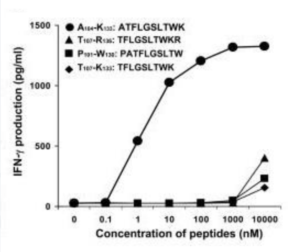


Smith CC, et al. *J Clin Invest.* 2018

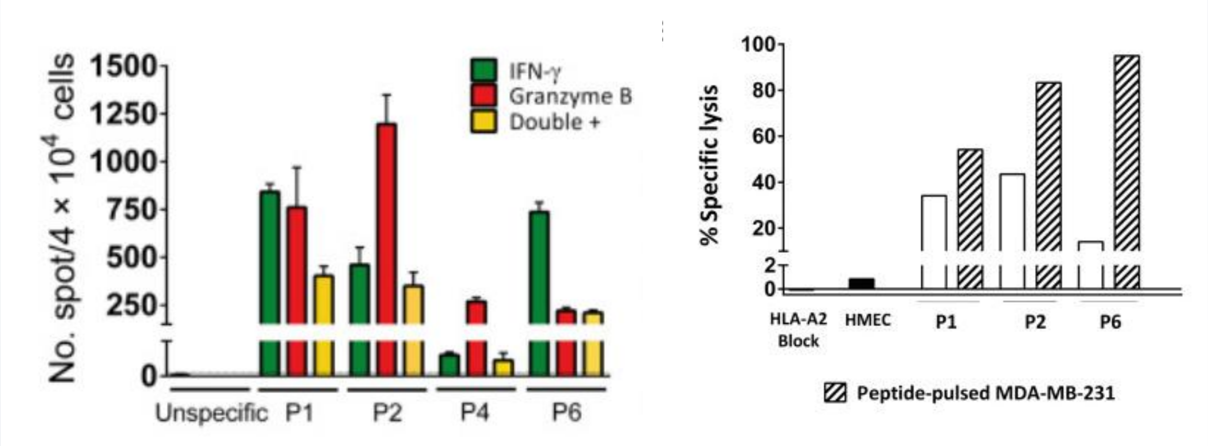
Activation lymphocytaire par les HERV



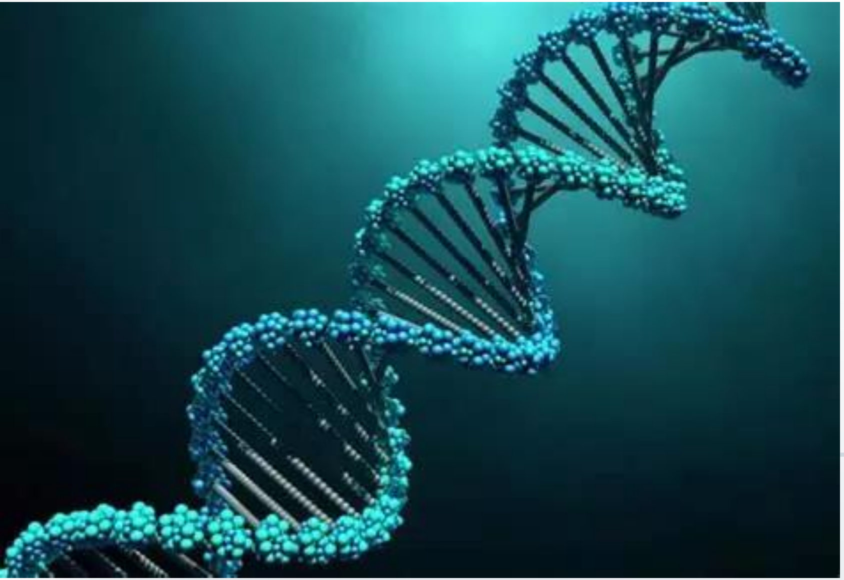
Smith CC, et al. *J Clin Invest.* 2018



Takahashi Y, et al. *J Clin Invest*. 2008



Bonaventura P, et al. *Sci Adv.* 2022

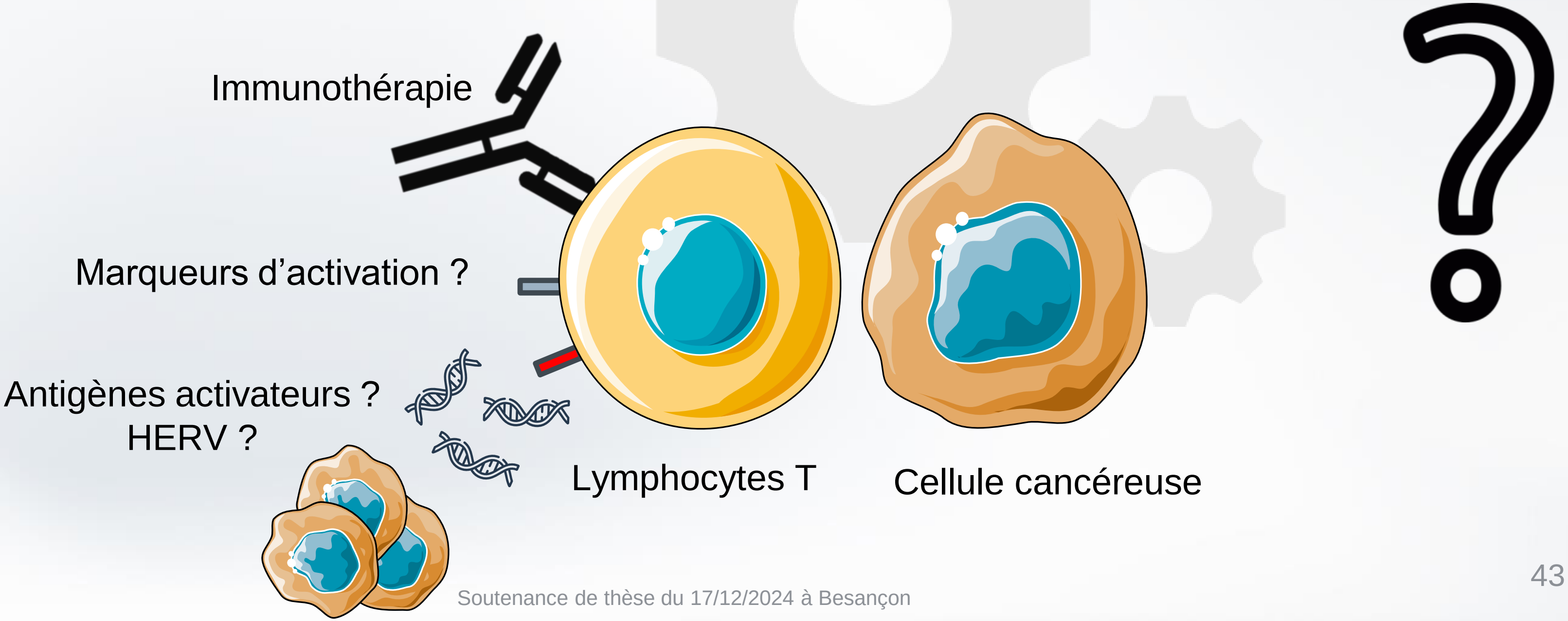


02

Problématique et méthode

Problématique et objectifs de cette thèse

Les HERV sont-ils source d'antigènes dans les métastases hépatiques de cancer colorectaux ?



Méthode d’Etude des HERV:
séquençage haut débit de l’ARN et Bioinformatique

Métastase hépatique de
Cancer colorectal

Séquençage ARN

Bioinformatique
=
Alignement sur
génome de
référence

Plusieurs centaines échantillons

	Cell1	Cell2	...	CellN
Gene1	3	2	.	13
Gene2	2	3	.	1
Gene3	1	14	.	18
...	.	.	.	.
...	.	.	.	.
...	.	.	.	.
GeneM	25	0	.	0

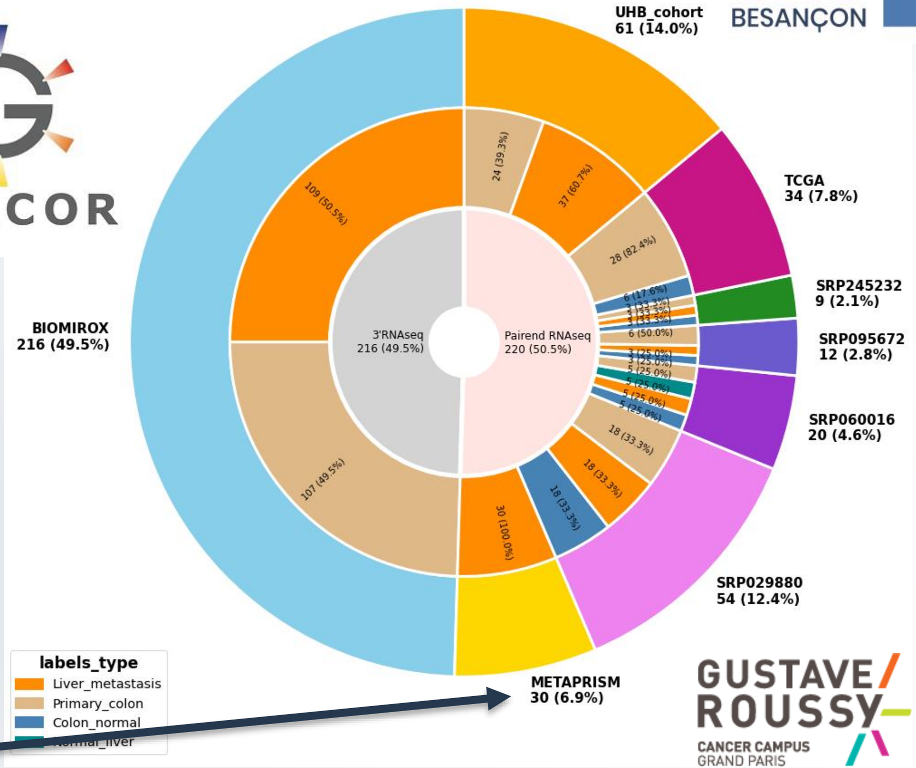
20 000-30 000
gènes annotés

~ 15 000 positions de
rétrovirus endogènes

03

Résultats

Constitution d'une meta-base de données



Base de Données Publiques

Pradat Y, **Viot J** et al. Cancer Discov. 2023

Découverte des TE et HERV

Colorectal Cancer

RNA-seq

Pseudoalignment
With Salmon

<u>REdiscoverTE</u>

=> Entities

\+

Genome-based
alignment

<u>TELESCOPE</u>

=> Loci

Kong et al. *Nature Com* 2019

Steiner MC, et al. *Cancer Res*. 2021

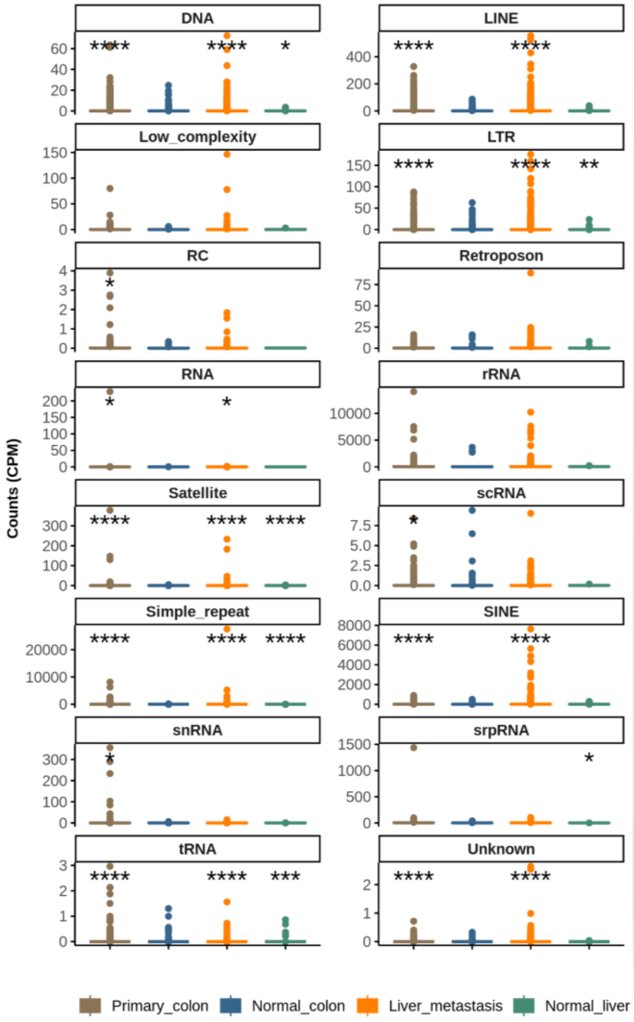
Annotation : RepeatMasker

eBioMedicine
Part of THE LANCET Discovery Science

Deciphering human endogenous retrovirus expression in colorectal cancers: exploratory analysis regarding prognostic value in liver metastases

Julien Viot,[a,b,*] Romain Loyon,[b] Nawfel Adib,[b] Pierre Laurent-Puig,[c,d] Aurélien de Reyniès,[d] Fabrice André,[e,f] Franck Monnien,[a,b] Thierry André,[g] Magali Svrcek,[h] Anthony Turpin,[i,n] Zohair Selmani,[a,b] Laurent Arnould,[j,k] Laura Guyard,[j,k] Nicolas Gilbert,[l] Anthony Boureux,[l] Olivier Adotevi,[a,b] Angélique Vienot,[a,b] Syrine Abdeljaoued,[b] Dewi Vernerey,[a] Christophe Borg,[a,b] and Daniel Gautheret[m]

eBioMedicine
2025;116: 105727
Published Online 16 May 2025
https://doi.org/10.1016/j.ebiom.2025.105727



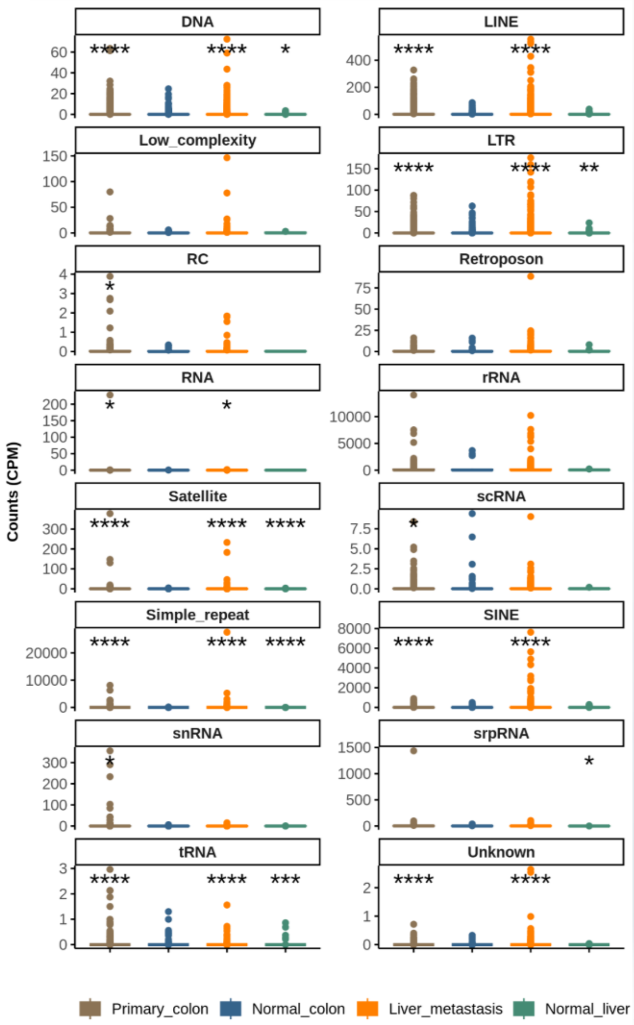
Distribution de l'expression des TE dans le mCRC

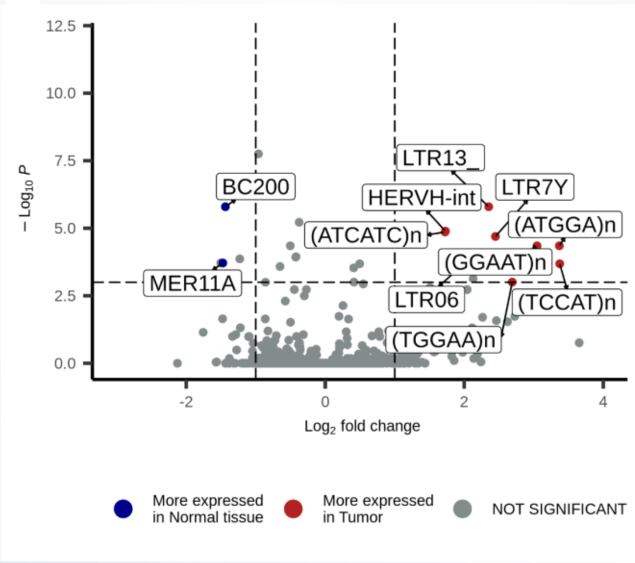
Méthode = REdiscoverTE

J Viot, et al. En révision dans eBioMedecine, 2024.

Distribution de l'expression des TE dans le mCRC

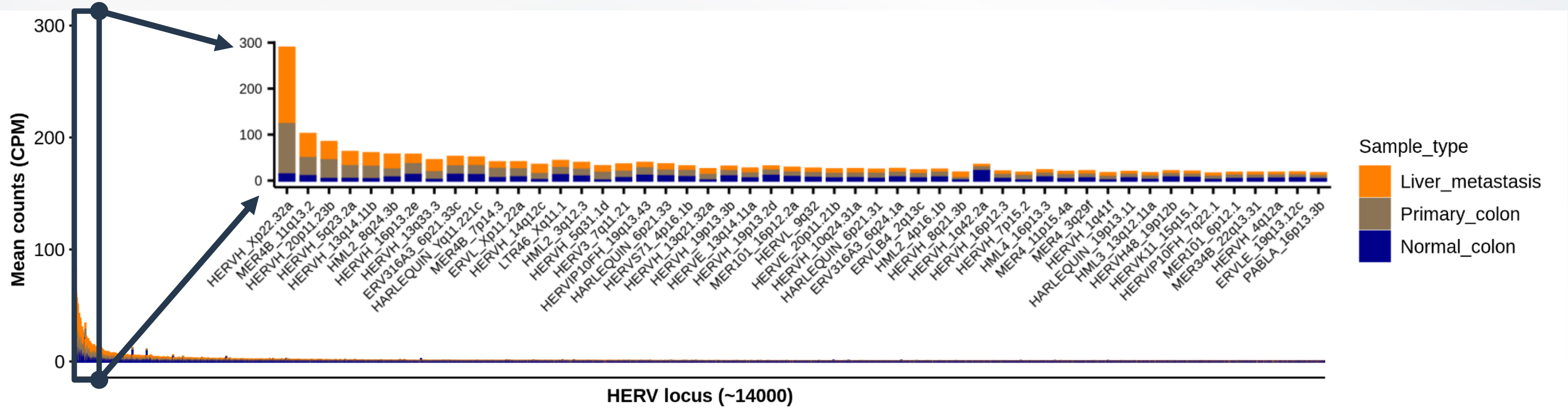
Méthode = REdiscoverTE





J Viot, et al. En révision dans eBioMedecine, 2024.

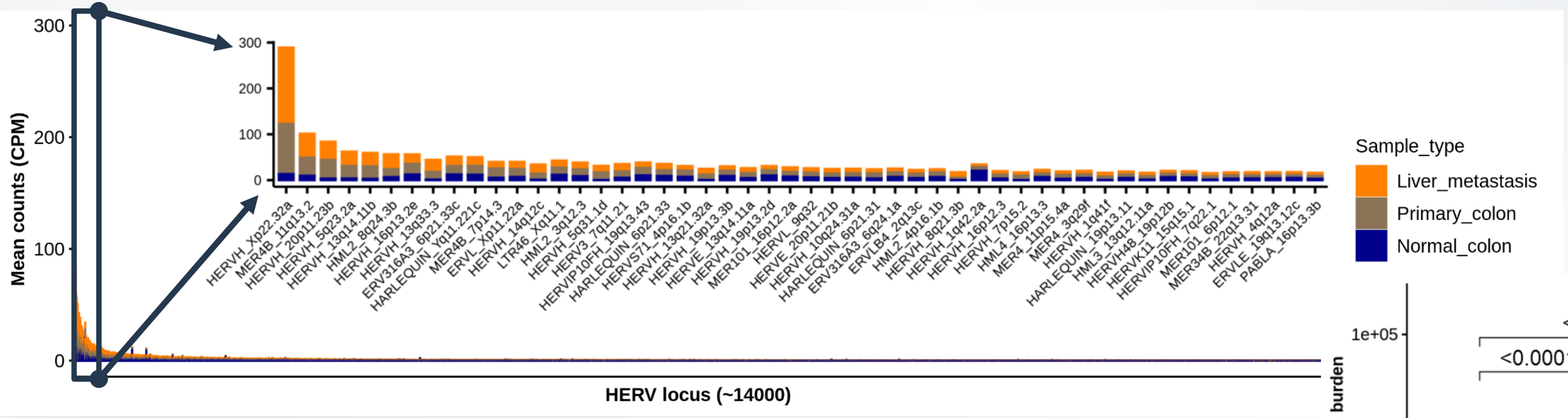
Distribution de l'expression des loci d'HERV dans le mCRC

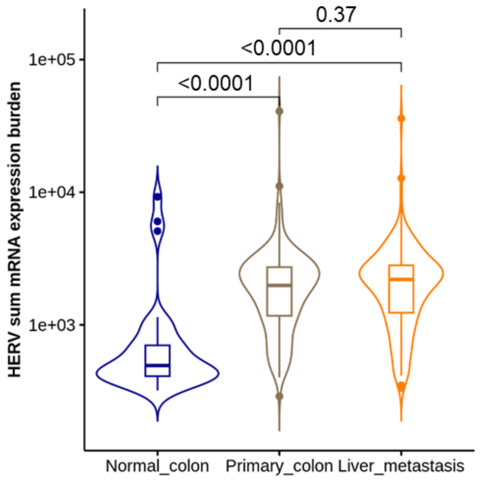


Méthode = Telescope

J Viot, et al. En révision dans eBioMedecine, 2024.

Distribution de l'expression des loci d'HERV dans le mCRC

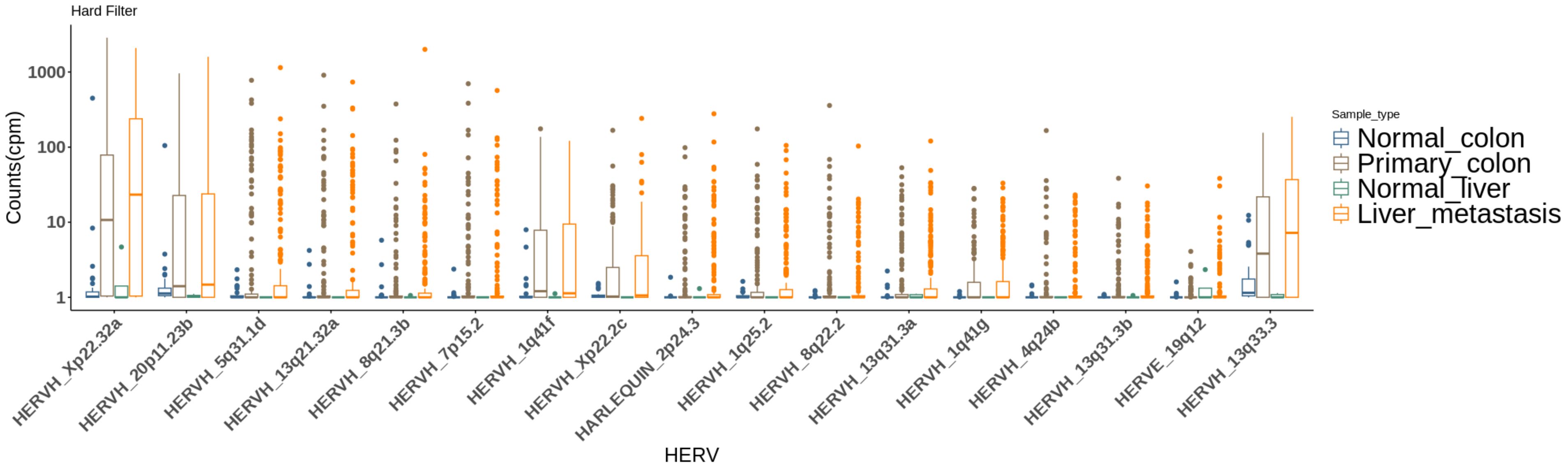




Méthode = Telescope

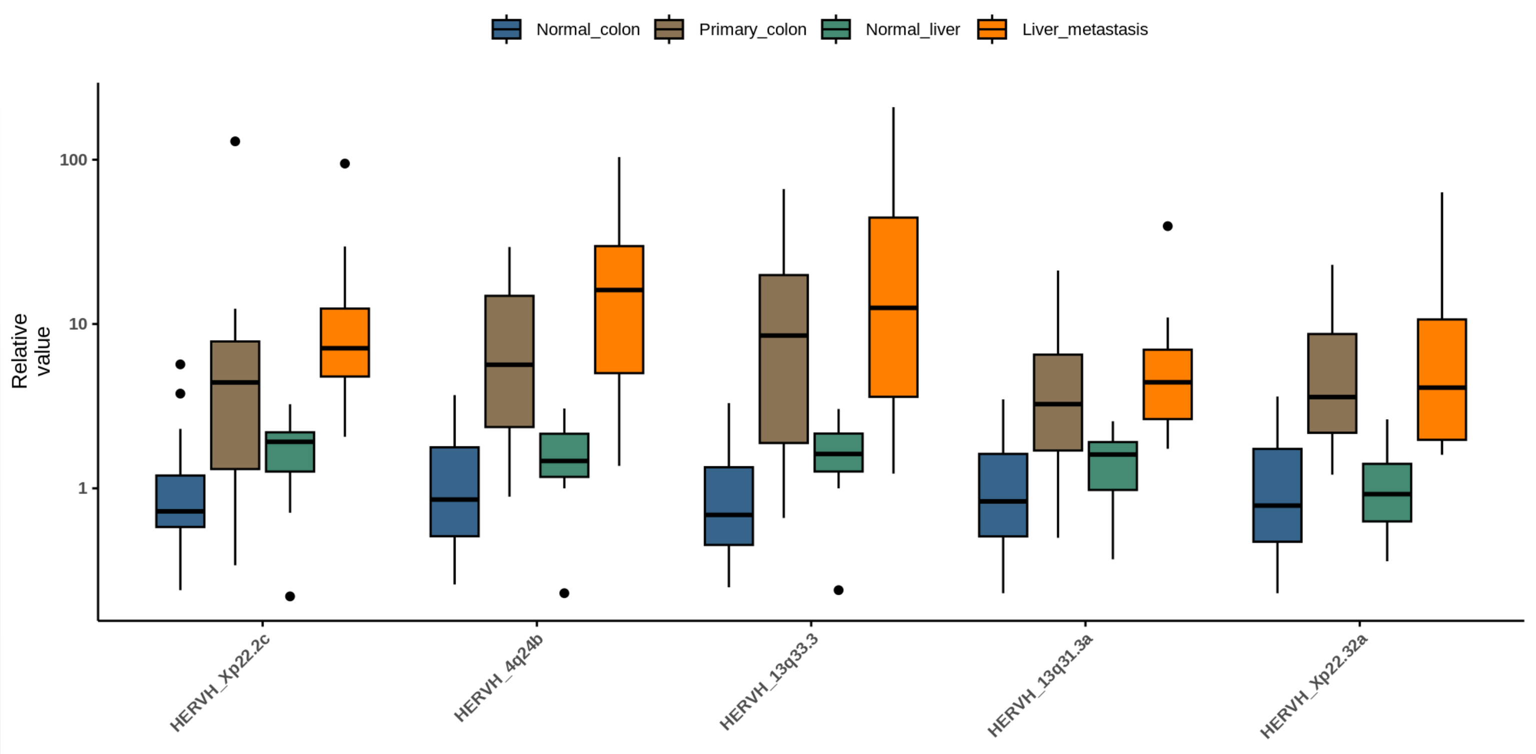
J Viot, et al. En révision dans eBioMedecine, 2024.

Identification de cibles immunologiques



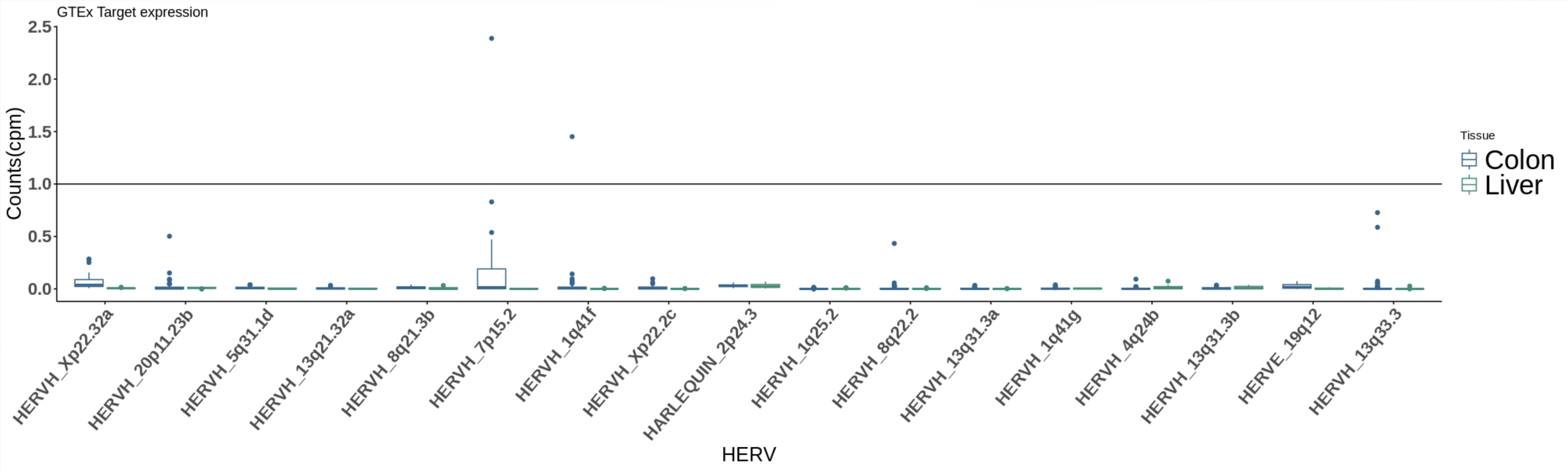
J Viot, et al. En révision dans eBioMedecine, 2024.

Validation en RT-PCR des cibles



J Viot, et al. En révision dans eBioMedecine, 2024.

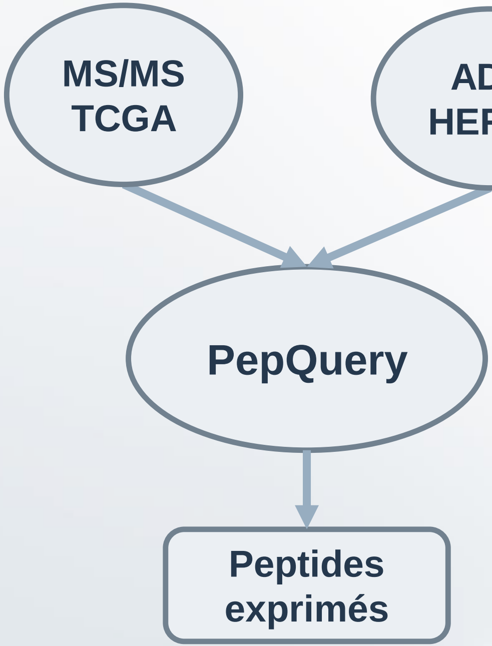
Validation GTEx des cibles HERV



J Viot, et al. En révision dans eBioMedecine, 2024.

Expression de peptides dérivés d'HERV

90 Patients
Cancer
colorectaux
primitifs

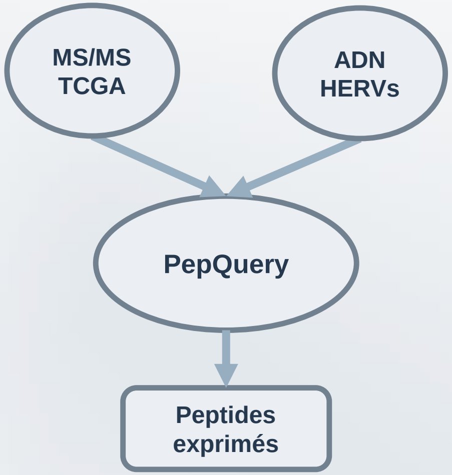


14000 locus

> 2000 peptides identifiés

Weng et al. *Genome Research* 2019

Expression de peptides dérivés d'HERV

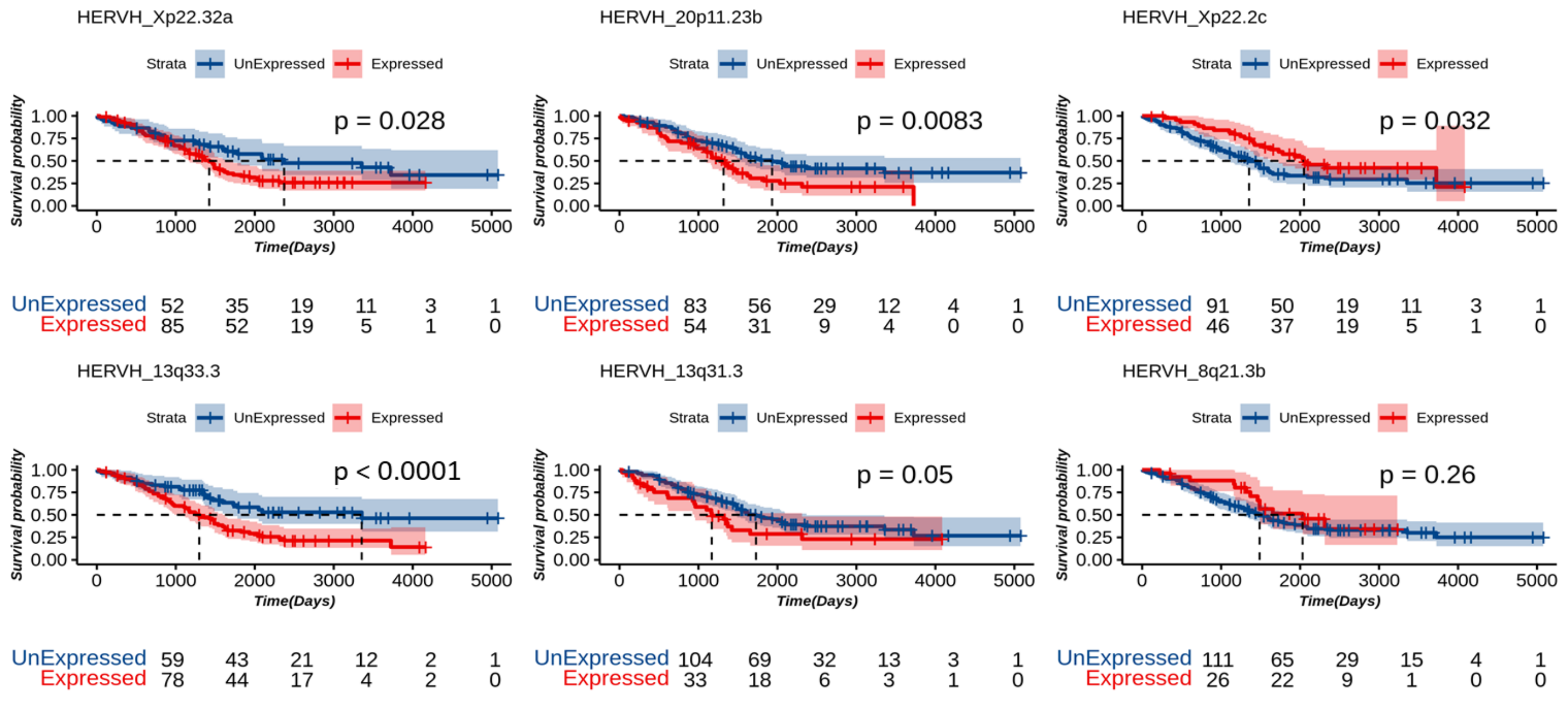


Weng et al. *Genome Research* 2019

Locus	HERV Family	LTR	qRT-PCR validation	GTEx expression	Associated Peptide	Prognostic value	TME modulation	Cell cycle correlation
Xp22.32a	HERVH	LTR7Y	yes	Not in colon	GGCSLVGRGGSHK	yes:poor	yes	yes
20p11.23b	HERVH	LTR7B	no	Not in Colon	none	yes:poor	no	yes
13q33.3	HERVH	LTR7Y	yes	Not in Colon	CFSGLLQAGLGAAWEPRVGEIK	yes:poor	yes	yes
5q31.1d	HERVH	LTR7Y	no	Never expressed	ICTLSTK	no	yes	yes
13q21.32a	HERVH	LTR7	no	Never expressed	none	no	yes	no
8q21.3b	HERVH	LTR7Y	no	Never expressed	none	yes:good	no	yes
7p15.2	HERVH	LTR7Y	no	Rarely expressed in colon	LYIPYGPPSSRK	no	yes	yes
1q41f	HERVH	LTR7Y	no	Never expressed	CFSGLLQAGLGAAWEPRVGEIK	no	partially	yes
Xp22.2c	HERVH	LTR7	yes	Never expressed	NTRALPADR	yes:good	partially	yes
2p24.3	HARLEQUIN	LTR2	no	Never expressed	none	no	no	yes
1q25.2	HERVH	LTR7B	no	Not in Colon	none	no	partially	yes
8q22.2	HERVH	LTR7	no	Not in Colon	none	no	partially	yes
13q31.3a	HERVH	LTR7Y	yes	Never expressed	CFSGLLQAGLGAAWEPRVGEIK	yes:poor	yes	yes
4q24b	HERVH	LTR7Y	yes	Not in colon	ESAKGHGVGPFYR	no	yes	yes
1q41g	HERVH	LTR7	no	Never expressed	CFSGLLQAGLGAAWEPRVGEIK GASTLNPFSFTLTGK	no	yes	no
13q31.3b	HERVH	LTR7	no	Never expressed	NTRALPADR	yes:poor	yes	yes
19q12	HERVE	LTR2	no	Not in colon	VVEMGETQSKPTPLGTMLK	no	no	no

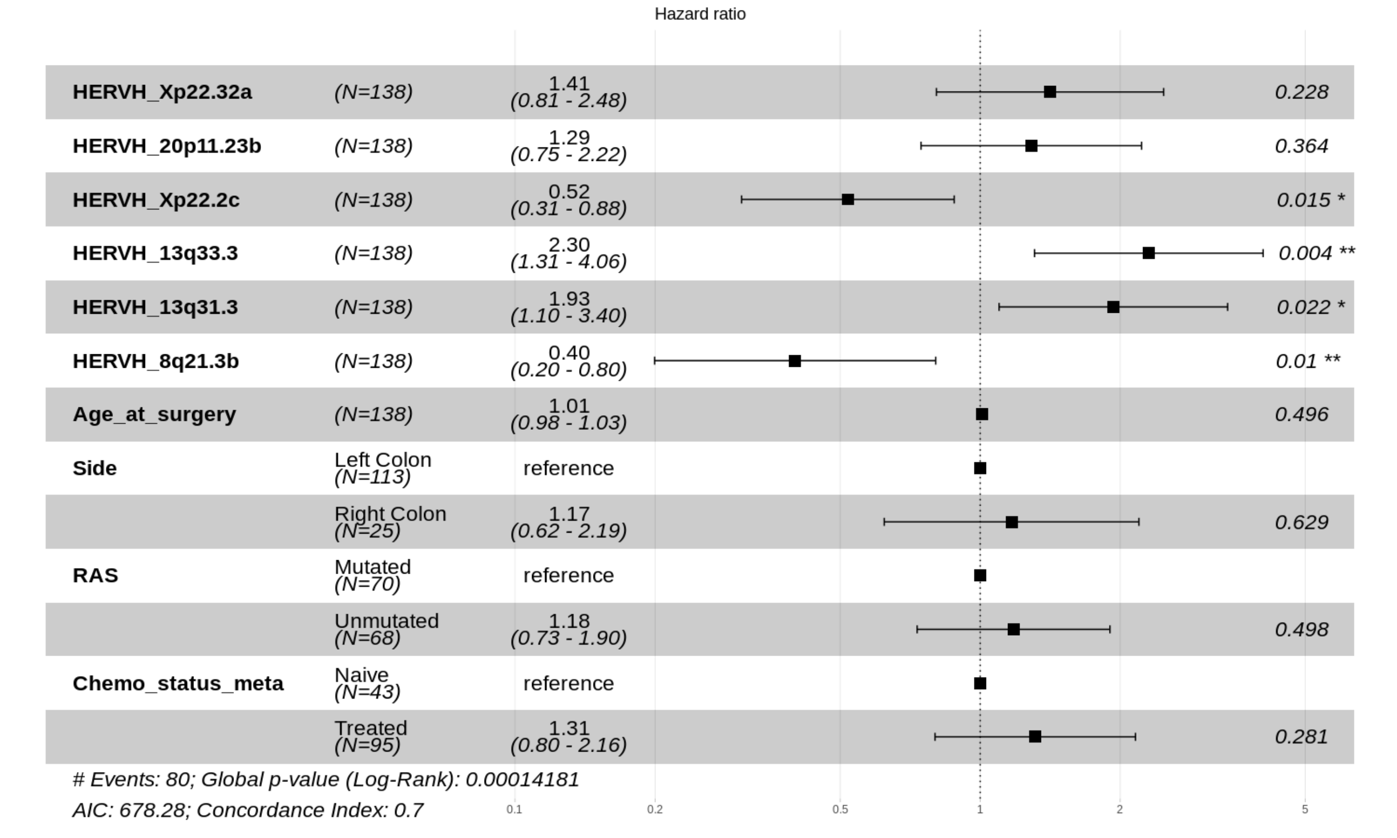
J Viot, et al. En révision dans eBioMedecine, 2024.

Valeur pronostique des HERV dans le mCRC



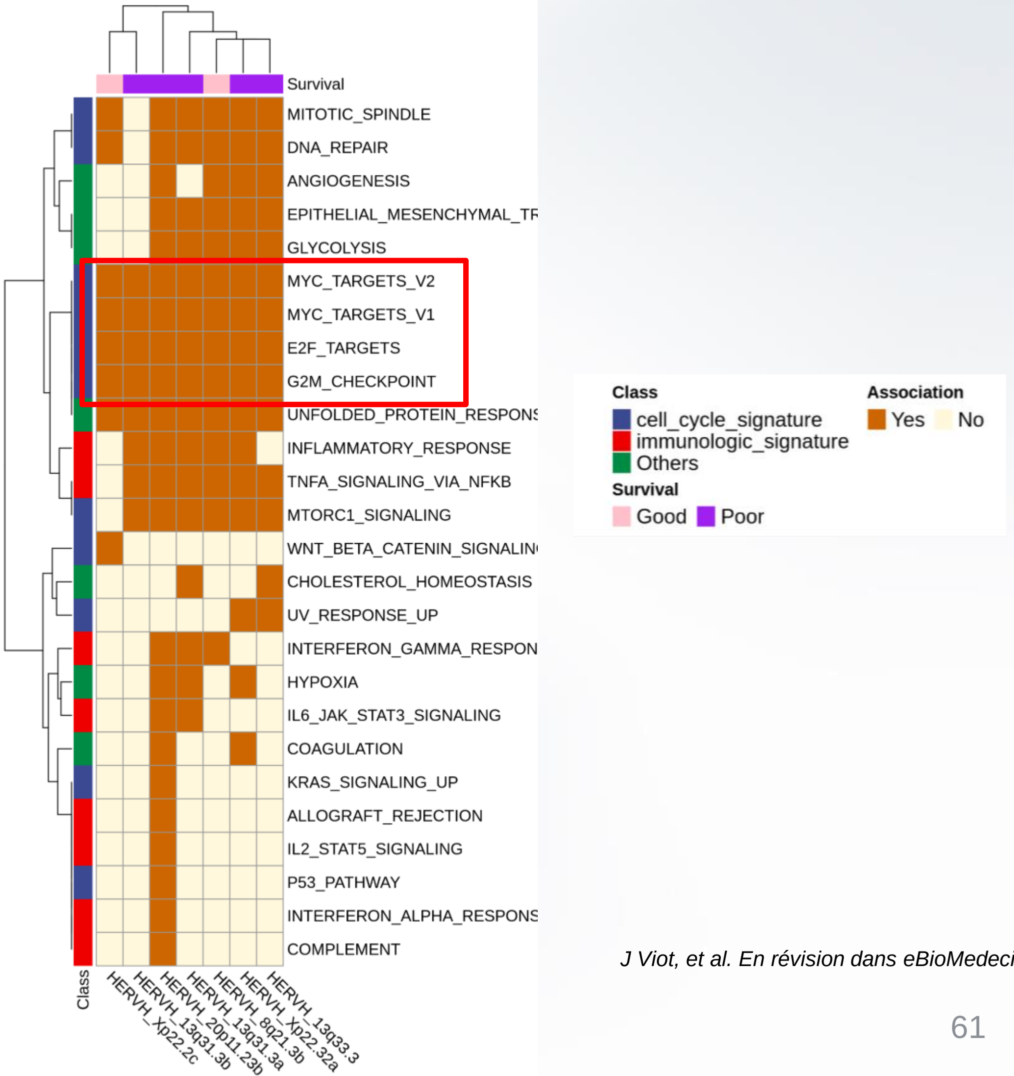
J Viot, et al. En révision dans eBioMedecine, 2024.

Modèle de survie multivariée incluant des locus d’HERV dans les mCRC



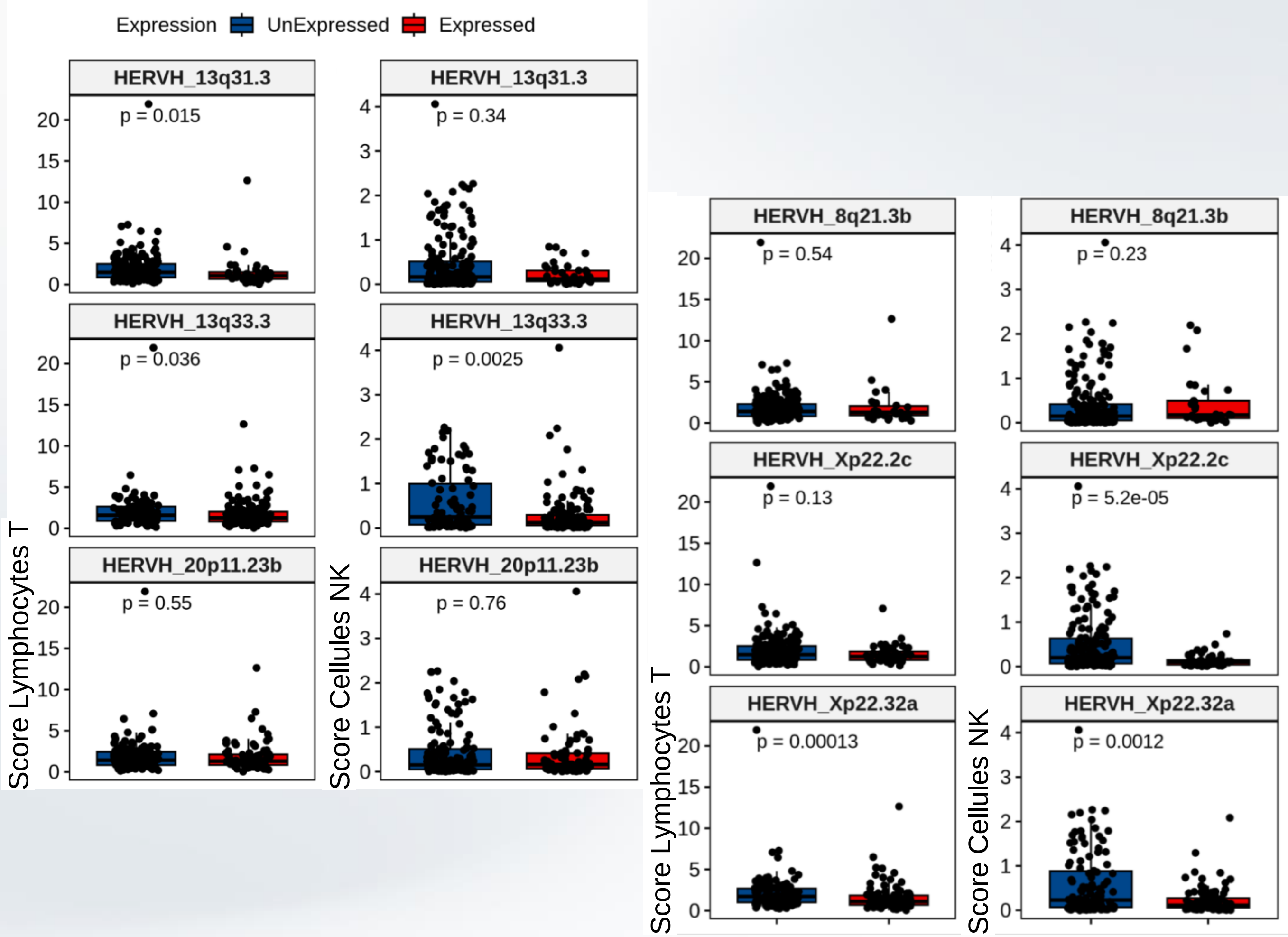
J Viot, et al. En révision dans eBioMedecine, 2024.

Les loci d'HERV sont associés à des voies de renouvellement et de croissance cellulaire



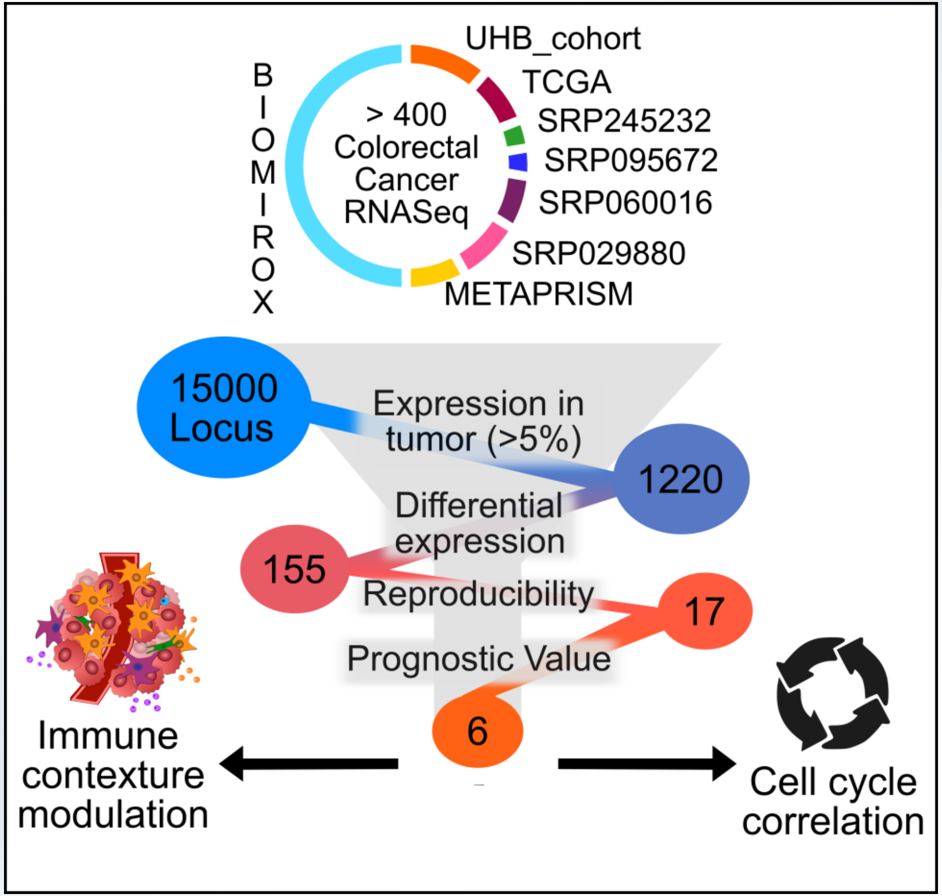
J Viot, et al. En révision dans eBioMedecine, 2024.

L'expression de certains HERV est associé à un environnement cytotoxique moins important



J Viot, et al. En révision dans eBioMedecine, 2024.

Conclusion de la 2e partie



J Viot, et al. En révision dans eBioMedecine, 2024.

04

Discussion

Cibles HERV partagées

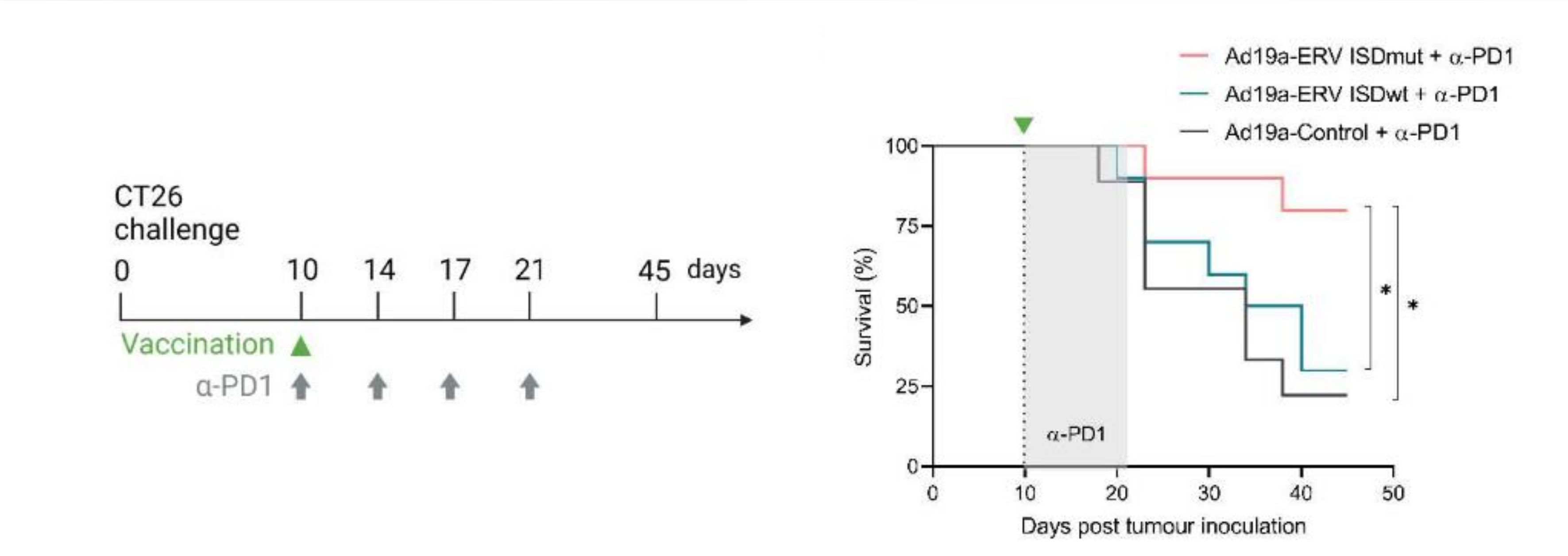
HERVH_Xp22.32a

ERVLE_19q13.31a,
HERVL74_2q11.2,
HML3_17q21.32,661
HERVL_17q21.32,
ERVLB4_11q23.3a

Cancers ORL
HERVH_18q22.3a, HERVH_8q21.3b et HERVH_4q24b

Steiner MC, et al. *Cancer Res*. 2021
Kolbe AR, et al. *Viruses*. 2020

Implication thérapeutique de l'utilisation de HERV dans le CRC



Daradoumis J, et al *Viruses*. 2023

Les HERV comme biomarqueurs ?

Diagnostic

- Initial
- Rechute

Pronostic

- Mieux connaitre la maladie à un niveau individuel
- Concentrer les efforts de traitements sur les patients qui en ont vraiment besoin

Thérapeutique

- Augmente le nombre de traitements disponibles
- Médecine de précision =

Augmente les chances de succès

Conclusion

- mCRC et immunothérapie
- Environnement immunitaire
- HERV = marqueurs de mCRC

Merci pour votre attention!

Pour les questions:

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Nawfel Adib
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Dr Syrine Abdeljaoued
Dr Zohair Selmani
Dr Angelique Vienot …
Et collaborateurs:
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