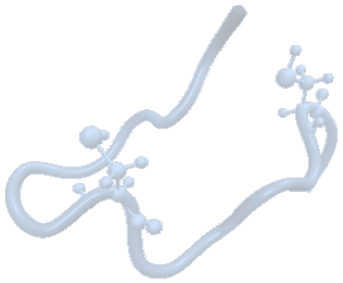
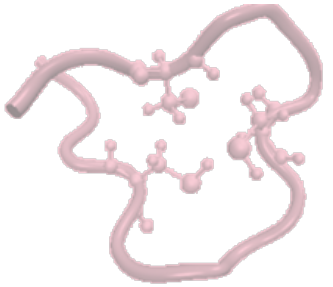


Développement de peptides antitumoraux ciblant l'interaction pro-cathepsine D/LRP-1



Tesnim Al-Khalifa, Elodie Lelièvre, Stéphanie Baud, Lise Chazée, Adeline Porcherie, Bruno Kieffer, Albin Jeanne, Stéphane Dedieu et **Nicolas Etique**

UMR CNRS 7369 Matrice Extracellulaire et Dynamique Cellulaire (MEDyC) Reims, France
Equipe « Matrice extracellulaire, Cancer et cibles thérapeutiques »

MEDyC

igbmc institut de génétique et de biologie moléculaire et cellulaire

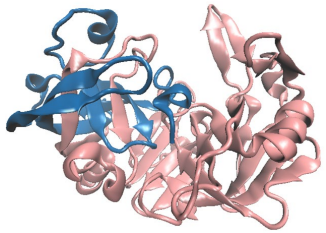
SATT Nord

Université de Reims Champagne-Ardenne

cnrs

APMONIA THERAPEUTICS

La (pro-)Cathepsine D

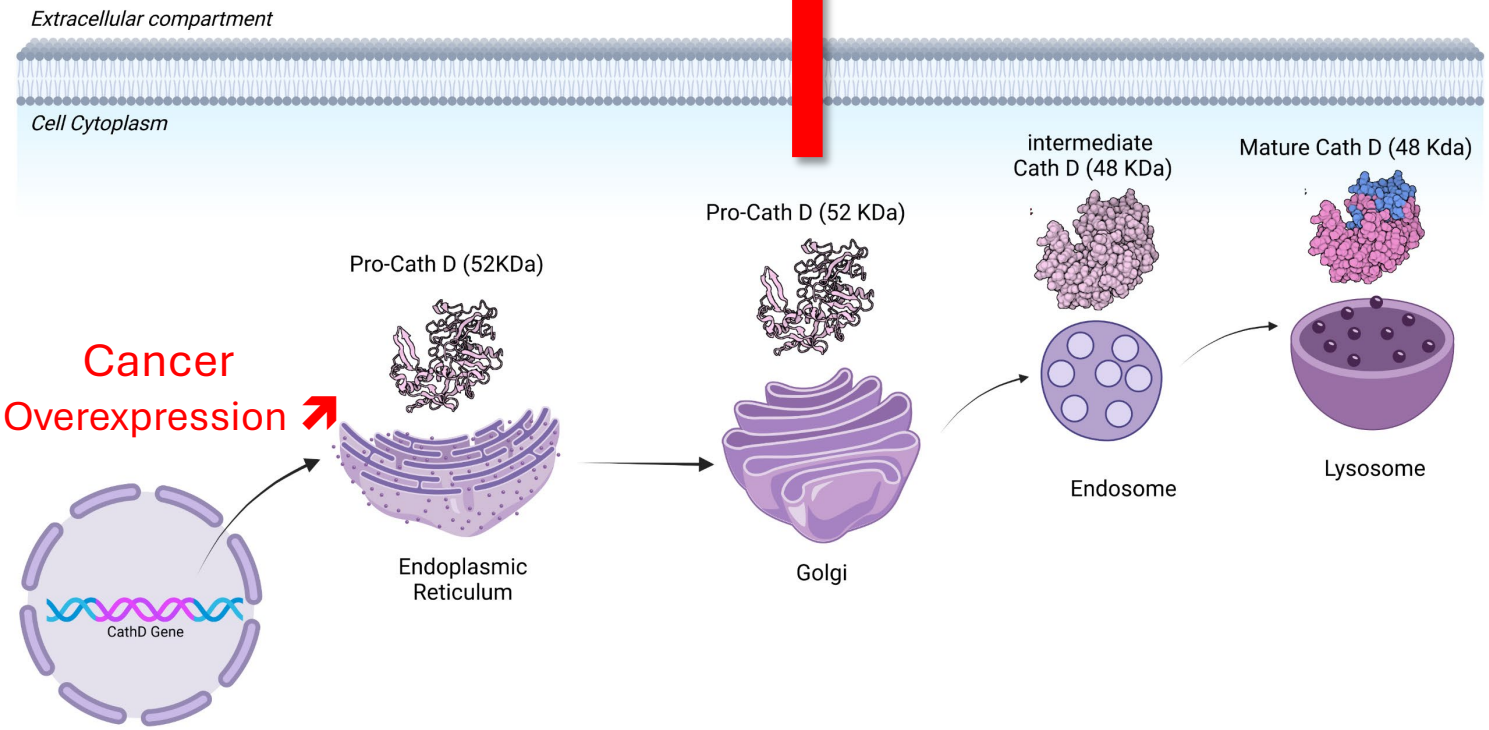


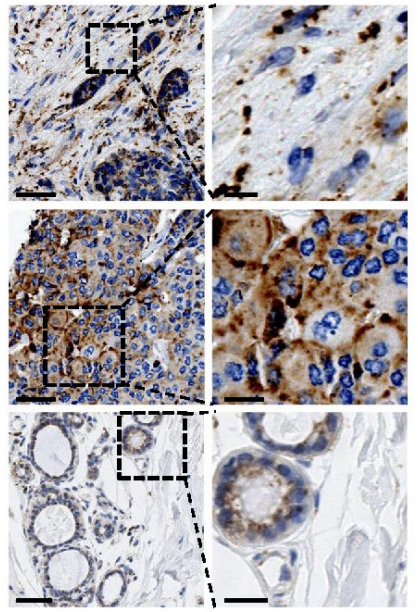
Effet paracrine

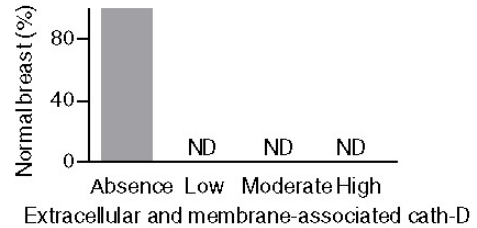
Activité protéolytique (Osteonectin, Aggrecan…)

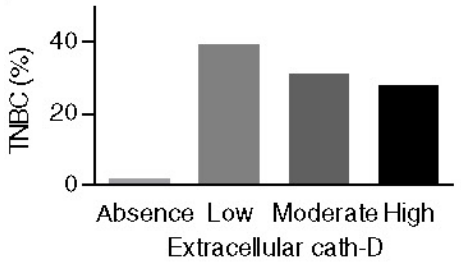
Alacarz et al. Theranostics 2021

Handley et al, Matrix Biol 2001



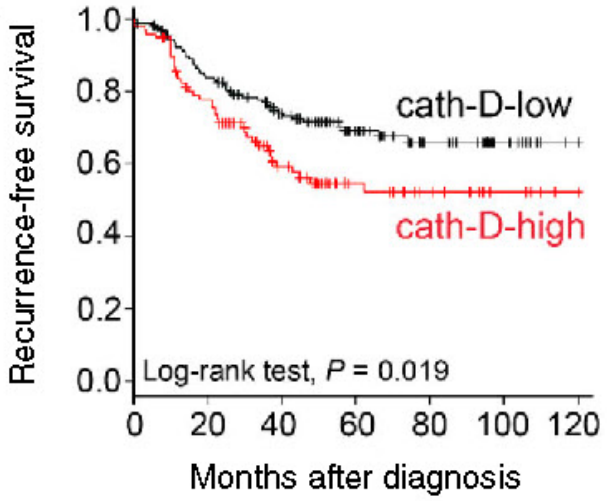






Ashraf et al., J immunother Cancer 2019

TNBC



Ashraf et al., J immunother Cancer 2019

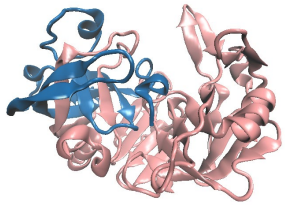
(Pro-)Cathepsine D et stroma tumoral

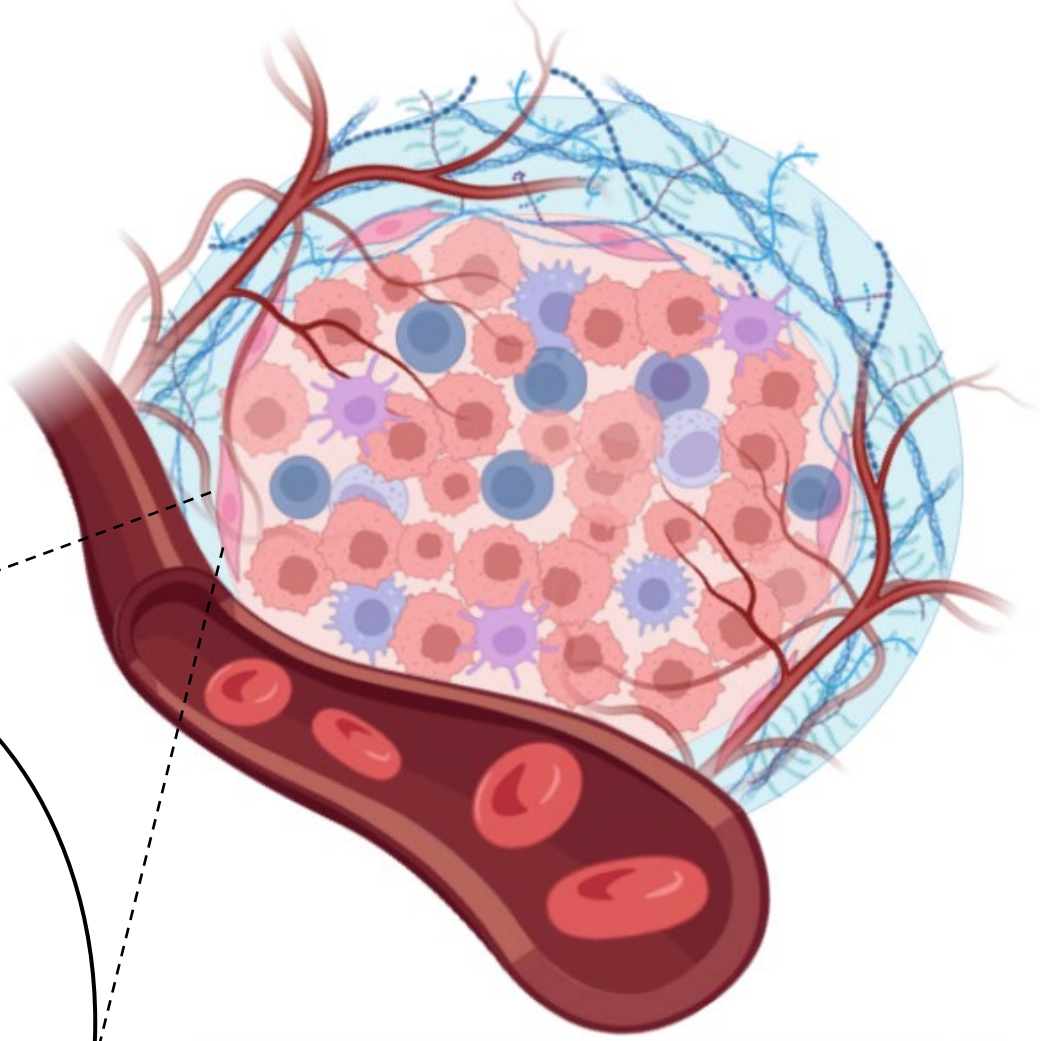
JCB: ARTICLE

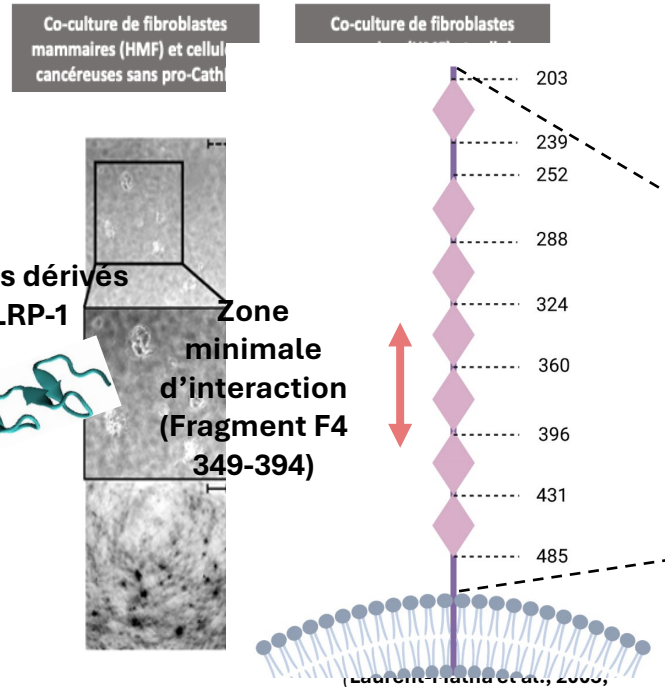
Catalytically inactive human cathepsin D triggers fibroblast invasive growth

Valérie Laurent-Matha,[1] Sharon Maruani-Herrmann,[1] Christine Prébois,[1] Mélanie Beaujouin,[1] Murielle Glondu,[1] Agnès Noël,[2] Marie Luz Alvarez-Gonzalez,[2] Sylvia Blacher,[2] Peter Coopman,[3] Stephen Baghdiguian,[4] Christine Gilles,[2] Jadranka Loncarek,[5] Gilles Freiss,[1] Françoise Vignon,[1] and Emmanuelle Liaudet-Coopman[1]

[1]INSERM U540 Endocrinologie Moléculaire et Cellulaire des Cancers, Université de Montpellier 1, 34090 Montpellier, France
[2]Laboratory of Tumor and Developmental Biology, University of Liège, Sart-Tilman, B-4000 Liège, Belgium
[3]CNRS UMR 5539 and [4]CNRS UMR 5554, Université Montpellier 2, 34095 Montpellier, France
[5]INSERM EMI 0229, Centre de Recherche en Cancérologie, CRLC Val d'Aurelle-Paul Lamarque, 34298 Montpellier, France



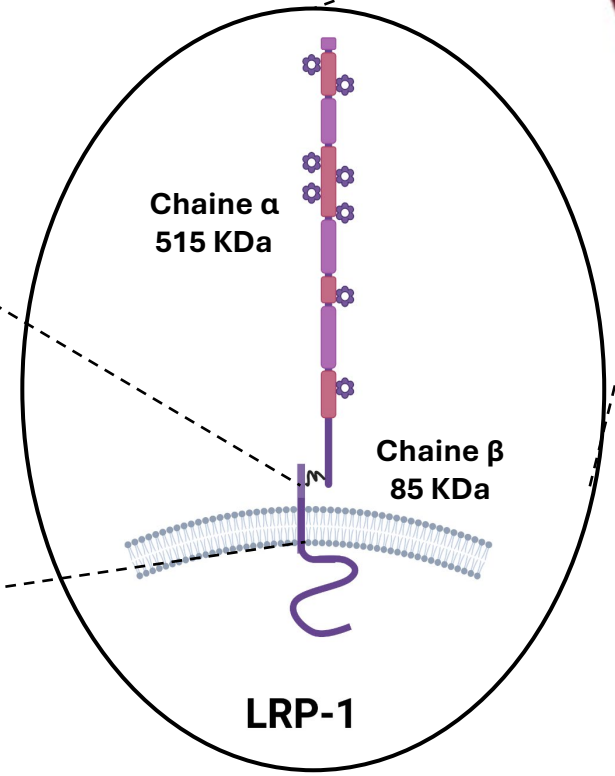




Peptides dérivés de LRP-1

Zone minimale d'interaction (Fragment F4 349-394)

(Laurent-Matha et al., 2005; Beaujouin et al., 2010)



Research Article 3336

Pro-cathepsin D interacts with the extracellular domain of the β chain of LRP1 and promotes LRP1-dependent fibroblast outgrowth

Mélanie Beaujouin[1–4], Christine Prébois[1–4], Danielle Derocq[1–4], Valérie Laurent-Matha[1–4], Olivier Masson[1–4], Sophie Pattingre[1–4], Peter Coopman[5], Nadir Bettache[5], Jami Grossfield[6], Robert E. Hollingsworth[6], Hongyu Zhang[7], Zemin Yao[7], Bradley T. Hyman[8], Peter van der Geer[9], Gary K. Smith[10] and Emmanuelle Liaudet-Coopman[1–4,*]

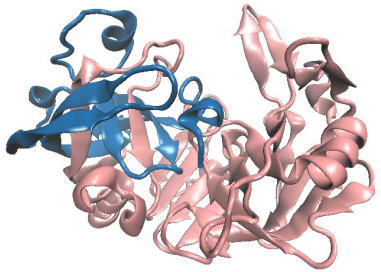
[1]IRCM, Institut de Recherche en Cancérologie de Montpellier, [2]INSERM, U896, [3]Université Montpellier 1, and [4]CRLC Val d'Aurelle Paul Lamarque, Montpellier, F-34298, France
[5]Centre de Recherche de Biochimie Macromoléculaire, CNRS UMR 5237, Université Montpellier 2, 34293 Montpellier Cedex 5, France
[6]Genetics Research, GlaxoSmithKline, Five Moore Drive, Research Triangle Park, NC 27709, USA
[7]Department of Biochemistry, Microbiology and Immunology, University of Ottawa, Ottawa K1Y4W7, Canada
[8]Alzheimer Disease Research Laboratory, Massachusetts General Hospital, Harvard Medical School, Charlestown, MA 02129, USA
[9]Department of Chemistry and Biochemistry, San Diego State University, 5500 Campanile Drive, MC 1030, San Diego, CA 92182-1030, USA
[10]Screening and Compound Profiling, GlaxoSmithKline, Five Moore Drive, Research Triangle Park, NC 27709, USA
*Author for correspondence (emmanuelle.liaudet-coopman@inserm.fr)

Etude de l'interaction Cathepsine D/LRP-1

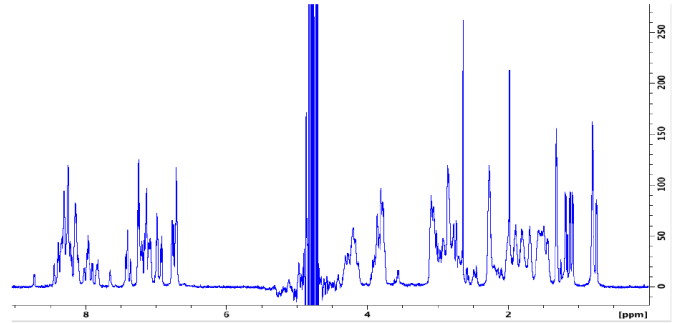
Collaboration Pr Bruno Kieffer
IGBMC

Collaboration Pr Stéphanie Baud
MEDyC

Choix des structures



Structure de la Cathepsine D (pCD)



Spectre RMN de la zone minimale d'interaction de LRP-1 (AA 349-394)

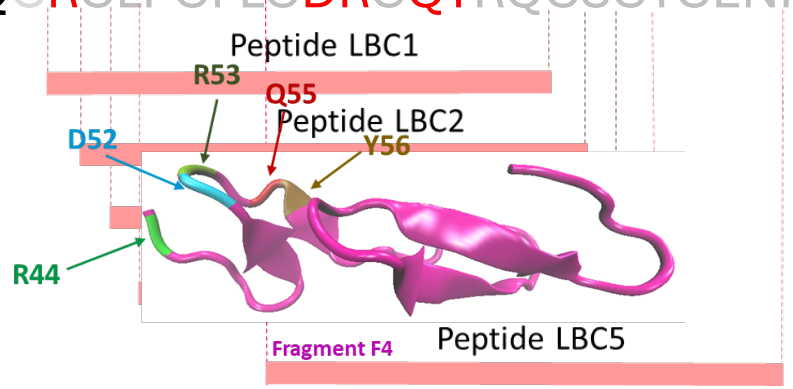
Simulations de dynamique moléculaire des fragments de LRP-1

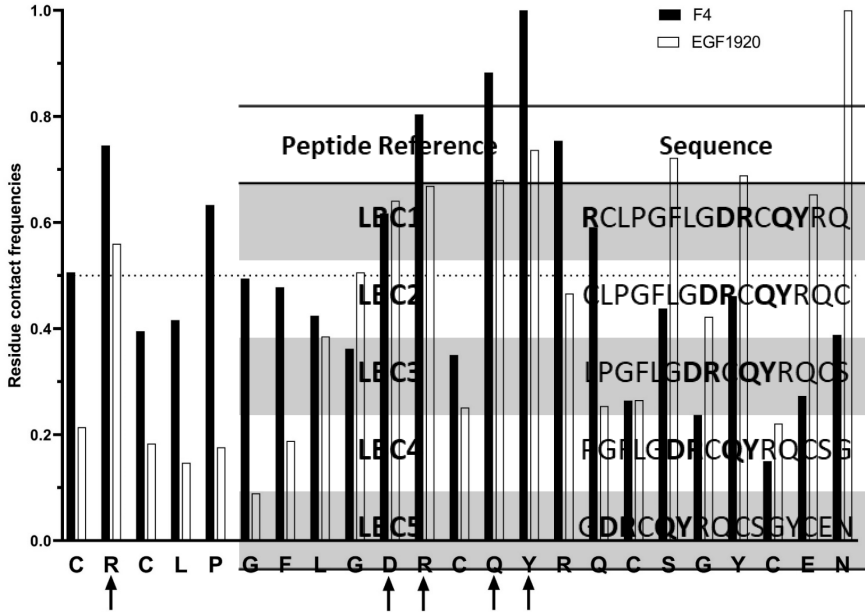
Identification des résidus clés de LRP-1

Chaine β LRP1 — LRP1 45 AA (Fragment AA 349-394)

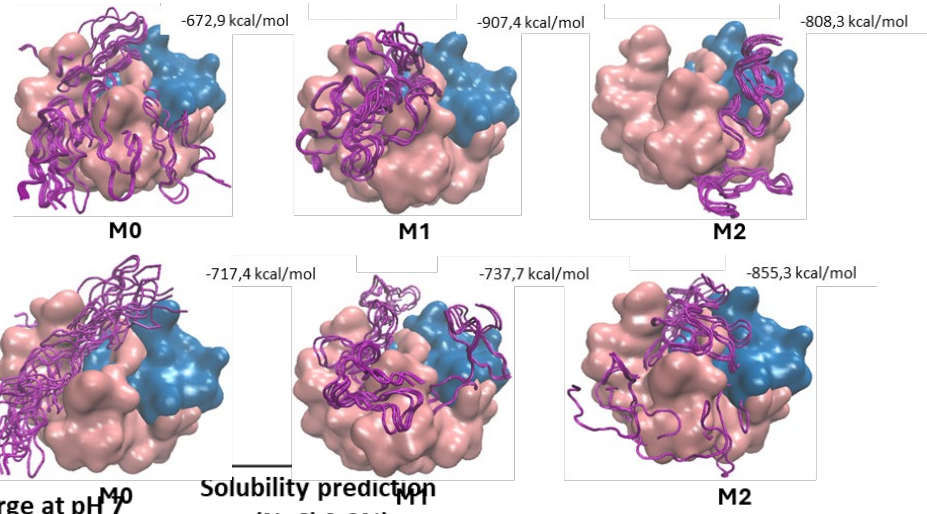
---STCTVNQGNQPQCRCLPGFLGDRCQYRQCSGYCENFGTCQMAADGSRQCRCTAYFEGSRC---

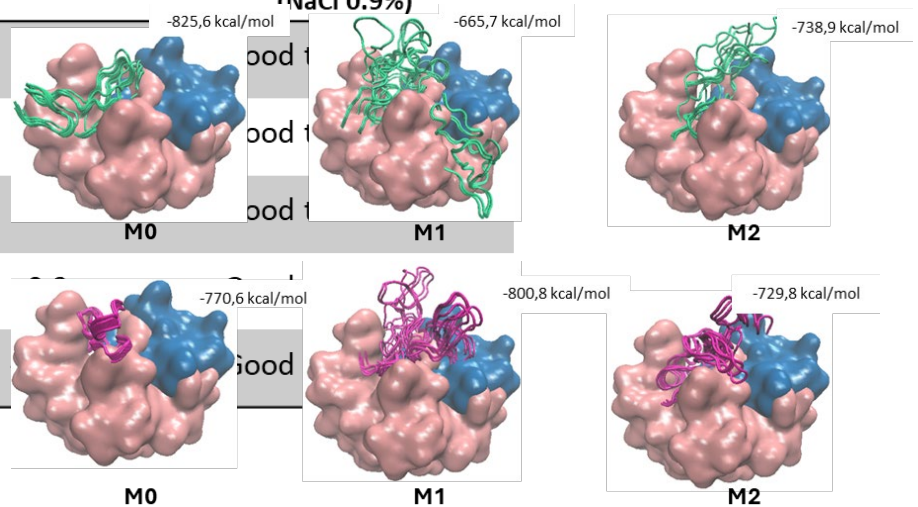
Design de 5 peptides de 15 AA…





Peptide Reference	Sequence	pKi	Net charge at pH 7	Solubility prediction (NaCl 0.9%)
LBC1	RCLPGFLG**DR**C**QY**RQ	8.74		
LBC2	CLPGFLG**DR**C**QY**RQC	7.86		
LBC3	LPGFLG**DR**C**QY**RQCS	8.10		
LBC4	PGFLG**DR**C**QY**RQCSG	8.09		
LBC5	GF**DR**C**QY**RQCSGYCEN	5.97		





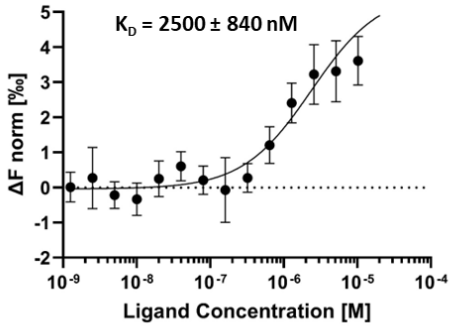
Patent N° EP23157848

Test et sélection des peptides

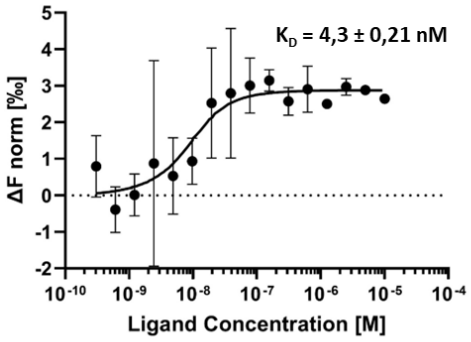
- Etude de l'affinité avec la pCD par MST

Peptide	Sequence	Net Charge at pH 7	Water Solubility	K_D (nM)
Fragment 45 AA	CRCLPGFLGDRCQYRQCSGYCENFG TCQMAADGSRQCRCTAYFEGS	ND	Yes	2500 ± 840
LBC1	RCLPGFLGDRCQYRQ	1,9	Yes	52.5 ± 2.62
LBC2	CLPGFLGDRCQYRQC	0,8	Yes	> 10 000
LBC3	LPGFLGDRCQYRQCS	0,9	Yes	340 ± 34
LBC4	PGFLGDRCQYRQCSG	0,9	Yes	4.3 ± 0.21
LBC5	GDRCQYRQCSGYCEN	-0,2	Yes	8.7 ± 0.43

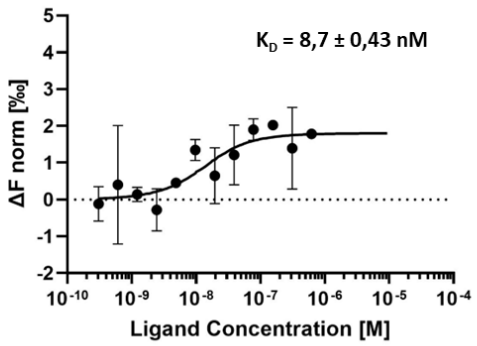
Fragment 45AA



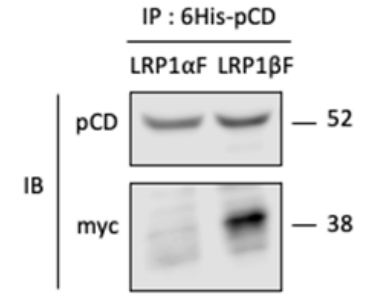
LBC4

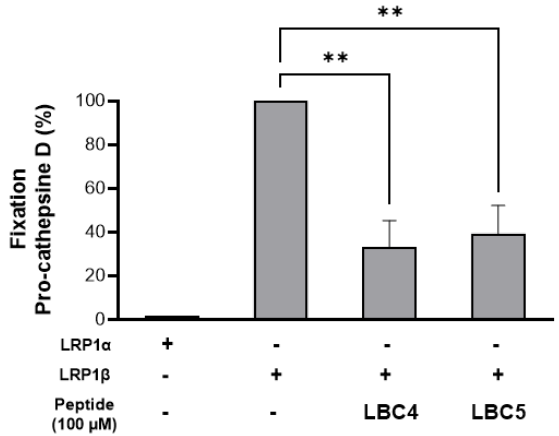


LBC5



- Etude du blocage de l'interaction par CoIP





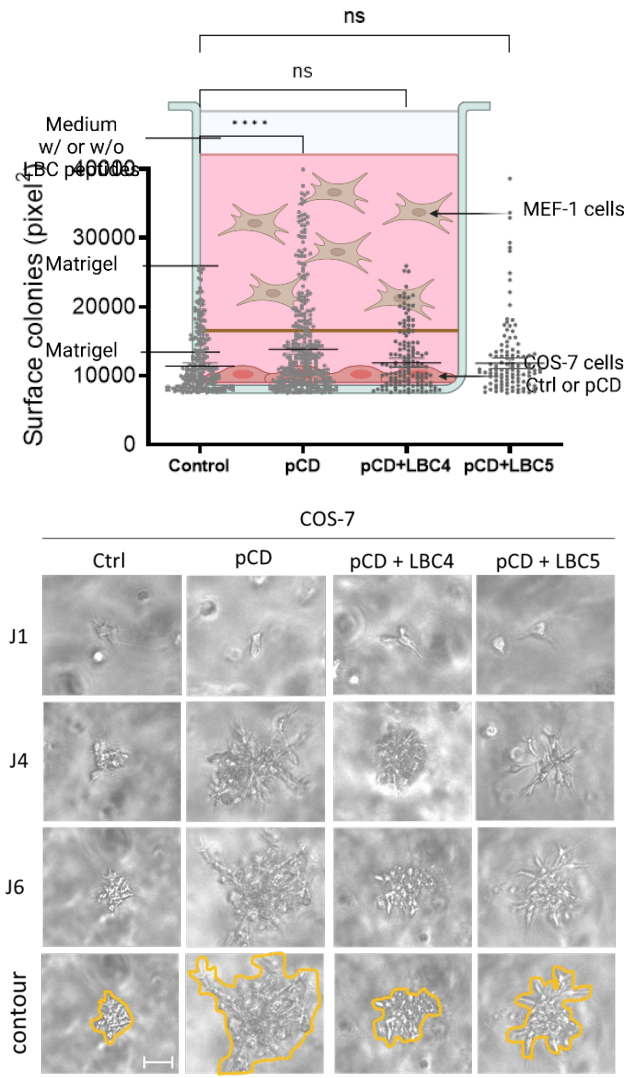
Les peptides LBC4 et LBC5 présentent chacun :

- **une bonne affinité pour la pCD**
- **une capacité à bloquer l'interaction pCD/LRP-1**

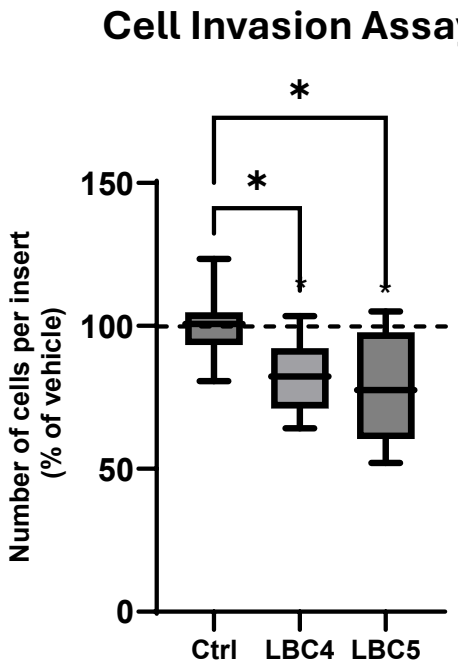
Patent N° EP23157848

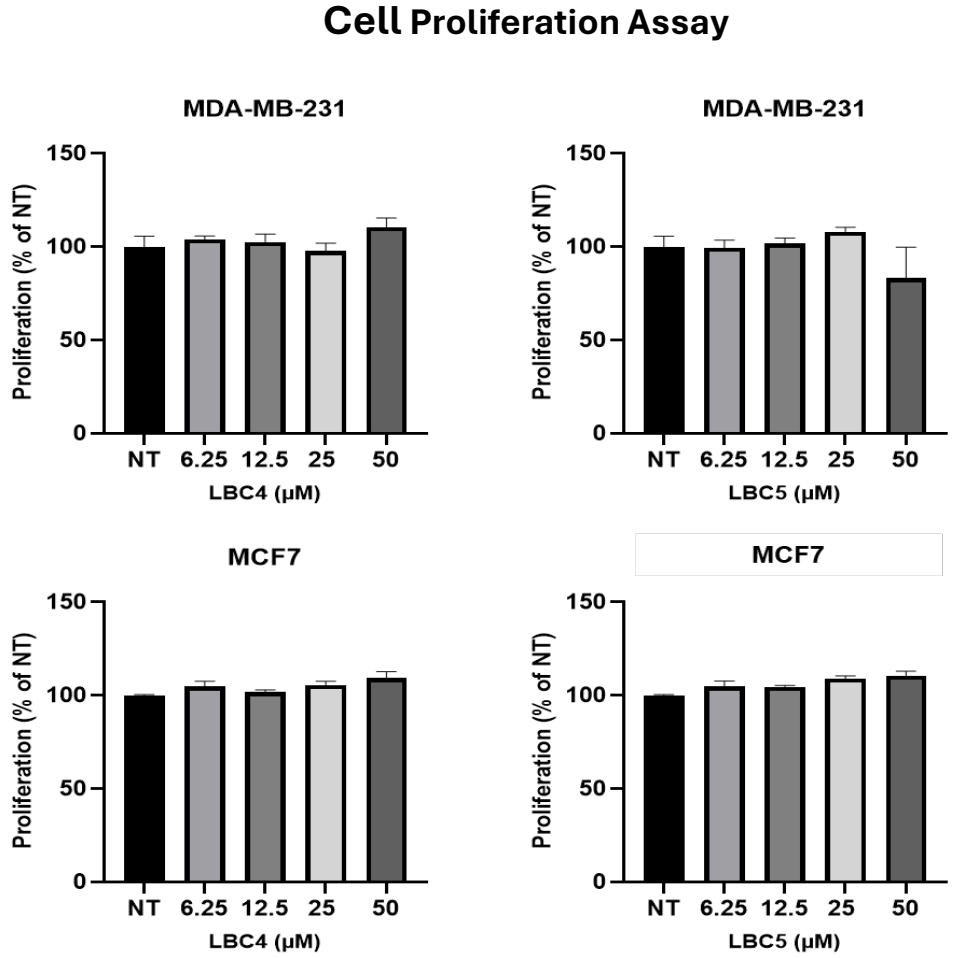
Effets in cellulo des peptides LBC4 et 5

- **Sur les fibroblastes :**



- **Sur les cellules tumorales :**





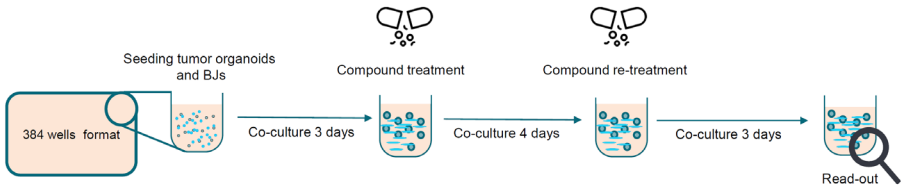
Les peptides LBC4 et LBC5 :

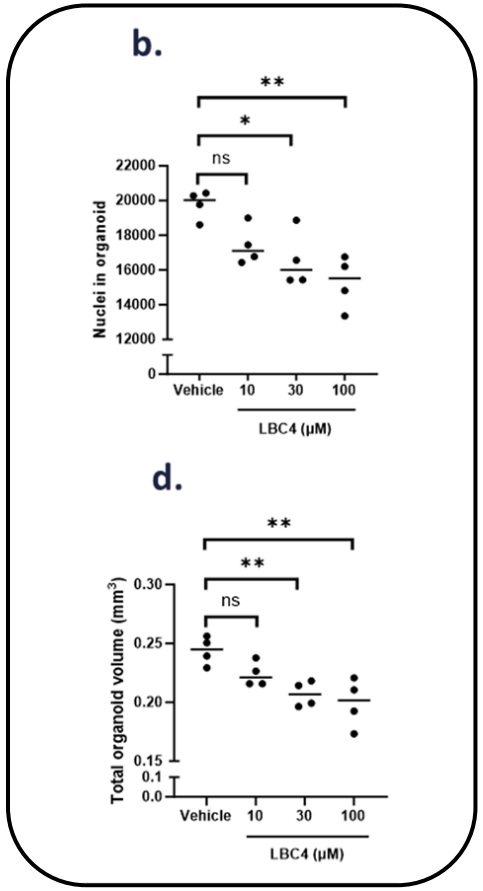
- **Bloquent l'effet de la pCD sur la croissance des fibroblastes**
- **diminuent l'invasion des cellules tumorales**
- **Ne présentent pas d'effet cytotoxiques**

***Patent N°* EP23157848**

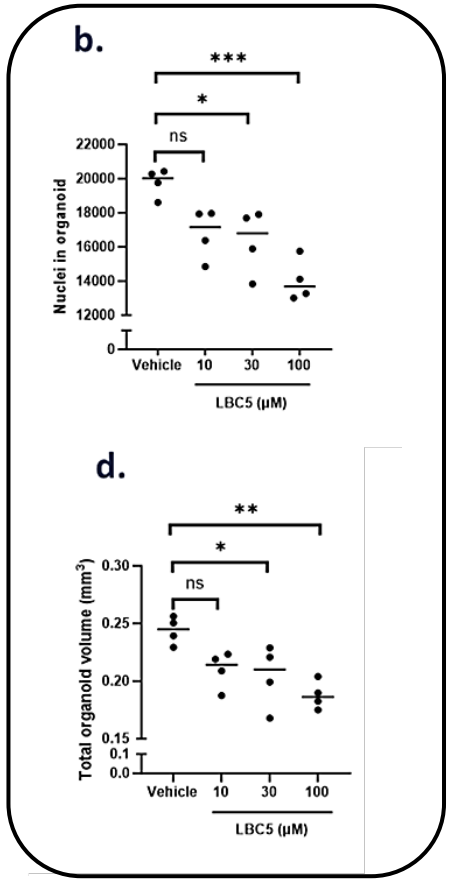
Effets anti-tumoral des peptides LBC4 et 5

- **Dans des organoïdes (PDO) issus de patientes TNBC…**





LBC4



LBC5

- **Dans un modèle immunocompétent (EO771/C57BL6)**

J0: injection dans le Fat Pad mammaire de cellules E0771

C57BL6/JRj mice

LBC4
(10 mg/kg)

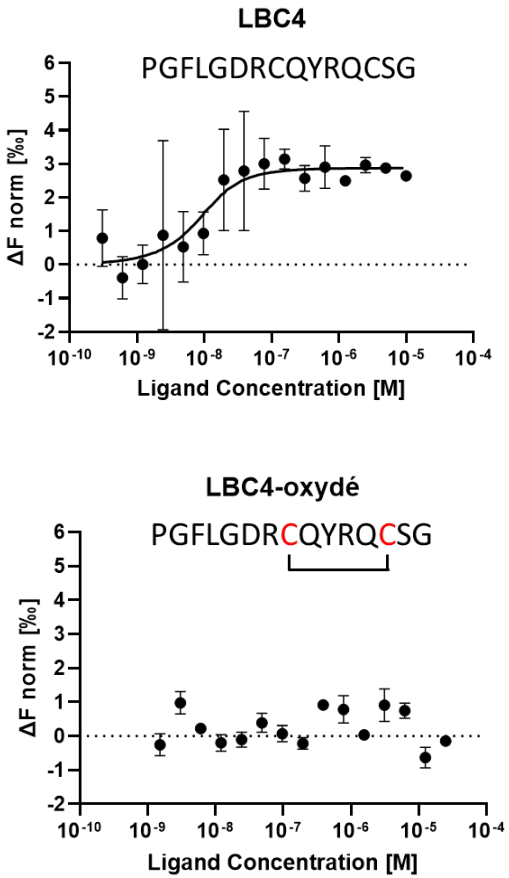
≈ J11 : Randomisation et début traitement
(VT > 50 mm^3)

Traitement tous les 3 jours jusqu'à VT = 1500 mm3

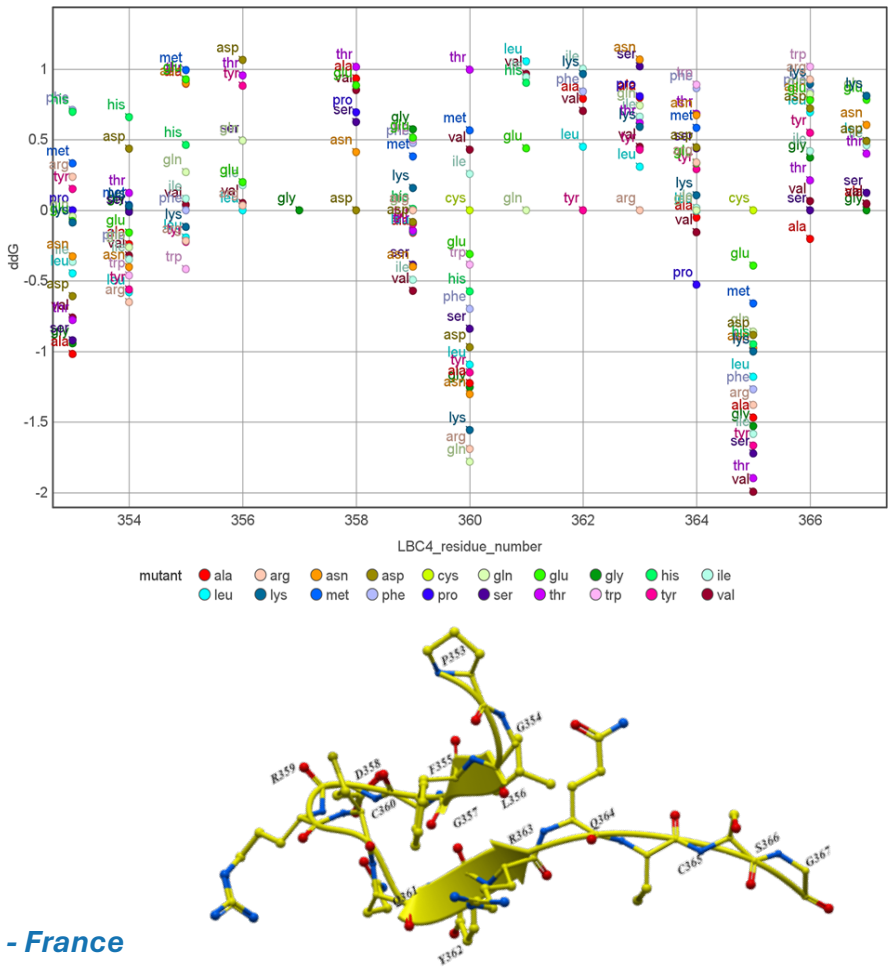
***Patent N°* EP23157848**

Optimisation du peptide LBC4

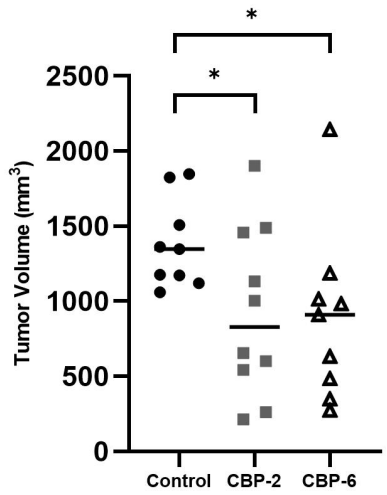
Perte d'affinité en milieu oxydant

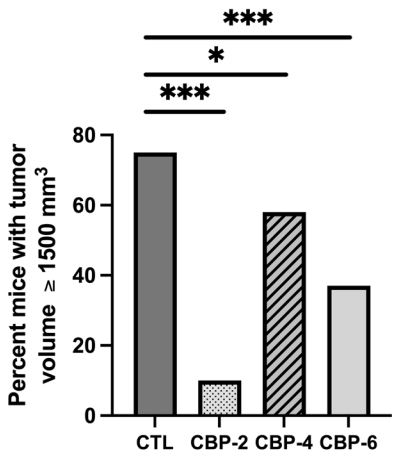


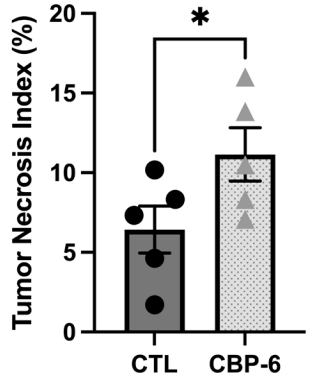
Optimisation du peptide LBC4 par mutagenèse in silico



Tests in vivo d'un nouveau lot de peptides optimisés dérivés de LBC4 (peptides CBP)







Patent N° EP24306284

Le programme « Emergence », un levier

Emergence - 2019
15 K€

Bourse ligue CCIR
Grand Est 2020
41 K€

Bourse ligue CCIR
Grand Est - 2019
45 K€

Programme Pré-Maturation SATT Nord
2022 - 70 K€

Dépôt Brevet 1
EP23157848
Février 2023

Programme Maturation SATT Nord
2023 - 549 K€

Partenariat Start-up
Apmonia Therapeutics

Signature d'un accord de **licence exclusive**

Dépôt Brevet 2
EP24306284
Aout 2024

Remerciements

UMR CNRS/URCA 7369 MEDyC, Reims

Dir. Pr. DUCA Laurent
Co-Dir. Dr BREZILLON Stéphane

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Dr AL KHALIFA Tesnim
Pr DEVY Jérôme
CHAZEE Lise (ITA)
HACHET Cathy (ITA)

Equipe 3 " Modélisation Moléculaire multi-Echelle »

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UMR CNRS 7104, IGBMC, Strasbourg

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