

Journée universitaire (JU) du département de radiologie, radio-oncologie et médecine nucléaire
4 février 2021

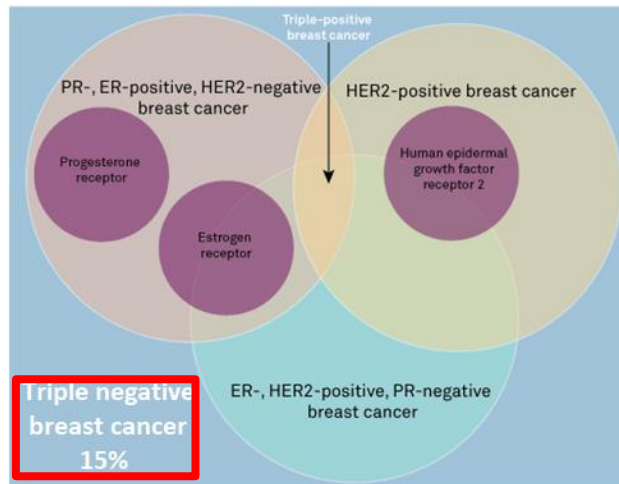
Synthetic lethality induce by the combinaison of parpi and senolyics in triple negative breast cancer

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- *Institut du Cancer de Montréal, Centre de recherche du CHUM (CRCHUM)*

Séminaire virtuel 2021

INTRODUCTION

BREAST CANCER SUBTYPES



Four main modalities for treating TNBC



Triple Negative Breast Cancer

Ovarian Cancer Genetics: Subtypes and Risk Factors | IntechOpen ; Hirst et al. *Ovarian Cancer - From Pathogenesis to Treatment* (2018)

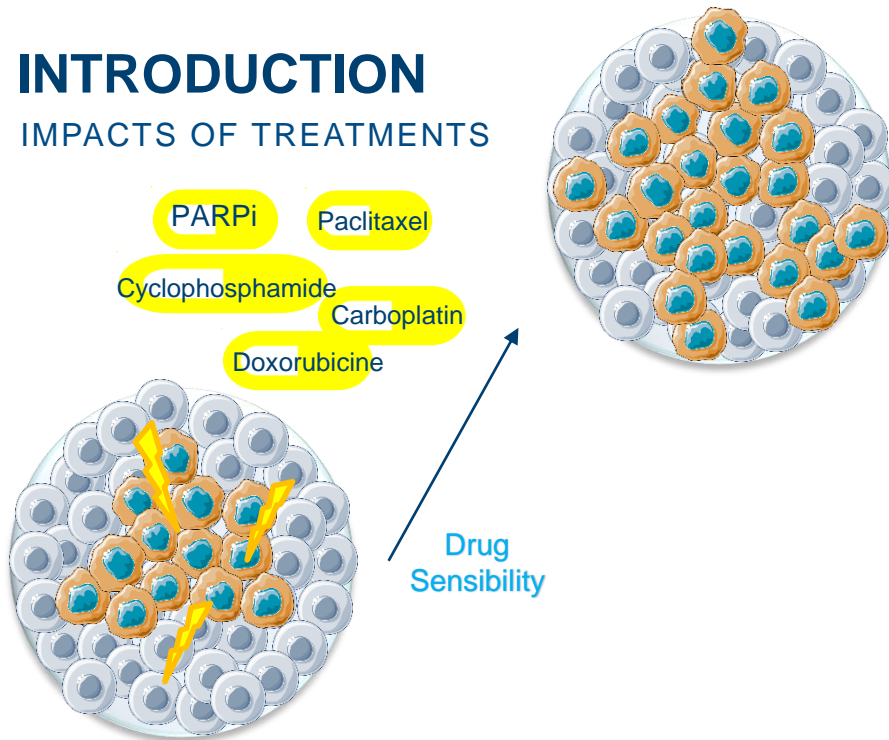
Divulgations (N/A)

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et médecine nucléaire
Faculté de médecine

Université de Montréal

INTRODUCTION

IMPACTS OF TREATMENTS



INNATE RESISTANCE

Cancer cells

Senescence cells

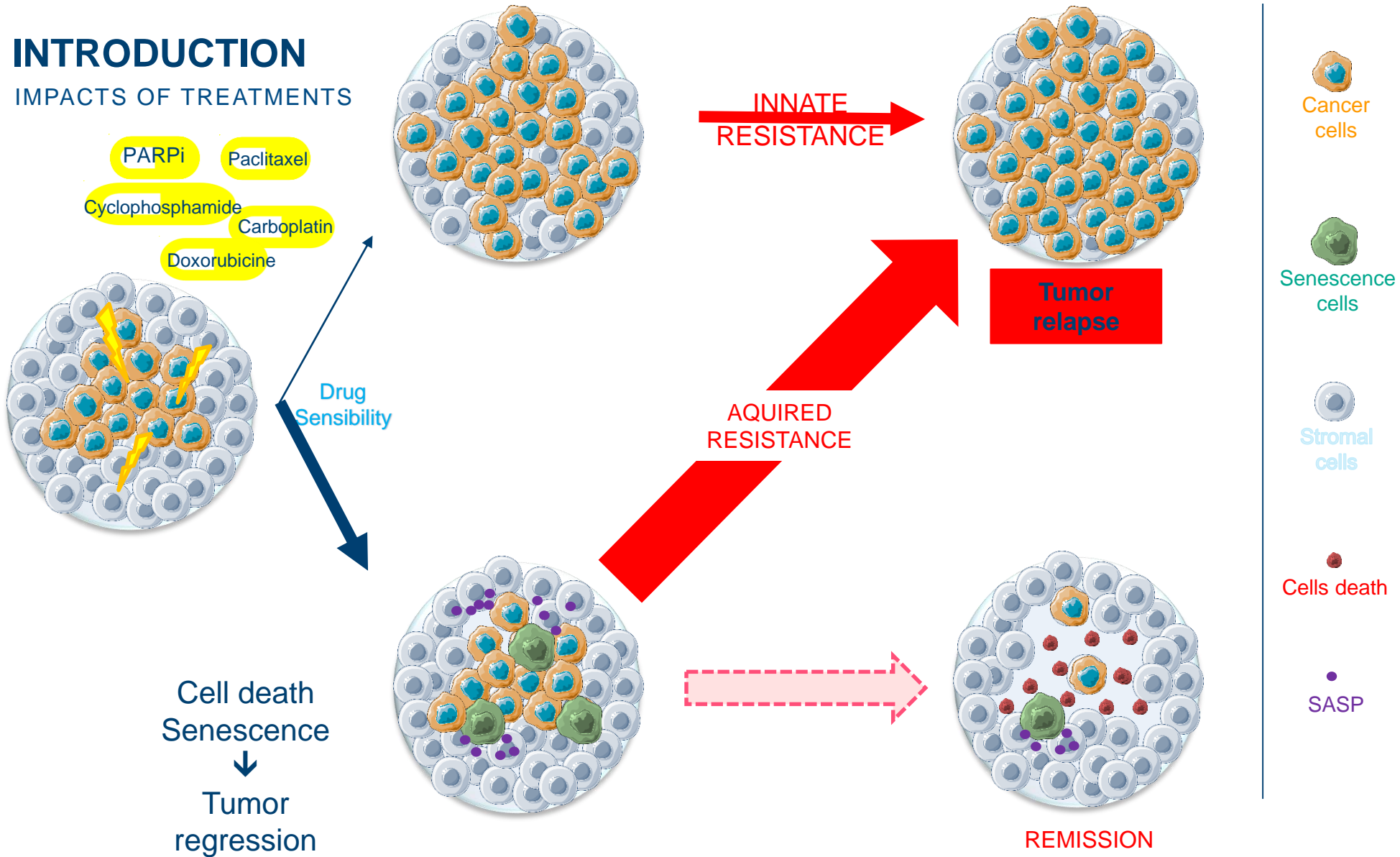
Stromal cells

Cells death

SASP

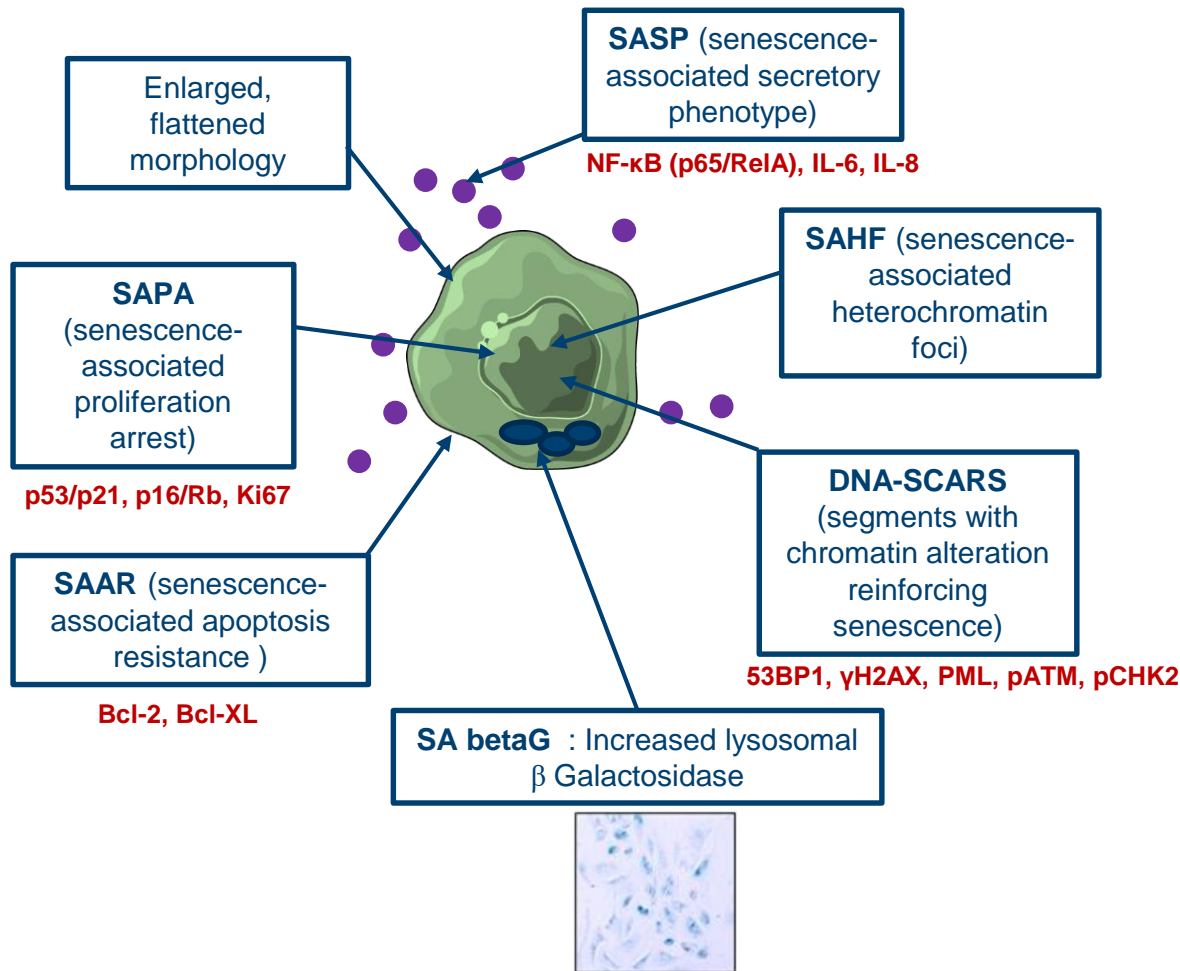
INTRODUCTION

IMPACTS OF TREATMENTS



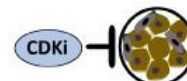


INTRODUCTION

CELLULAR SENEESCENCE PHENOTYPES

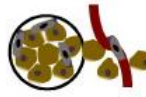



BENEFICIAL

Embryonic development 	Wound healing 	Cancer suppression 
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- Proliferation arrest (SAPA)
- Immune Clearance (SASP)

DELETERIOUS

Cancer progression 	Aging 
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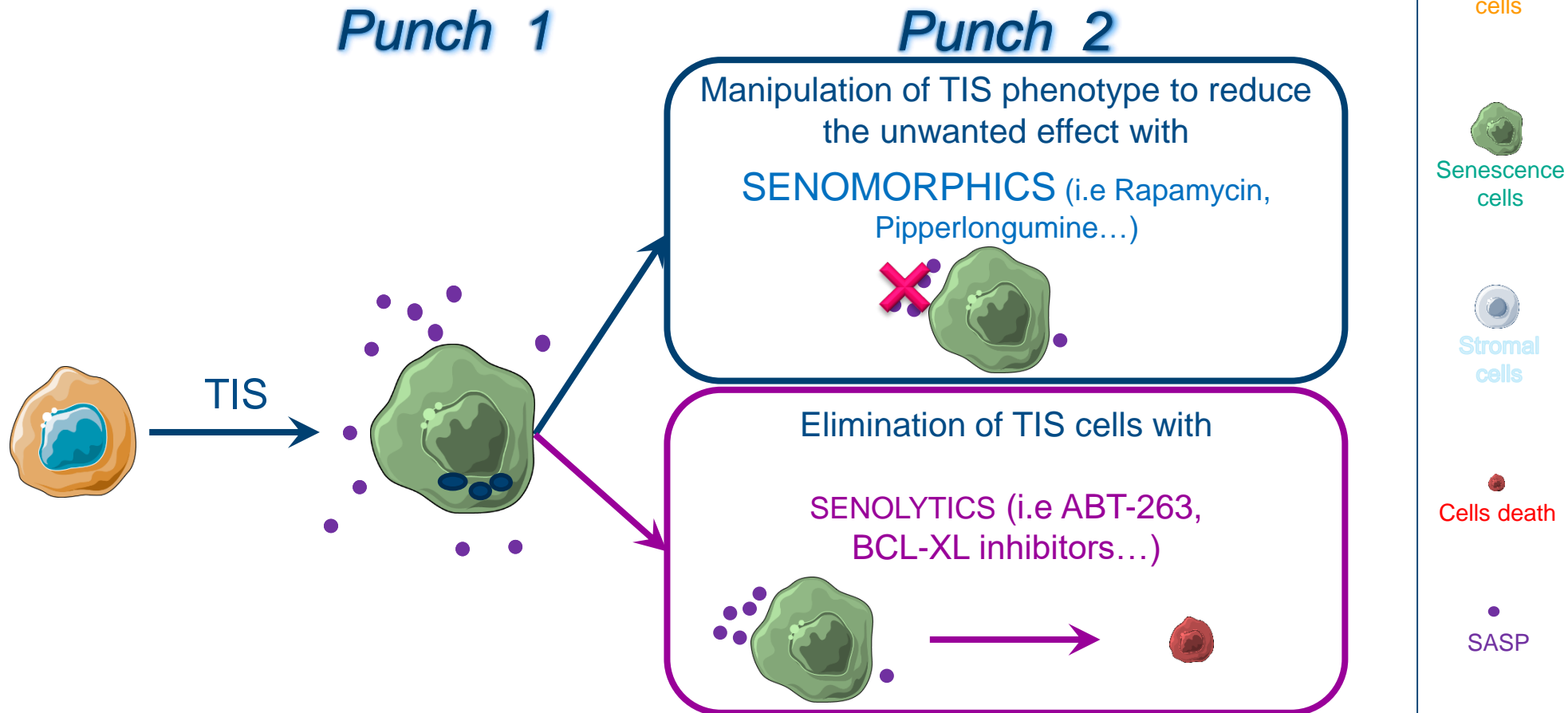
- Therapy resistance (SAPA)
- Unstable SAPA in p53 or p16 mutated cells
- Pro-inflammatory microenvironment (SASP)
- Apoptosis resistance (SAAR)

Malaquin et al. *Exp Gerontol* (2016), Collado and Serrano (2006)

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INTRODUCTION

TARGETING SENESENCE IN TNBC – « ONE TWO PUNCH »



HYPOTHESIS :

TIS of cancer cells induced by therapies used in clinics may be beneficial and used in PARPi treatment of patients with HGSC in order to refine drug administration patterns.

INTRODUCTION

PUBLISH DATA

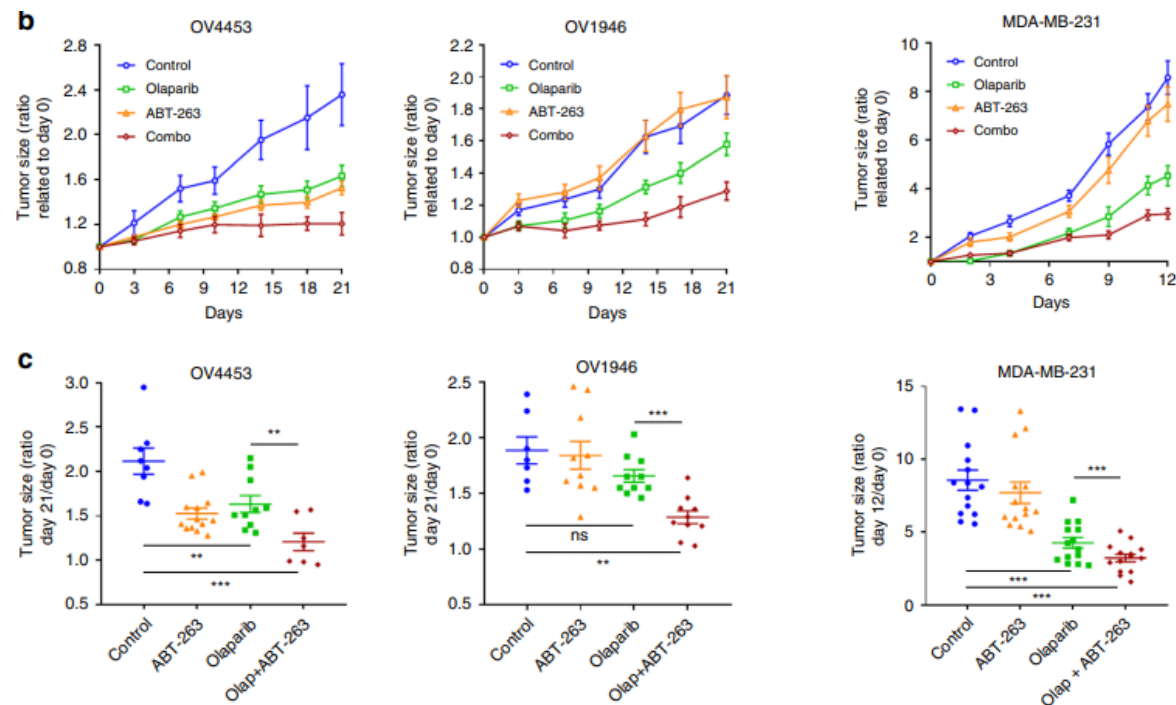
Exploiting interconnected synthetic lethal interactions between PARP inhibition and cancer cell reversible senescence

Hubert Fleury^{1,2,6}, Nicolas Malaquin^{1,2,6}, Véronique Tu^{1,2}, Sophie Gilbert^{1,2}, Aurélie Martinez^{1,2}, Marc-Alexandre Olivier^{1,2}, Alexandre Sauriol^{1,2}, Laudine Communal^{1,2}, Kim Leclerc-Desaulniers^{1,2}, Euridice Carmona^{1,2}, Diane Provencher^{1,2,3}, Anne-Marie Mes-Masson^{1,2,4} & Francis Rodier^{1,2,5}

High Grade Serous Cancer (HGSC)

TNBC

In vivo : Olaparib synergizes with ABT-263 in HGSC and TNBC mouse model xenograft



High Grade Serous Cancer

Fleury et al. Nature Communication (2019)

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RESULTS

TNBC - MDA-MB-231 XENOGRAFT MOUSE MODEL

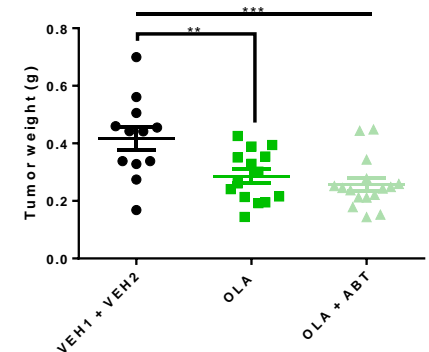
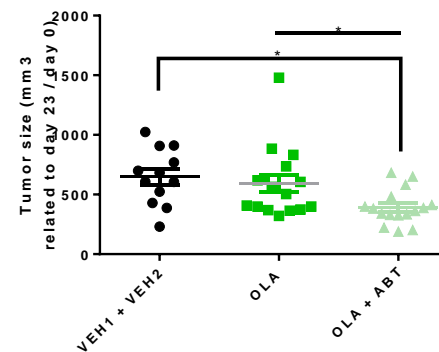
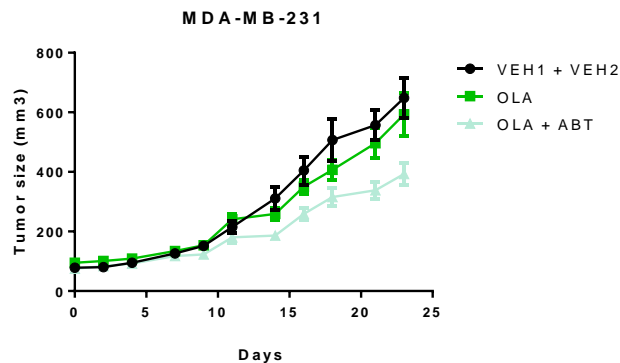
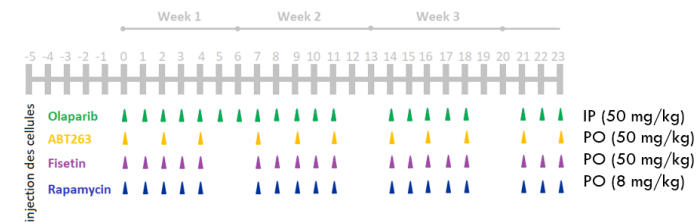
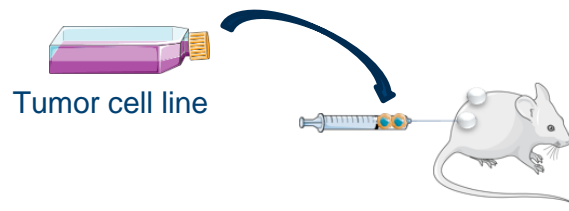
Phase 1 : *In vitro* evaluation of new combinaisons targeting senescence phenotypes (enhancement of TIS) to subsequently potentiate the senolysis induced. **SENOMORPHICS** vs **SENOLYTICS**

Phase 2 : *In vivo* validation and characterisation of new combinaisons targeting senescence phenotypes to subsequently potentiate the senolysis induced

Mouse model :

- Xenograft (NRG) – MDM- MB-231
- 2 tumors /mouse → n=16/condition

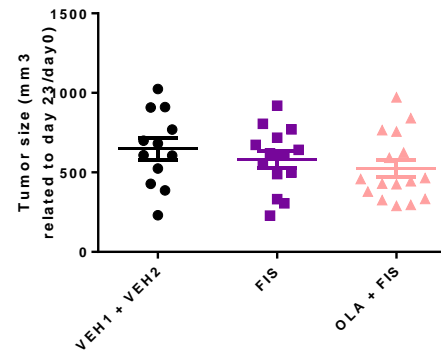
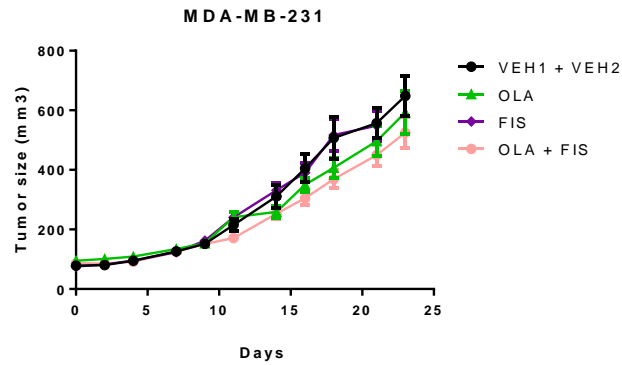
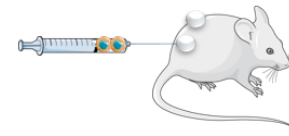
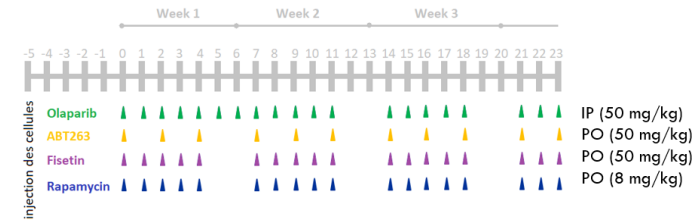
1 experiments N=70



Reference combo : Olaparib synergizes with ABT-263 in TNBC mouse model xenografts

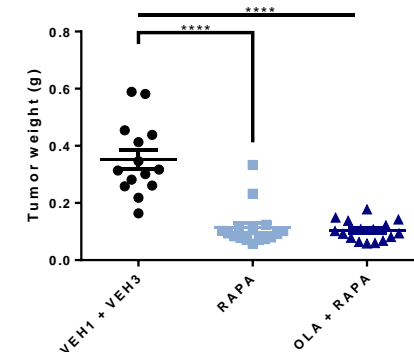
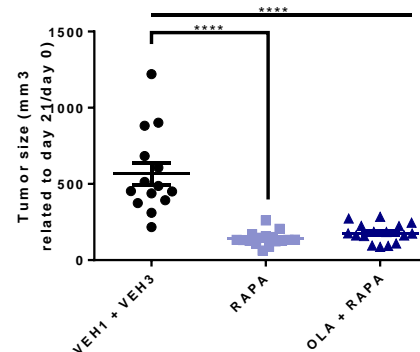
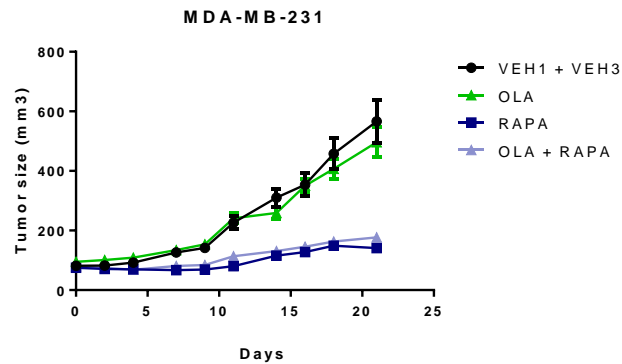
RESULTS

TNBC - MDA-MB-231 XENOGRAFT MOUSE MODEL



No tumor weight data

Fisetin does not have effect on tumor progression
 Fisetin does not synergizes with Olaparib in TNBC mouse model xenografts



The most effective single drug and combo is rapamycin and rapamycin + PARPi

CONCLUSIONS – PERSPECTIVES

- Confirm that rapamycin can modulate specifically phenotype related to senescence (senomorphic effects in combination with PARPi) or can induce senescence on its own.
- Fisetin : we will not investigate this compound any further in the context of breast cancer.
- More TNBC cells lines

- Drug screening :

	Treatment	Target	TIS target
SENOMORPHICS	Rapamycine	mTOR	SAPA SASP
	Chloroquine	The bond between the autophagosome and the lysosome	SAPA
	Palbociclib	CDK4/6	SAPA
	Ribociclib	CDK4/6	SAPA
SENOLYTICS	ABT263	Bcl2	SAAR
	Fisetin	PI3K AKT mTOR	SASP SAPA
	Piperlongumine	Antioxydant	SAPA

 la Vie en Rose

CRCHUM
CENTRE DE RECHERCHE



INSTITUT
DU CANCER
DE MONTRÉAL

Thank you for your attention !

Dr Rodier team

- Nicolas Malaquin
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