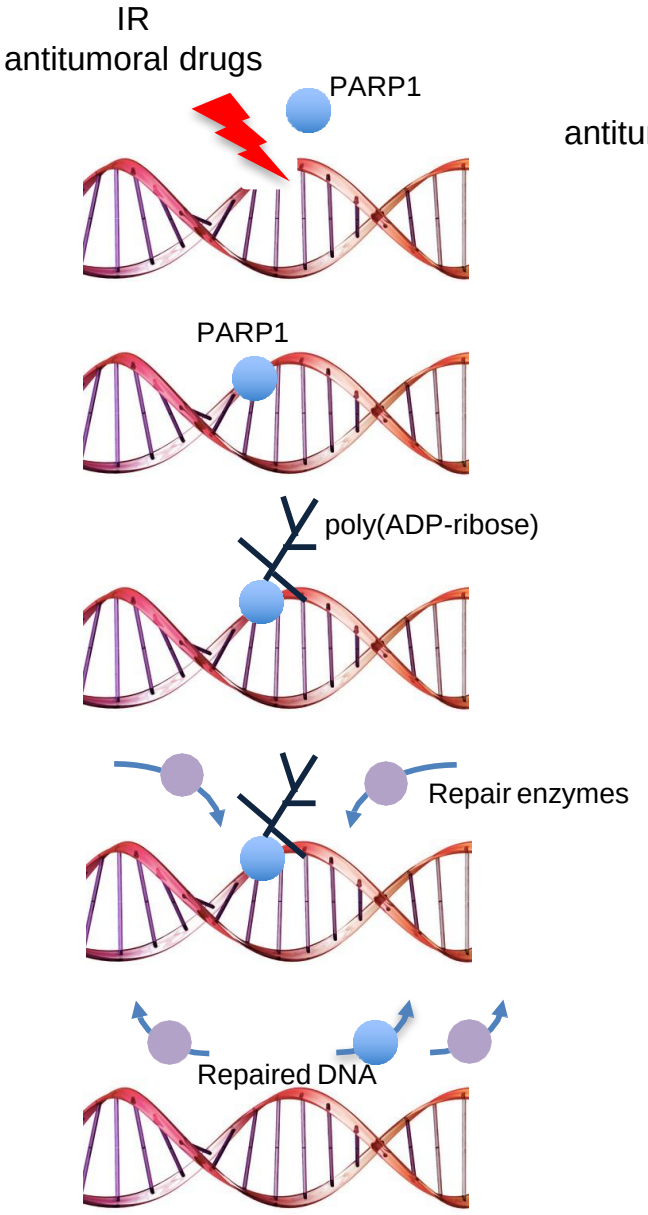
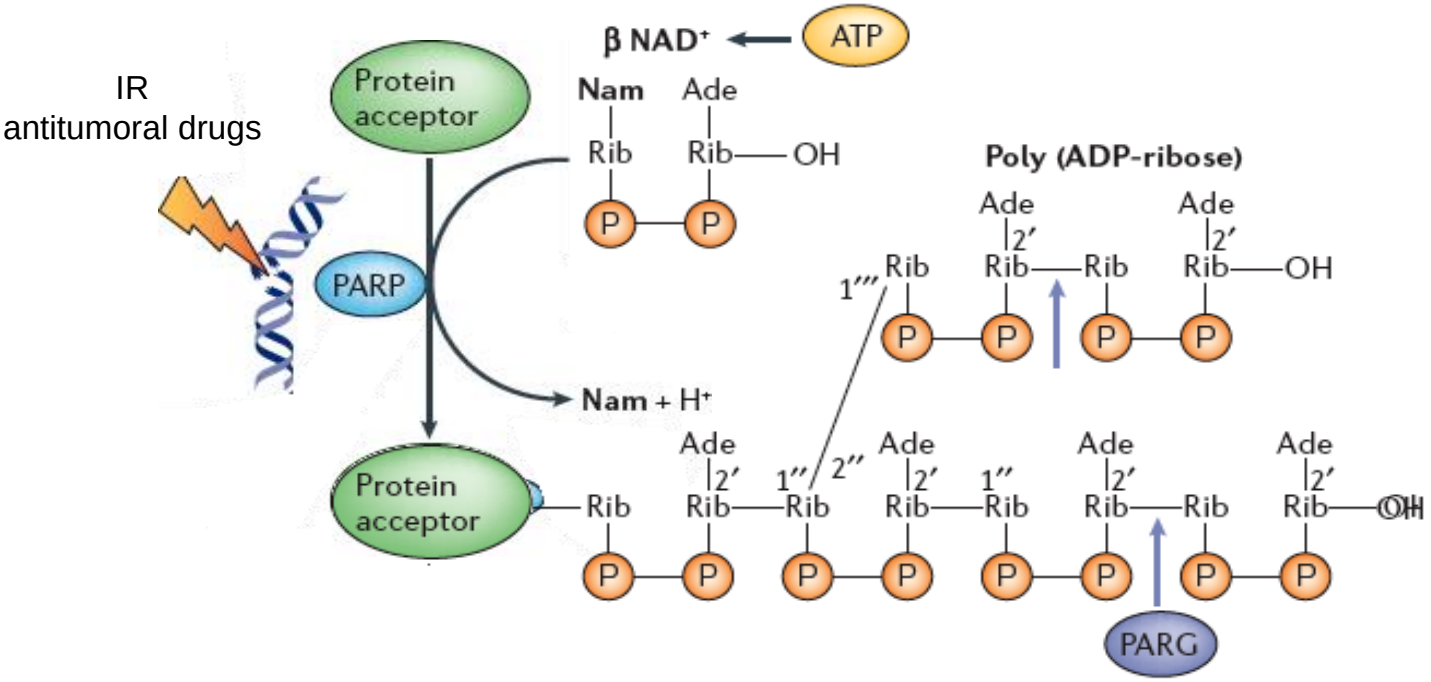
Les PARP ADN-dépendantes et leur inhibition catalytique dans la réparation de l'ADN et au delà.

Focus sur PARP1 et PARP3

F. Dantzer
Poly(ADP-ribosyl)ation and Genome Integrity Team
UMR7242-Biotechnology and Cell signaling
IREBS, Illkirch, France

L’inhibition de PARP1 en thérapie du cancer: cibler son activité de réparation





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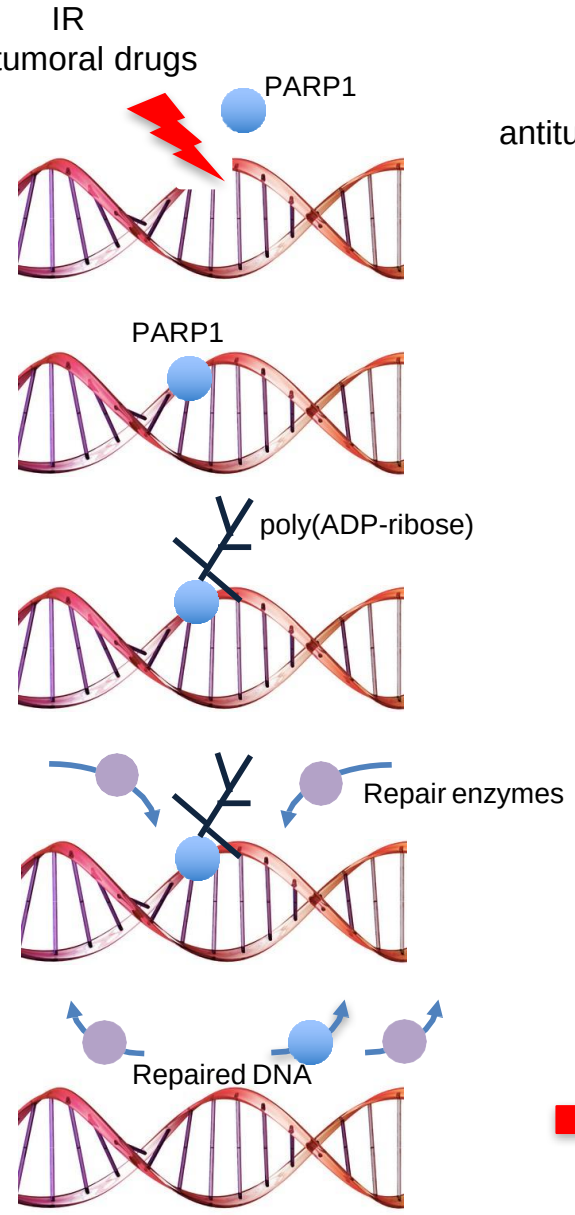
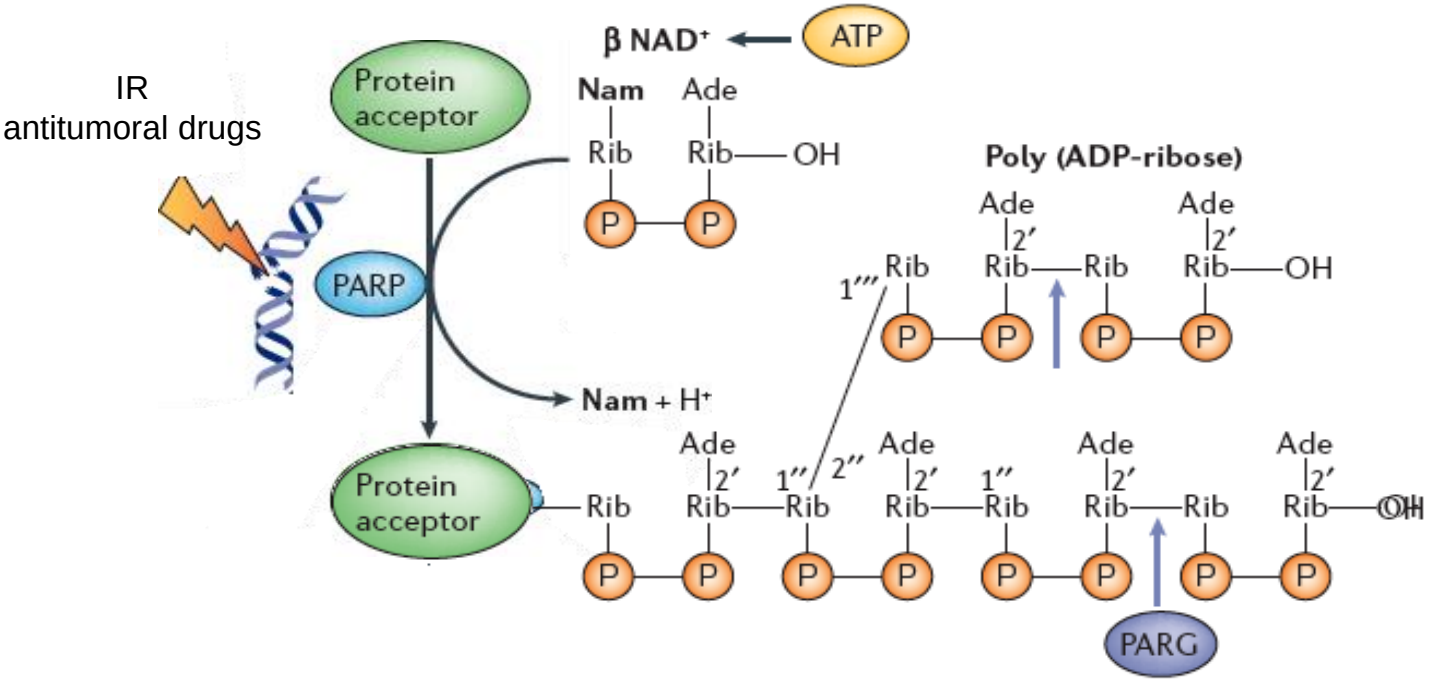
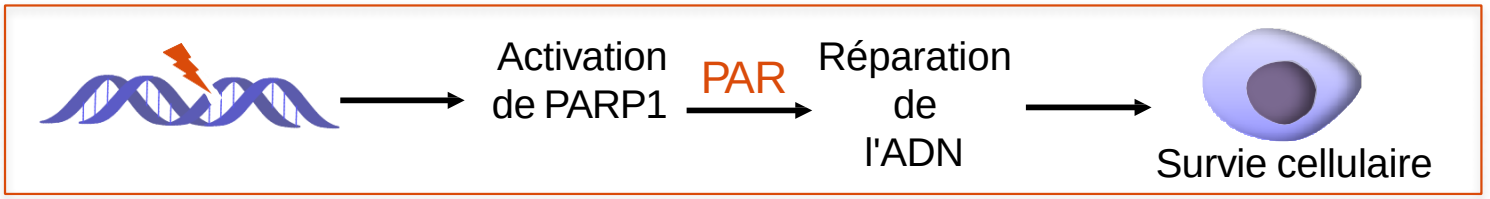


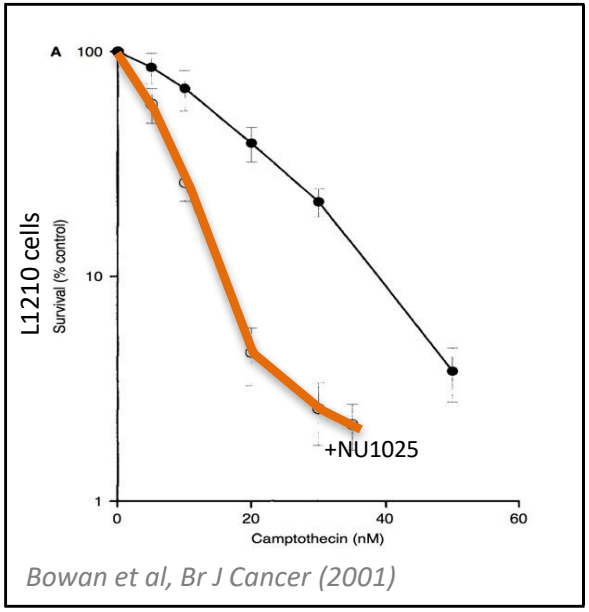


Réparation

L'absence ou l'inhibition de PARP1 sensibilise les cellules ou les souris aux agents génotoxiques



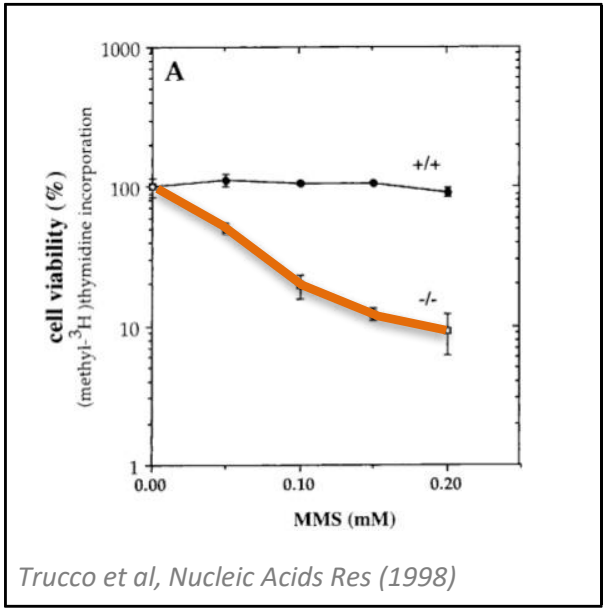
Inhibiteur de topoisomérase (CPT)



Bowan et al, Br J Cancer (2001)

Inhibiteur PARP (NU1025)

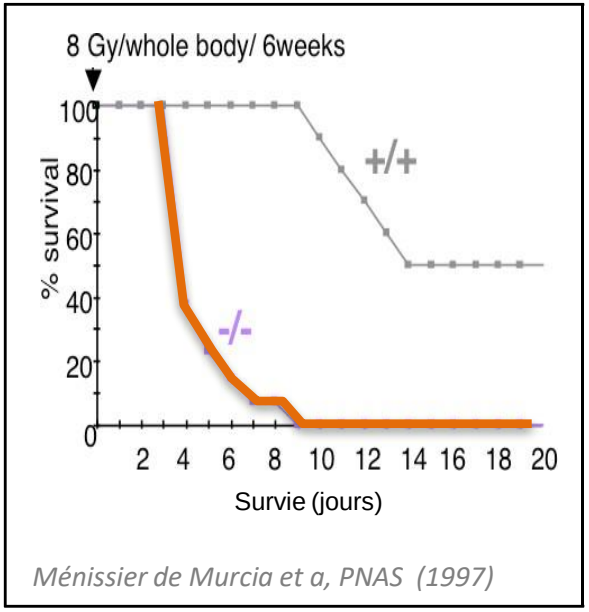
Agent alkylant (MNNG)



Trucco et al, Nucleic Acids Res (1998)

Cellules PARP-1$^{-/-}$

Radiations ionisantes (rayons X)



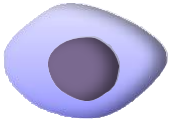
Ménissier de Murcia et a, PNAS (1997)

Souris PARP-1$^{-/-}$

Inhibition de PARP dans des stratégies anticancéreuses

1. Pour potentialiser les chimio- ou radiothérapies

Agent génotoxique antitumoral:
TMZ, CPT, IR…

Activation de PARP1 → Réparation de l'ADN →  Survie cellulaire

Dommages à l'ADN
- Cassures simple brin
- Cassures double brin
- Bases endommagées

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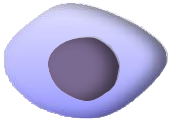
Activation de PARP1

PAR

Réparation de l'ADN



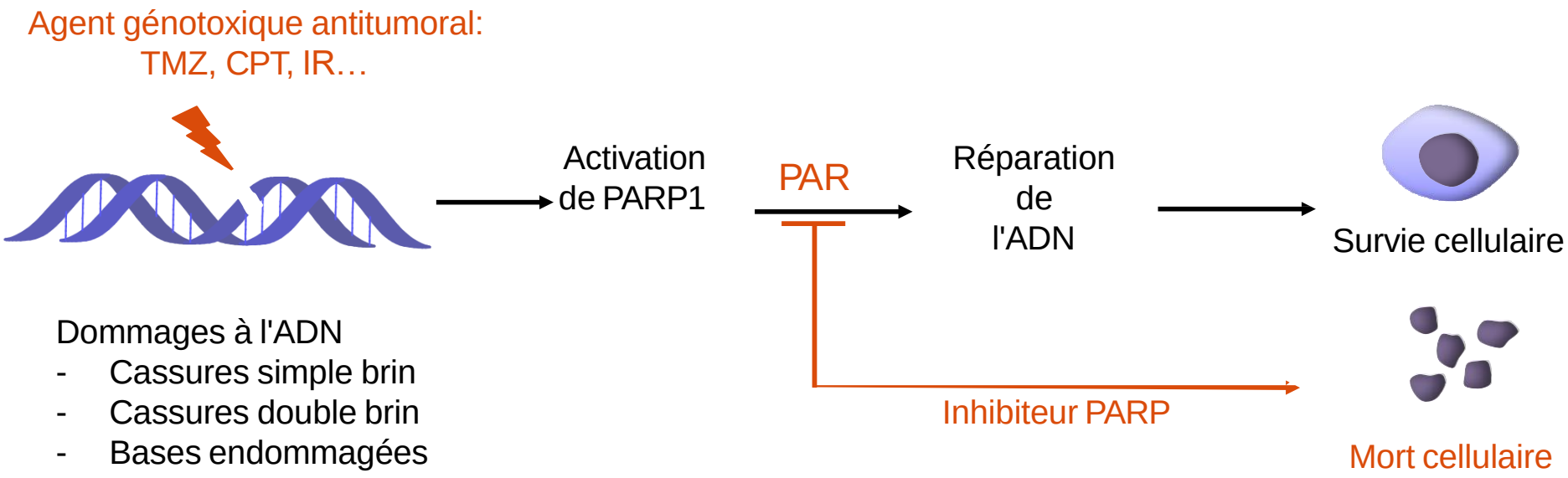
Survie cellulaire

Inhibiteur PARP

Mort cellulaire

Inhibition de PARP dans des stratégies anticancéreuses

1. Pour potentialiser les chimio- ou radiothérapies

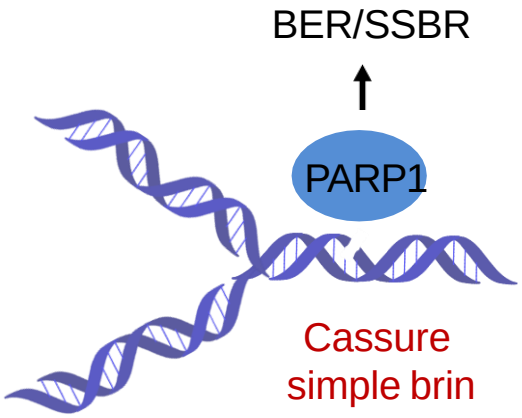


2003: Premier essai clinique Phase I (TMZ+ PARPi/mélanomes)
Agouron Pfizer, La Jolla, CA; Curtin N., Newcastle, UK

Essais cliniques phase I à III en cours:
Mélanome, glioblastome, sein, ovaire, prostate, poumon, leucémie…

Inhibition de PARP dans des stratégies anticancéreuses

2. Pour cibler des tumeurs déficientes en réparation des cassures double brin par recombinaison homologue (ex: BRCA1, BRCA2):



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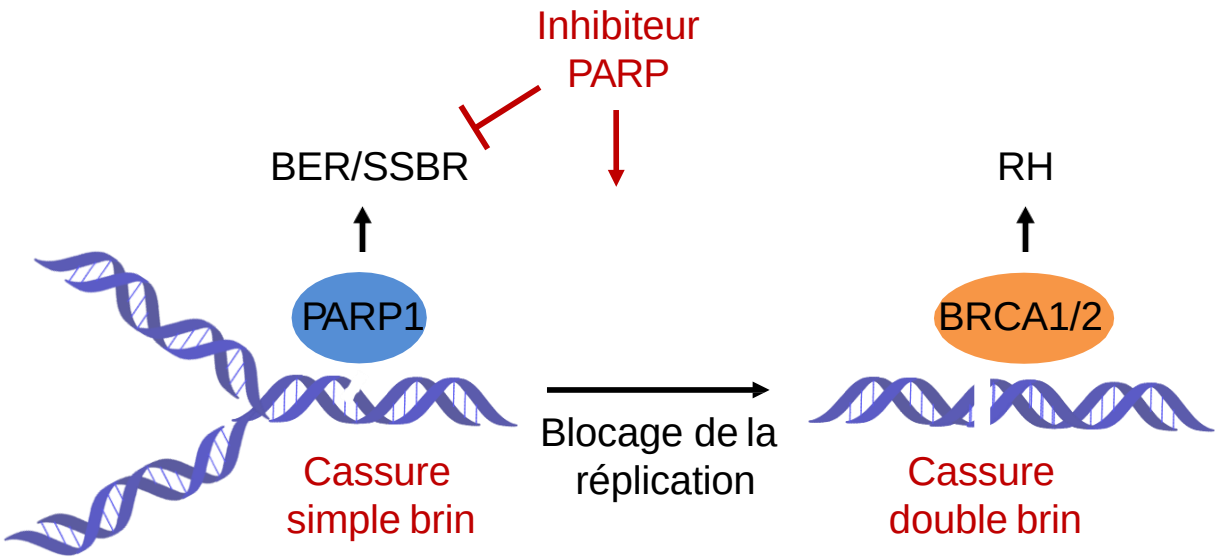

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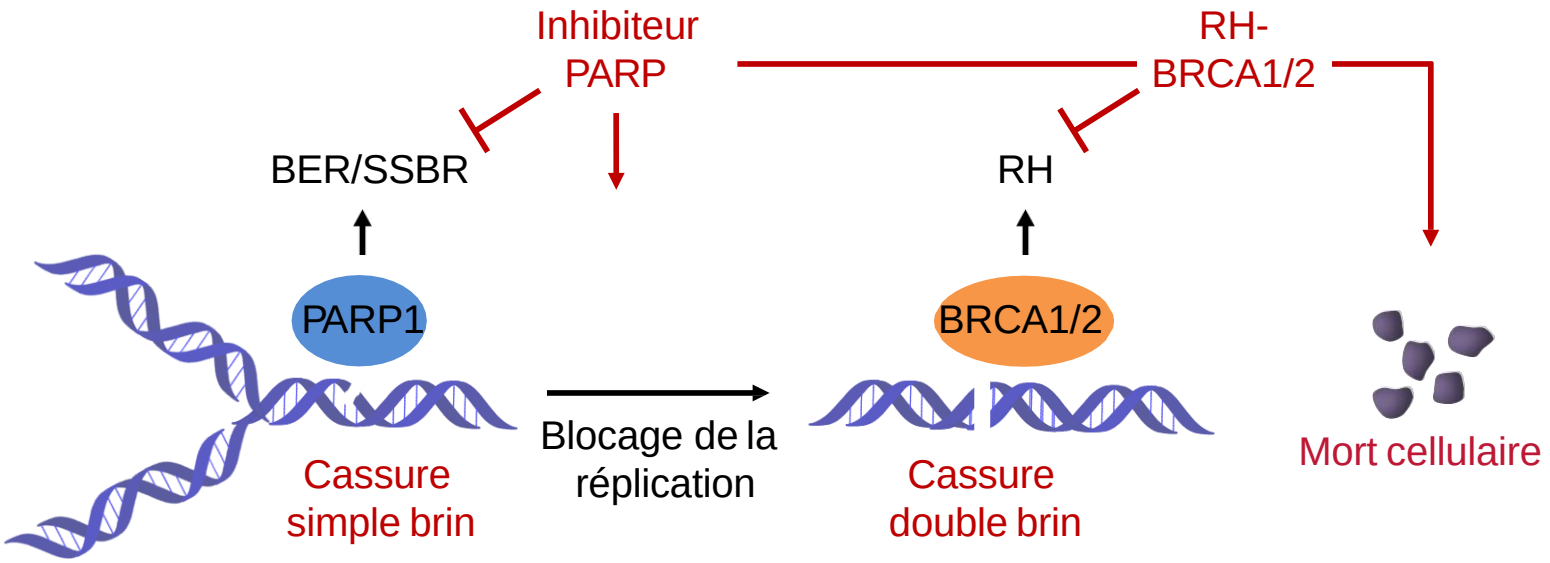
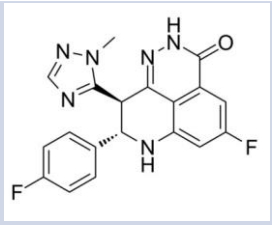
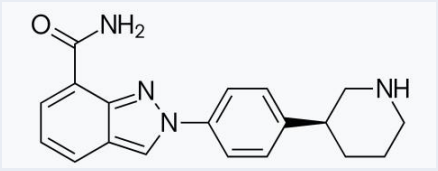
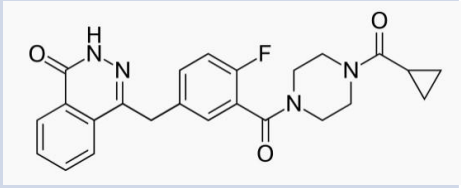
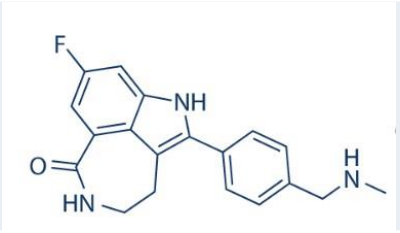
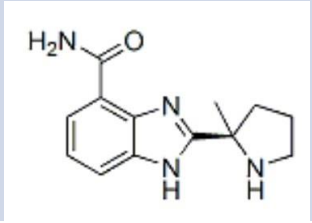


= létalité synthétique

Les inhibiteurs PARP en essais cliniques

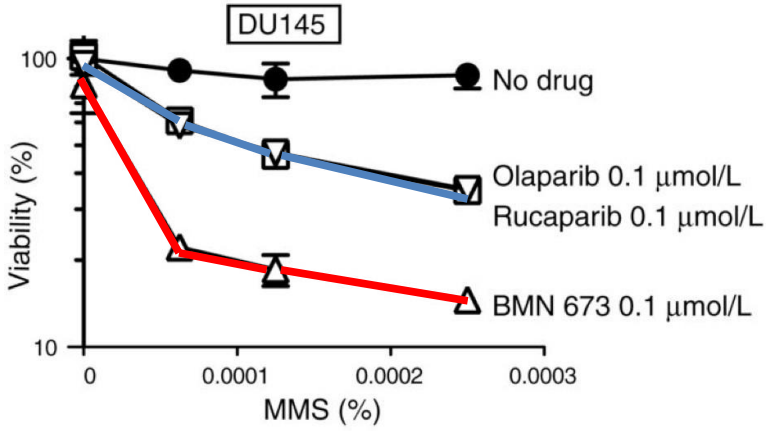
Inhibiteur	Structure	IC50	Compagnie
Talazoparib BMN-673		0,57 nM	BioMarin, Pfizer
Niraparib MK-4827		3,8 nM	Tesaro
Olaparib AZD-2281 Lynparza		**5 nM**	**AstraZeneca AMM 2014**
Rucaparib AG-014699		2 nM	ClovisOncology AMM
Veliparib ABT-888		4,7 nM	Abb Vie

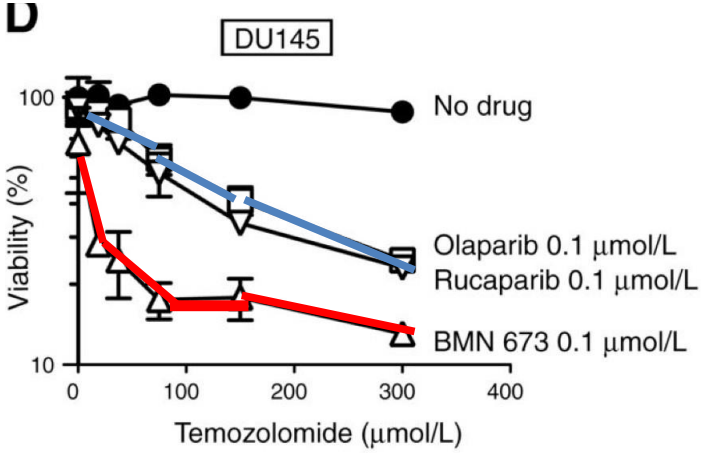
Classification des inhibiteurs PARP en fonction de leur capacité à piéger PARP1 sur l'ADN

Trapping

Talazoparib >> Niraparib >> **Olaparib**=Rucaparib >> Veliparib
BMN-673 MK-4827 **Lynparza** AG-014699 ABT-888
AZD-2281

> dans les modèles pré-cliniques !



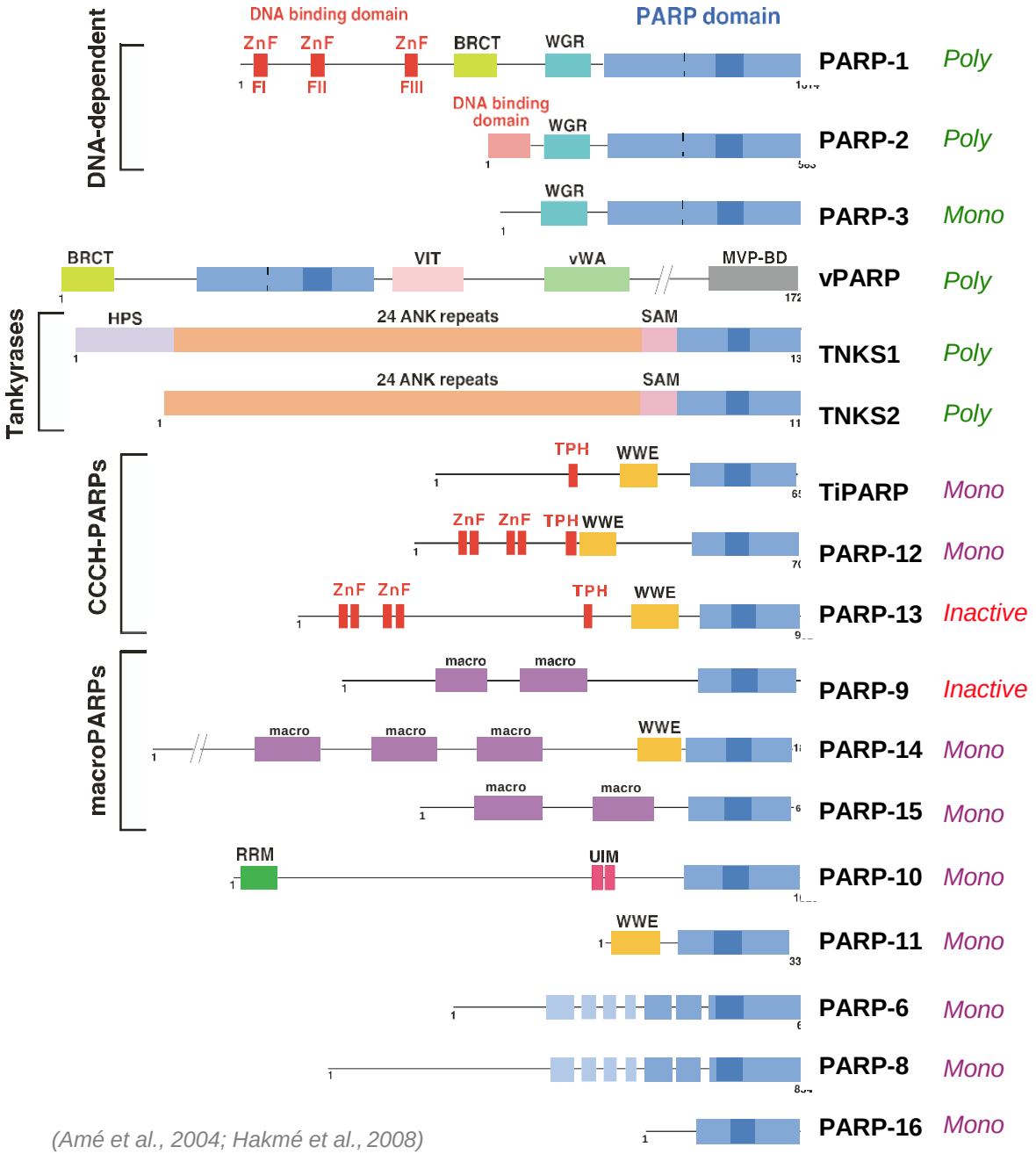


DU145: prostate cancer

Pommier et al. Science Tans. Med. 2016
Murai et al. mol. Cancer Ther. 2014

La famille PARP

17 membres, un domaine catalytique conservé

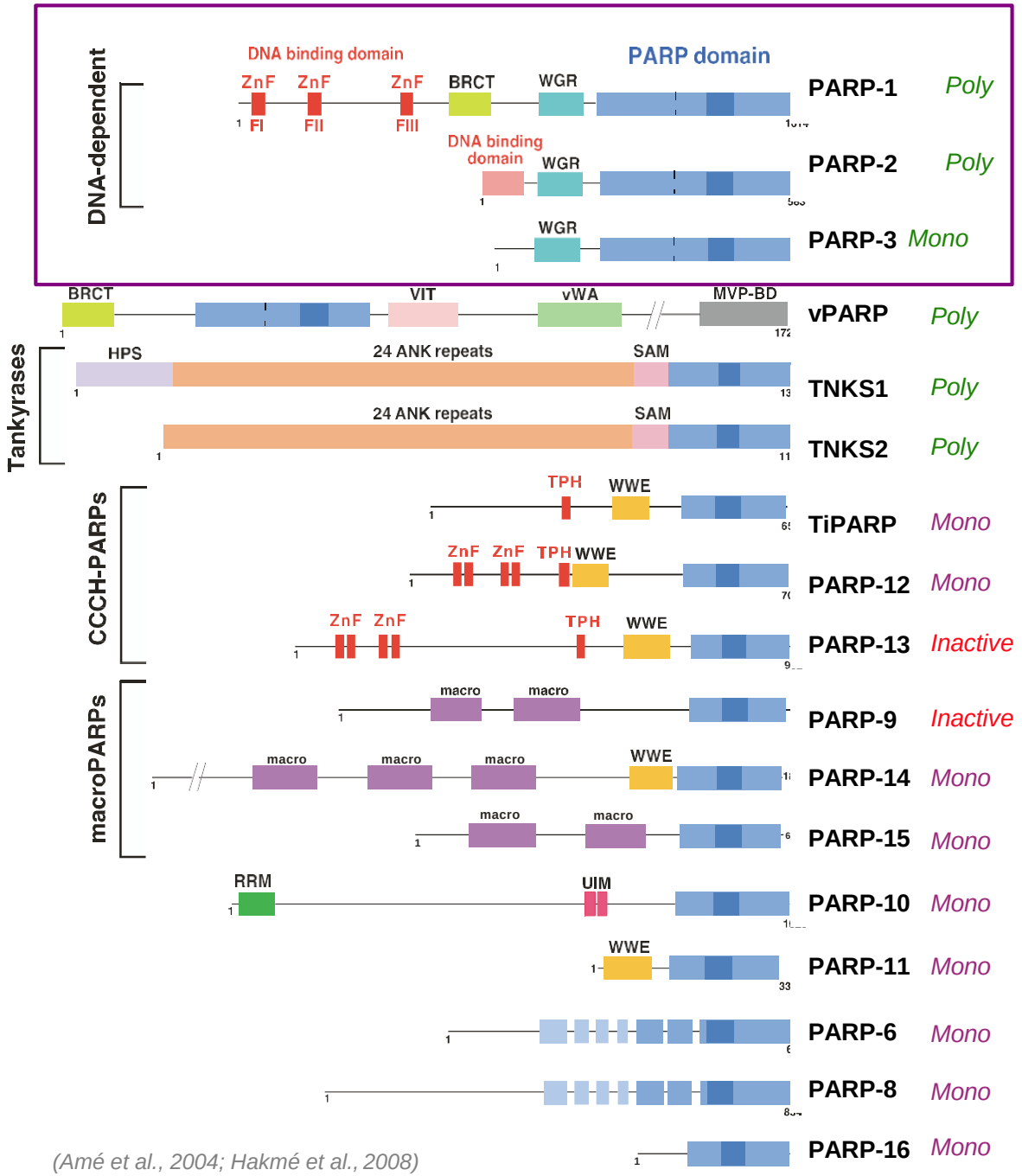


(Amé et al., 2004; Hakmé et al., 2008)

La famille PARP

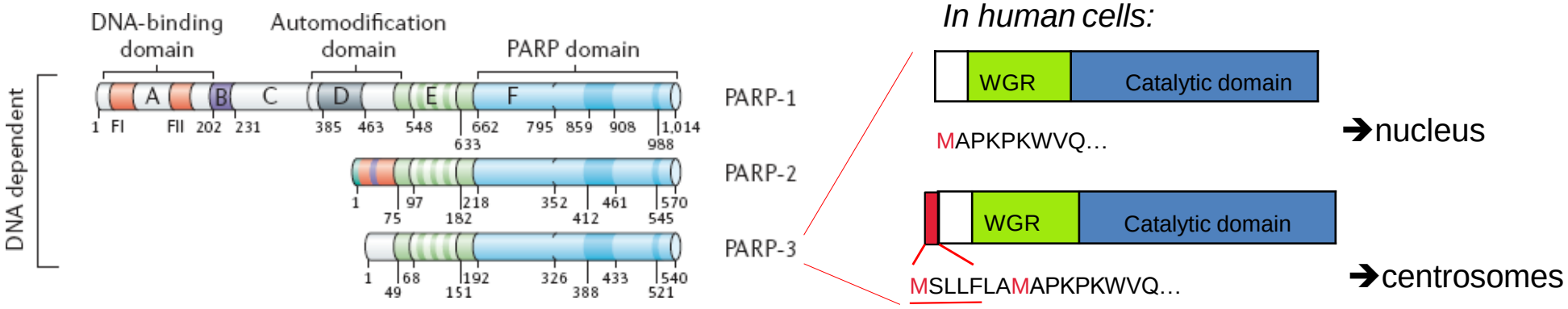
PARP1, PARP2, PARP3
Activées par les cassures dans l'ADN

17 membres, un domaine catalytique conservé

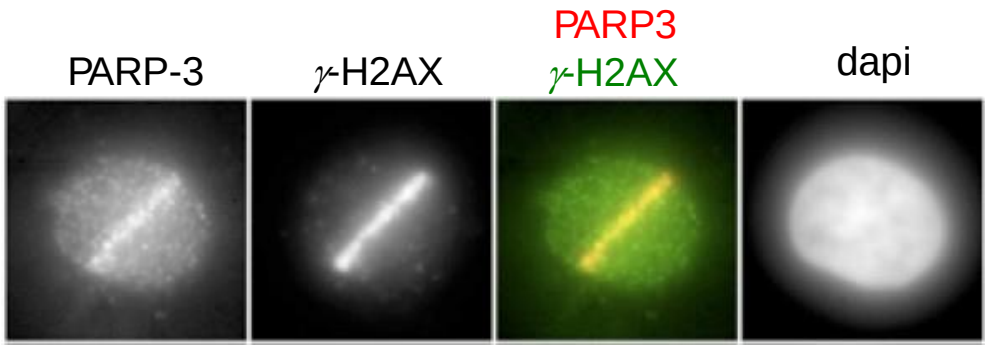


(Amé et al., 2004; Hakmé et al., 2008)

PARP3: réparation, et …différentiation



PARP3 favorise la réparation des cassures double-brins



Boehler et al. PNAS 2011

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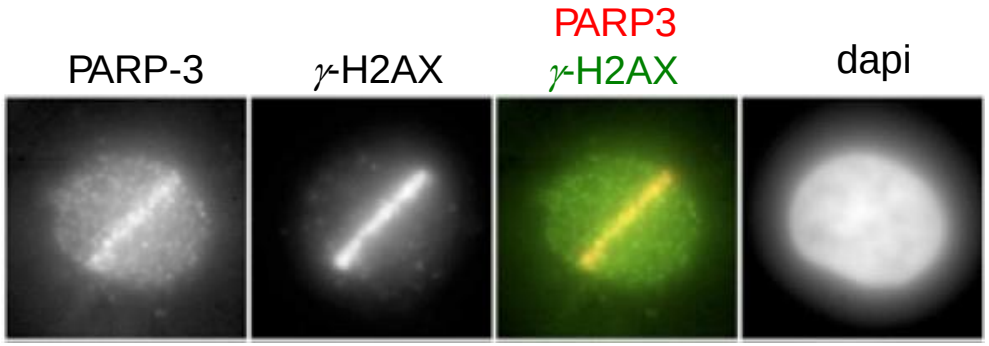
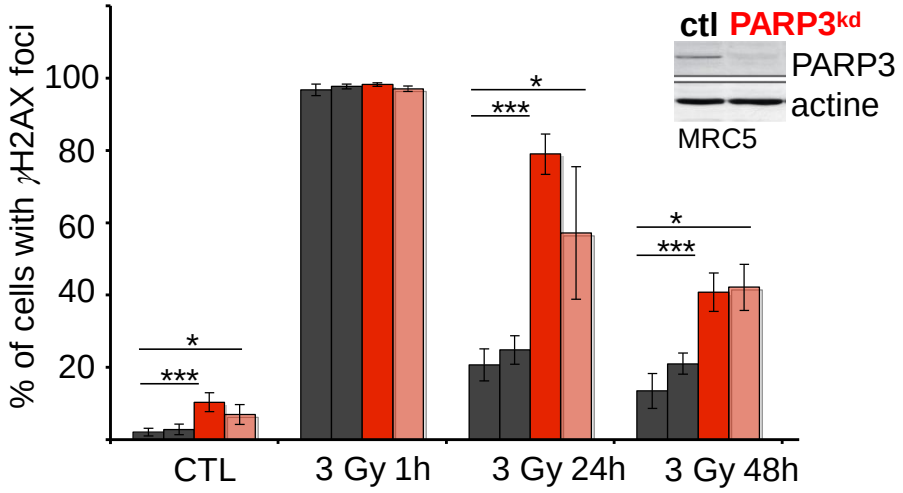


Boehler et al. PNAS 2011

Persistance de foyers γH2AX radio-induits (X-rays)



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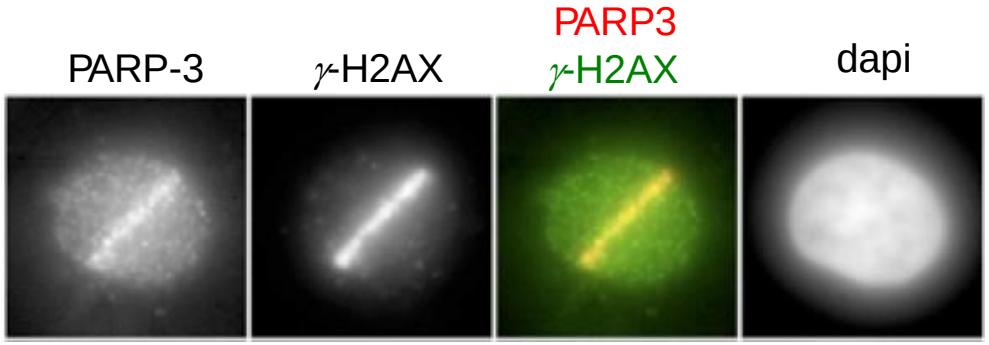

Boehler et al. PNAS 2011

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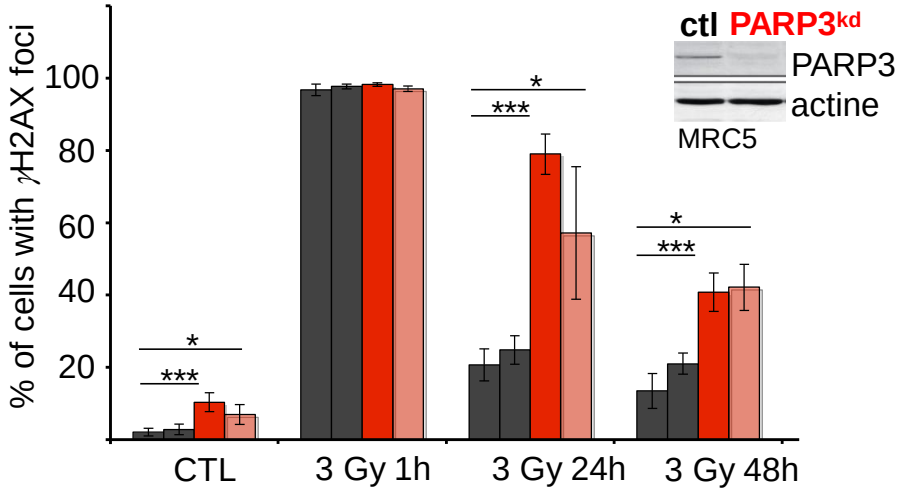
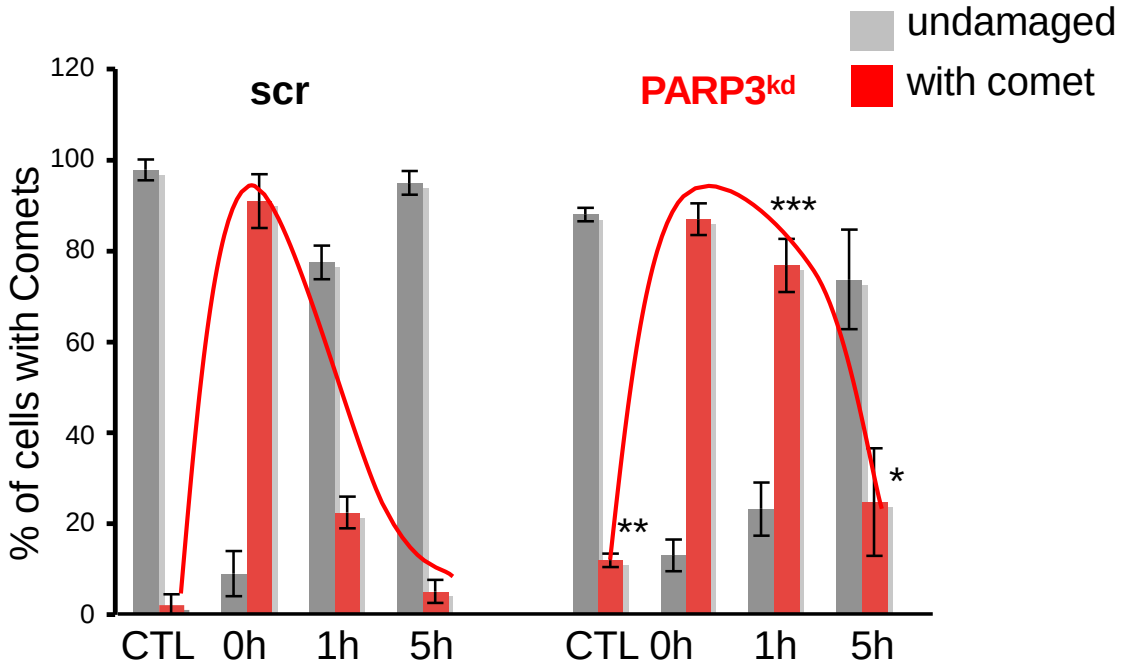


Délai dans la réparation des DSB (X-rays)



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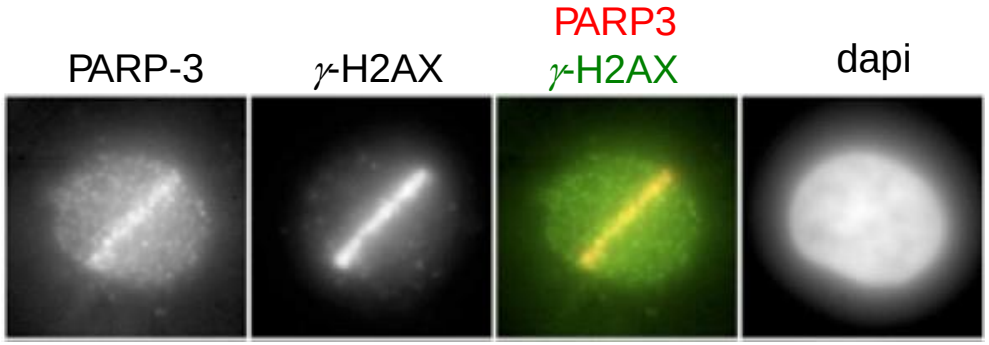

Boehler et al. PNAS 2011

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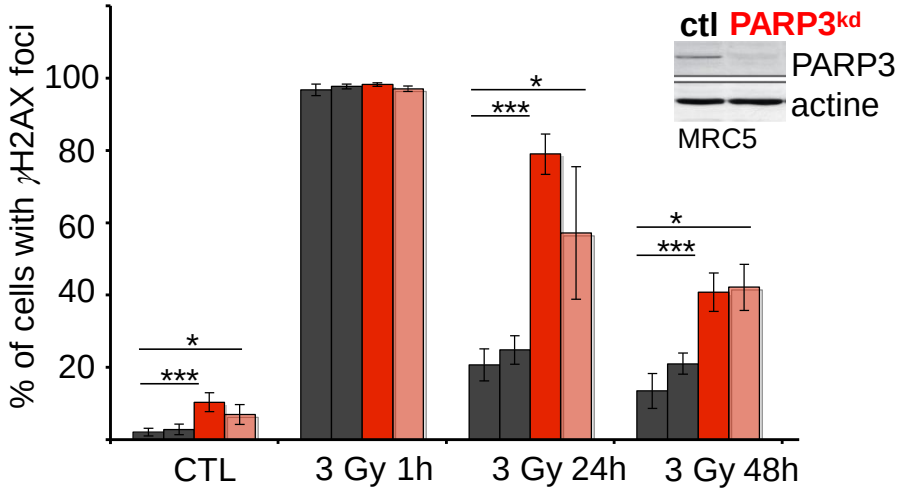

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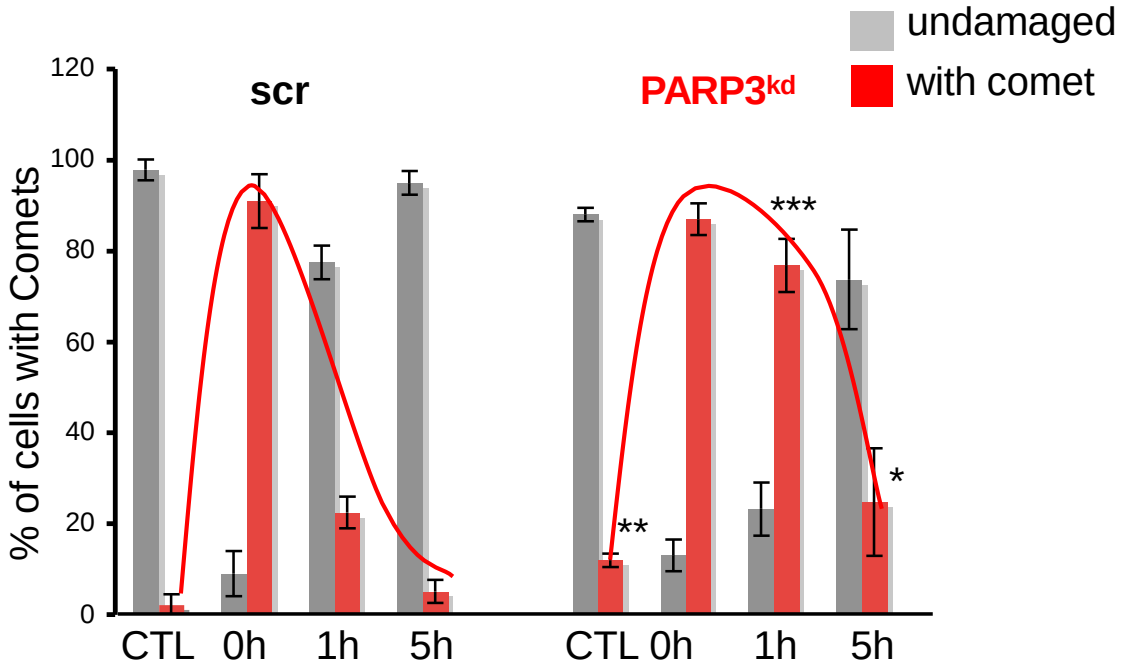
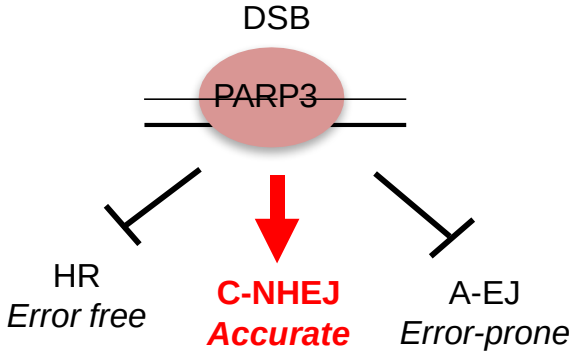




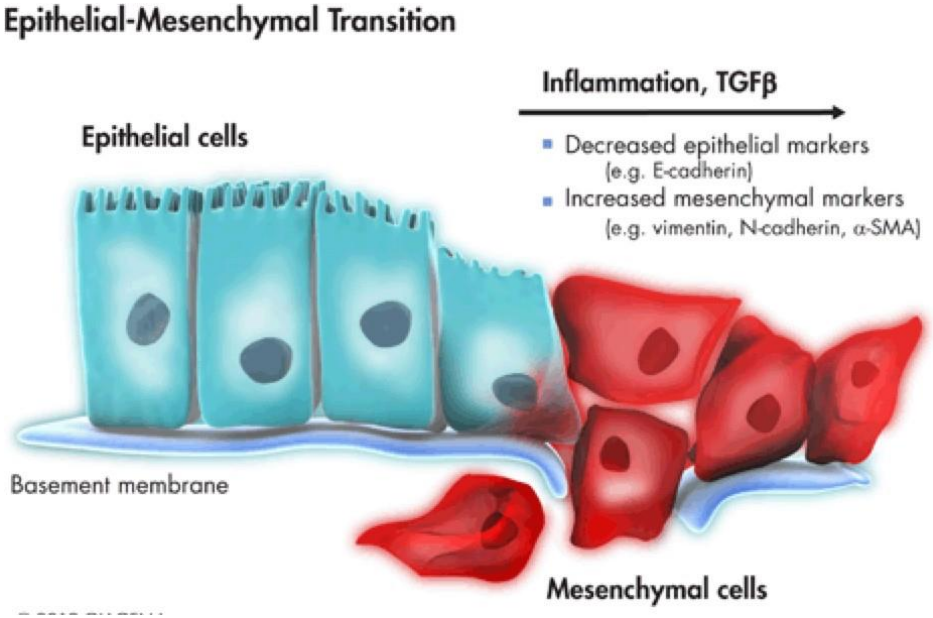
Beck et al. NAR 2014

PARP3, d’une protéine de réparation des DSB…

vers un rôle dans des évênements de différenciation cellulaire

PARP3 favorise l'EMT induite par TGFβ dans le cancer du sein

TGFβ > ROS ➡ EMT



Karicheva et al. Oncotarget 2016

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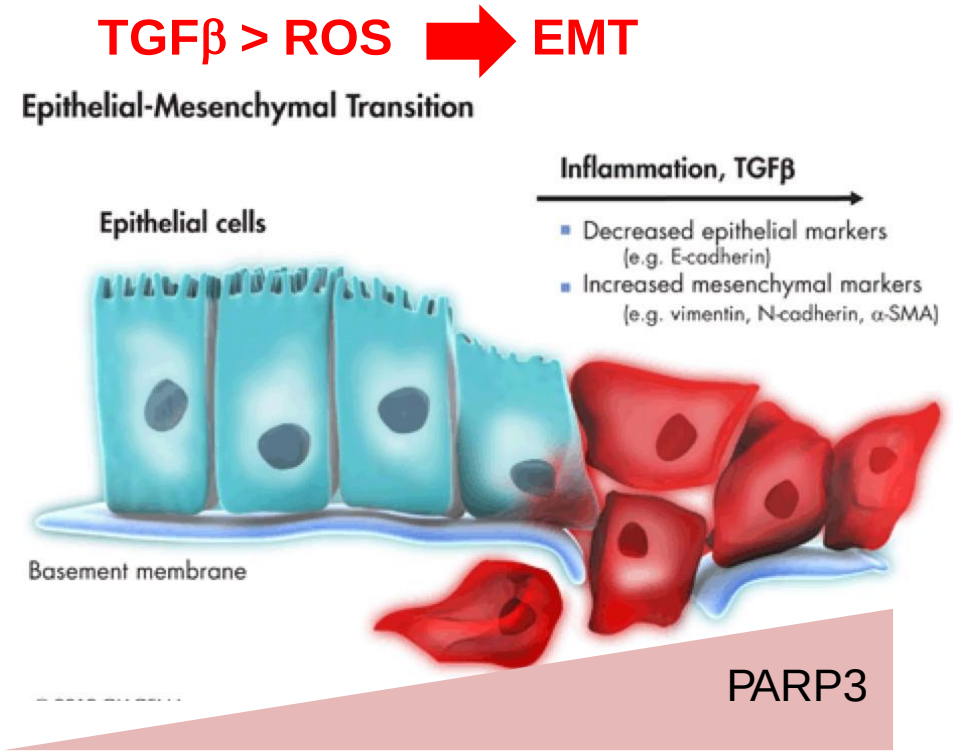

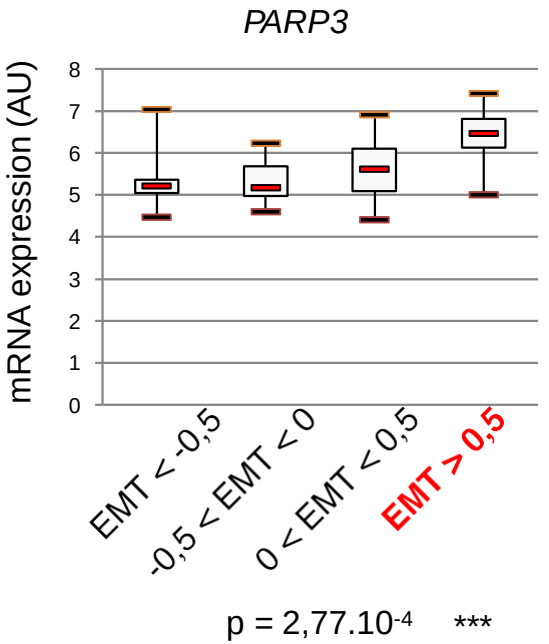

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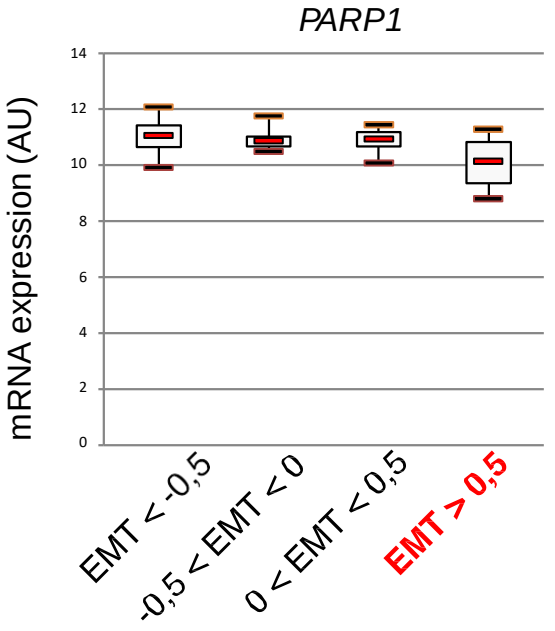
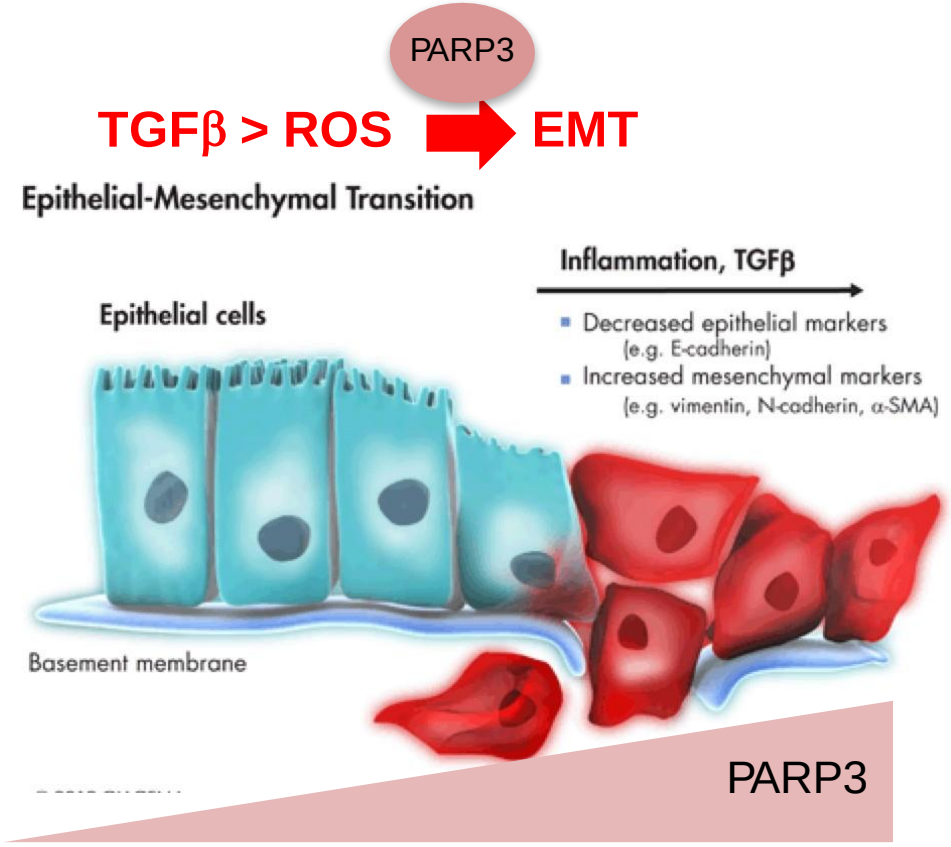


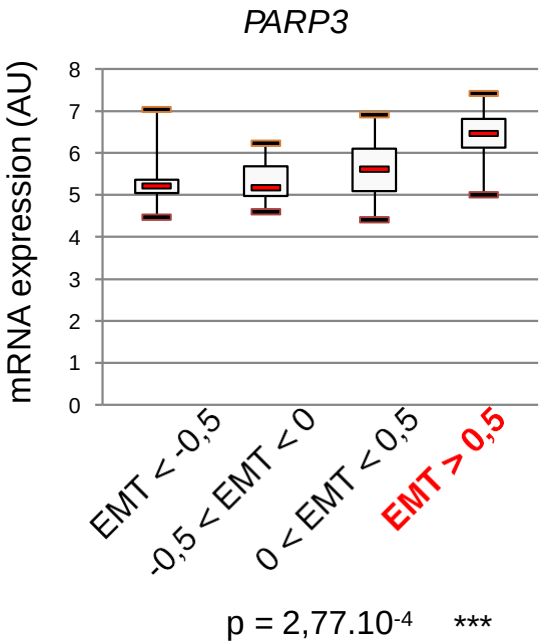
CCLE Encyclopedia

Karicheva et al. Oncotarget 2016

PARP3 favorise l'EMT induite par TGFβ dans le cancer du sein



Migration
Chimioresistance
Cellules souches



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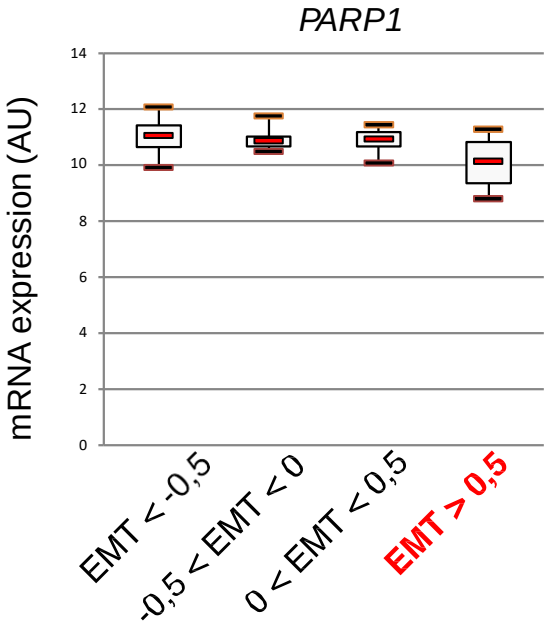

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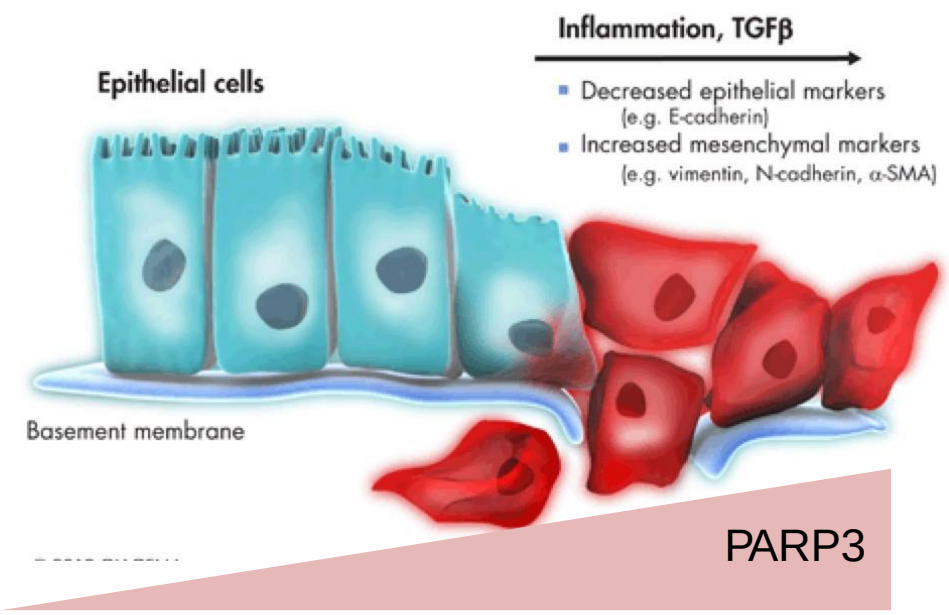
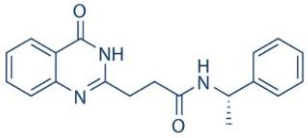
Karicheva et al. Oncotarget 2016

PARP3 favorise l'EMT induite par TGFβ dans le cancer du sein

PARP3

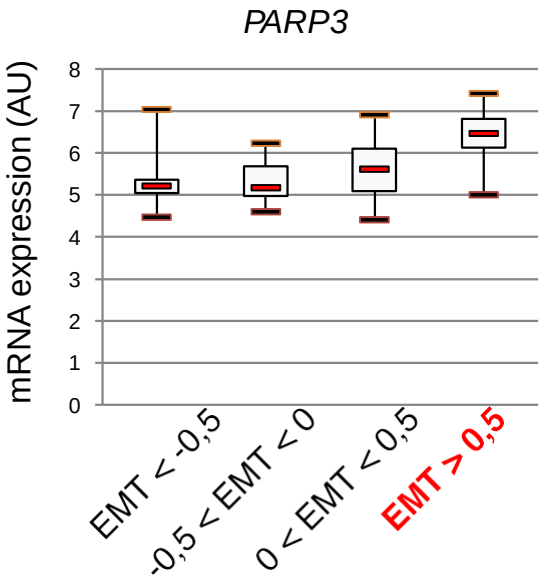
TGFβ > ROS ➡ **EMT**





PARP3i

Migration
Chimioresistance
Cellules souches



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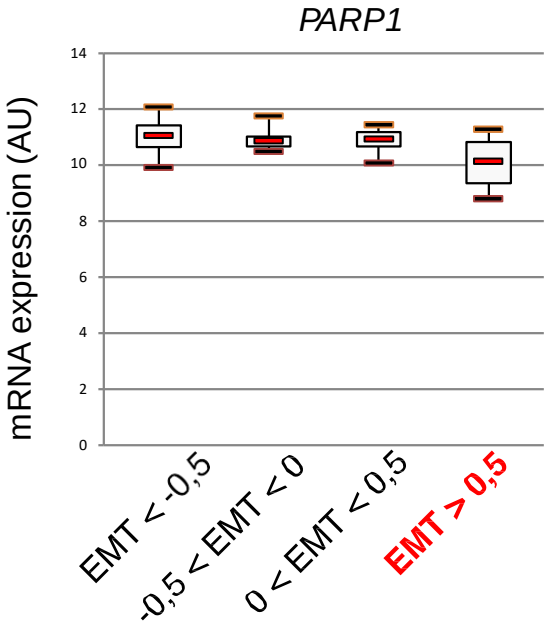
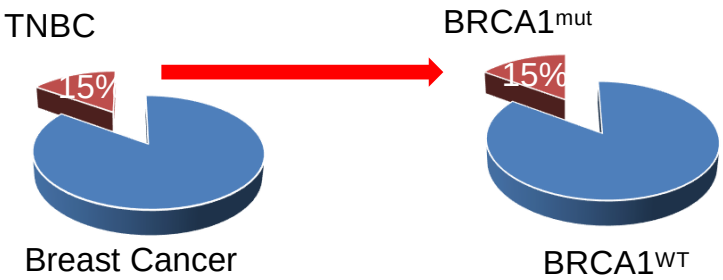


CCLE Encyclopedia

Karicheva et al. Oncotarget 2016

PARP3 active la voie oncogénique mTORC2 dans les cancers du sein BRCA1^{mut}



Beck et al. Cell Death Diff. 2019

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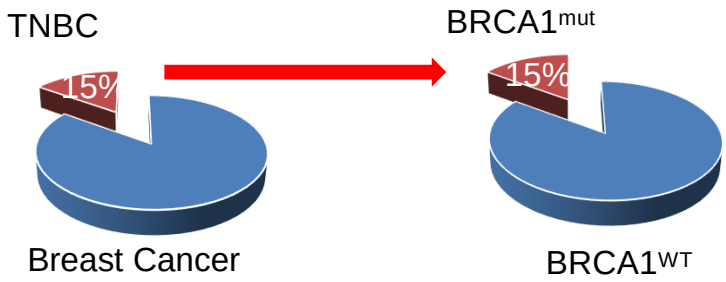

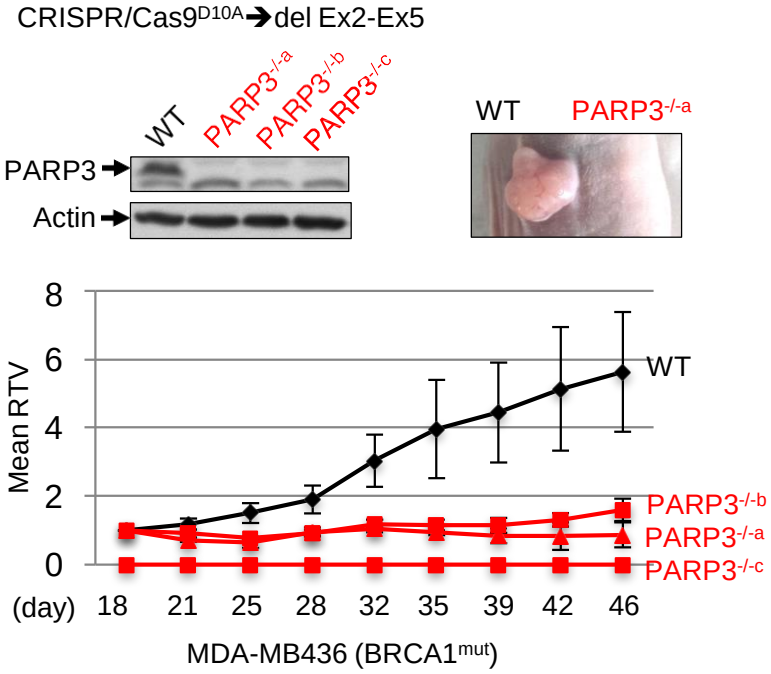

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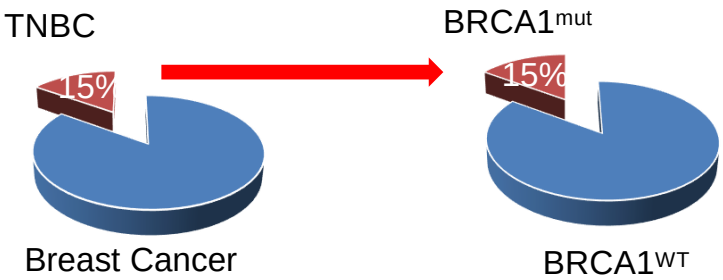
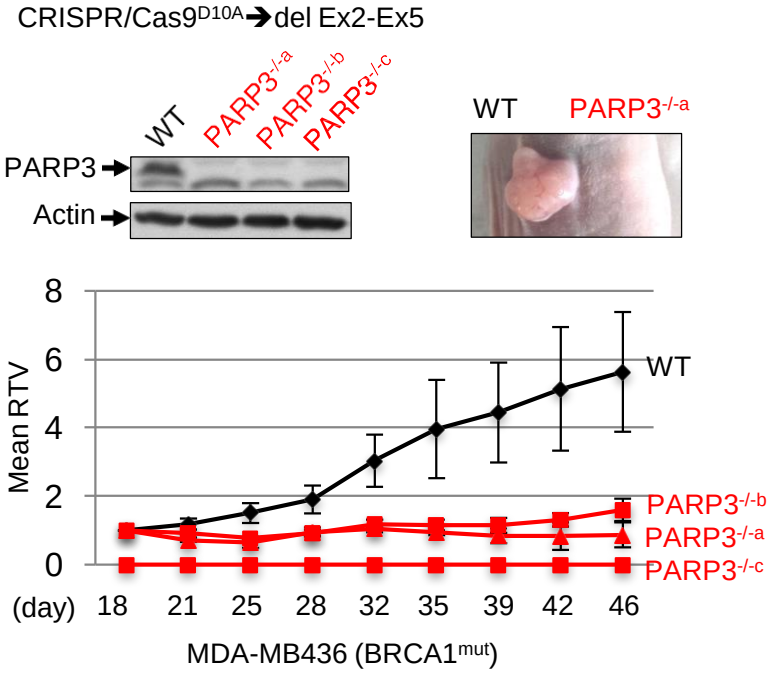
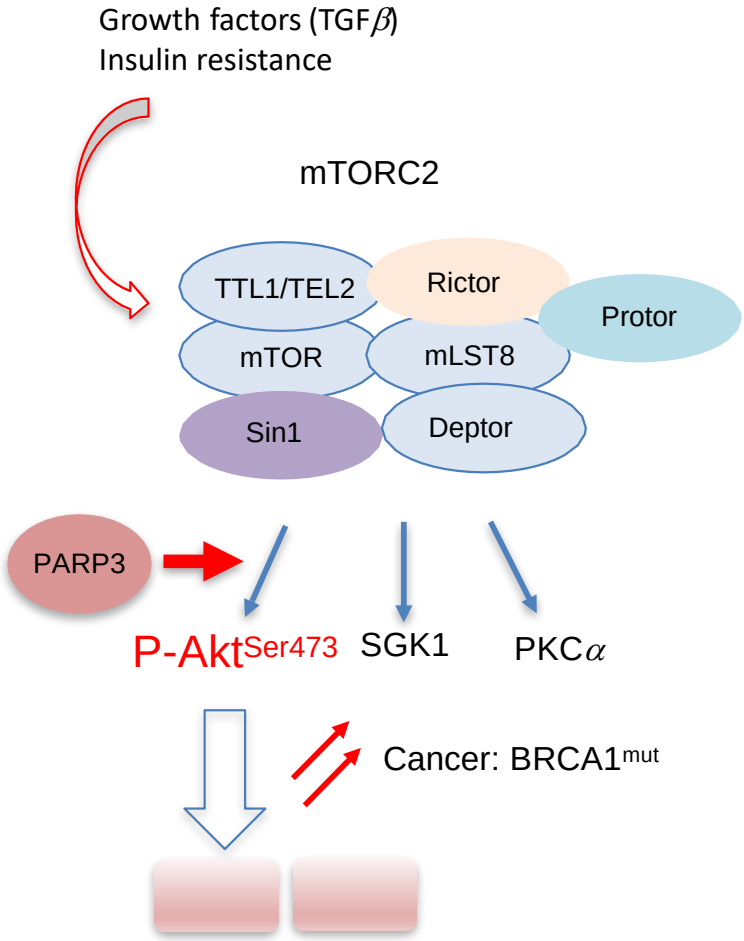
PARP3 active la voie oncogénique mTORC2 dans les cancers du sein BRCA1^{mut}

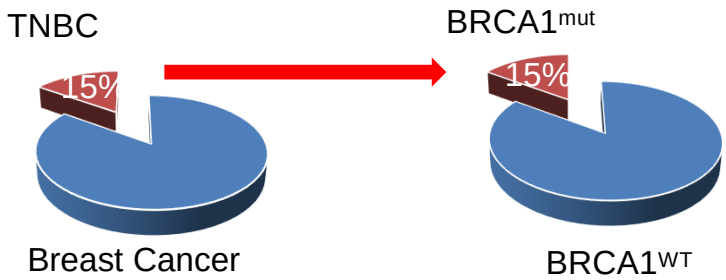


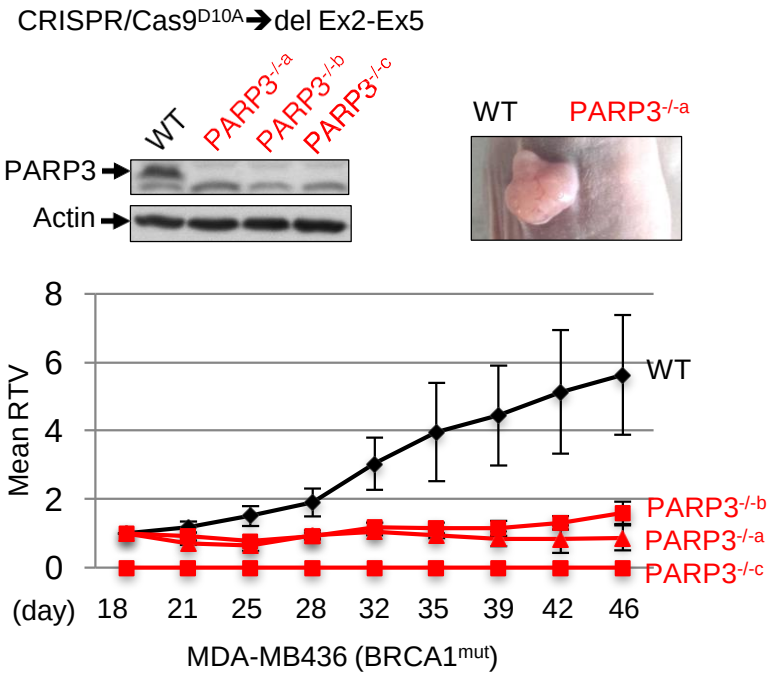


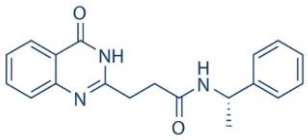


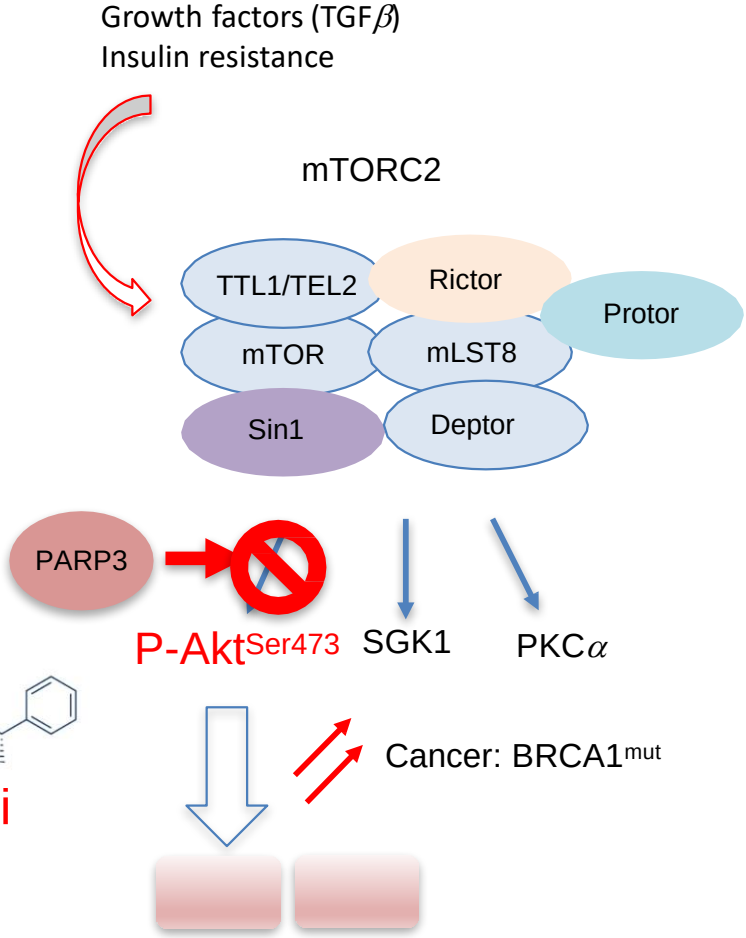
Beck et al. Cell Death Diff. 2019

PARP3 active la voie oncogénique mTORC2 dans les cancers du sein BRCA1^{mut}





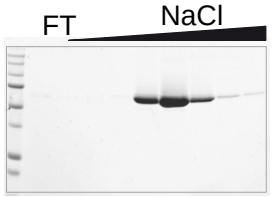




Beck et al. Cell Death Diff. 2019

Methodologies and expertise

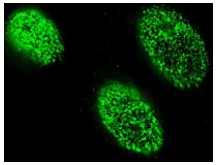
PARP purification

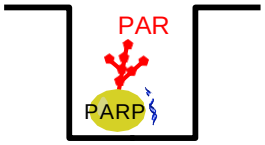


Human PARP3
(SF9, 5 mg)

PARP activity

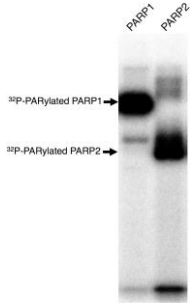
anti-PAR





Elisa

PARP antibodies



PARP-knockout models

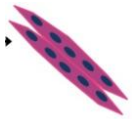
Parp1KO
Parp2KO
Parp3KO
Parp9KO
Parp1KO;Parp2Flox
Parp3Flox
Parp9Flox

Phenotyping

Mouse Embryonic Fibroblasts

Myogenesis

Muscle Satellite Stem Cells



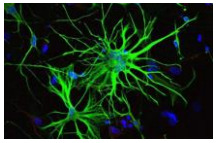
Myotubes

Neurogenesis

Neural Progenitor Stem Cells

Neurons

Astrocytes



AFMTELETHON
INNOVER POUR GUERIR

USIAS

DNA repair, Tumorigenesis

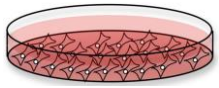
medalis

Association pour la Recherche sur le Cancer

LA LIGUE CONTRE LE CANCER

Cell biology

siRNA
Crispr/nCas9^{D10A}



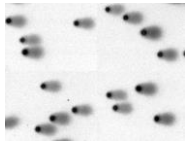
Survival assays

Genome instability, DNA repair

Kinetics of γH2AX, 53BP1, Rad51

Recruitment to laser-induced DNA damage sites

Comet assays
HR, NHEJ assays



Xenogreffes

Zuleyha Yildirim (PhD)
Lisa Roegel (PhD)

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