



SFT

Société Française de Toxicologie



Natural Molecules as therapeutic adjuvants: Resveratrol and anticancer drugs

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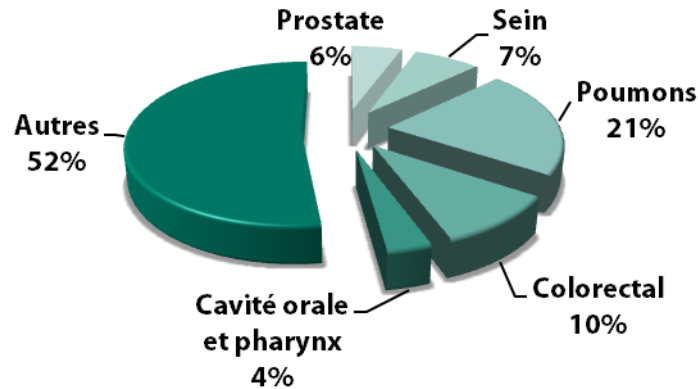
Inserm Research Center U1231 "Lipids, Nutrition, Cancers"

" Bioactive Molecules and Health " research group

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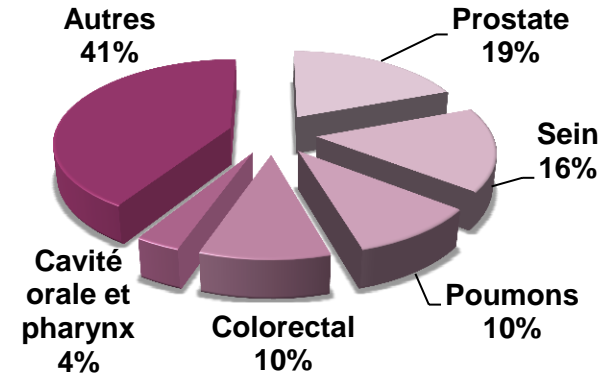
Cancer, epidemiological data and strategies

➤ Second causes of mortality in the world



Mortality

➤ Since 20 years, incidence increases



Incidence

➤ First causes of mortality in France ~ 153 000 death / year

✓ Main objectives to fight cancers



Cancer, epidemiological data and strategies

➤ Good practices or resolutions to prevent cancer development :



5 a day

An apple a day keeps the doctor away - literally. Eating **fruit and veg** may reduce risks for many cancers.



Shake off salt

Too much salt increases your risk of stomach cancer. Eat no more than **5g** a day.



Stay out of the red

Eating lots of **beef, pork and lamb**, bacon and sausages is associated with colorectal cancers.



Not so sweet

Sugary soft drinks, **sweet and fatty foods** cause weight gain, which increases your cancer risk. **Water's better.**



Good for the gut

Eating lots of **fibre** (in fruit and veg and wholegrains) cuts your risk of colorectal cancer.



Get sweaty

30 mins of physical activity a day (**60 mins** for children) reduces risk for several major cancers.



Know your limits

Alcohol increases cancer risk. No more than two drinks for men and one for women per day.



Love your skin

Sizzling in the **sun** - or on a sunbed - increases your risk of developing **skin** cancer, especially if you're under 30.



Quit!

The world's single, biggest cause of cancer. More than **25%** of all cancer deaths. **10%** of all adult deaths.



Downsize

Being **overweight** is linked with several cancers such as oesophagus, colorectal, breast and kidney.



Get vaccinated

Infections like Hep B, C and HPV cause up to 20% of cancer deaths in developing countries (9% in developed).

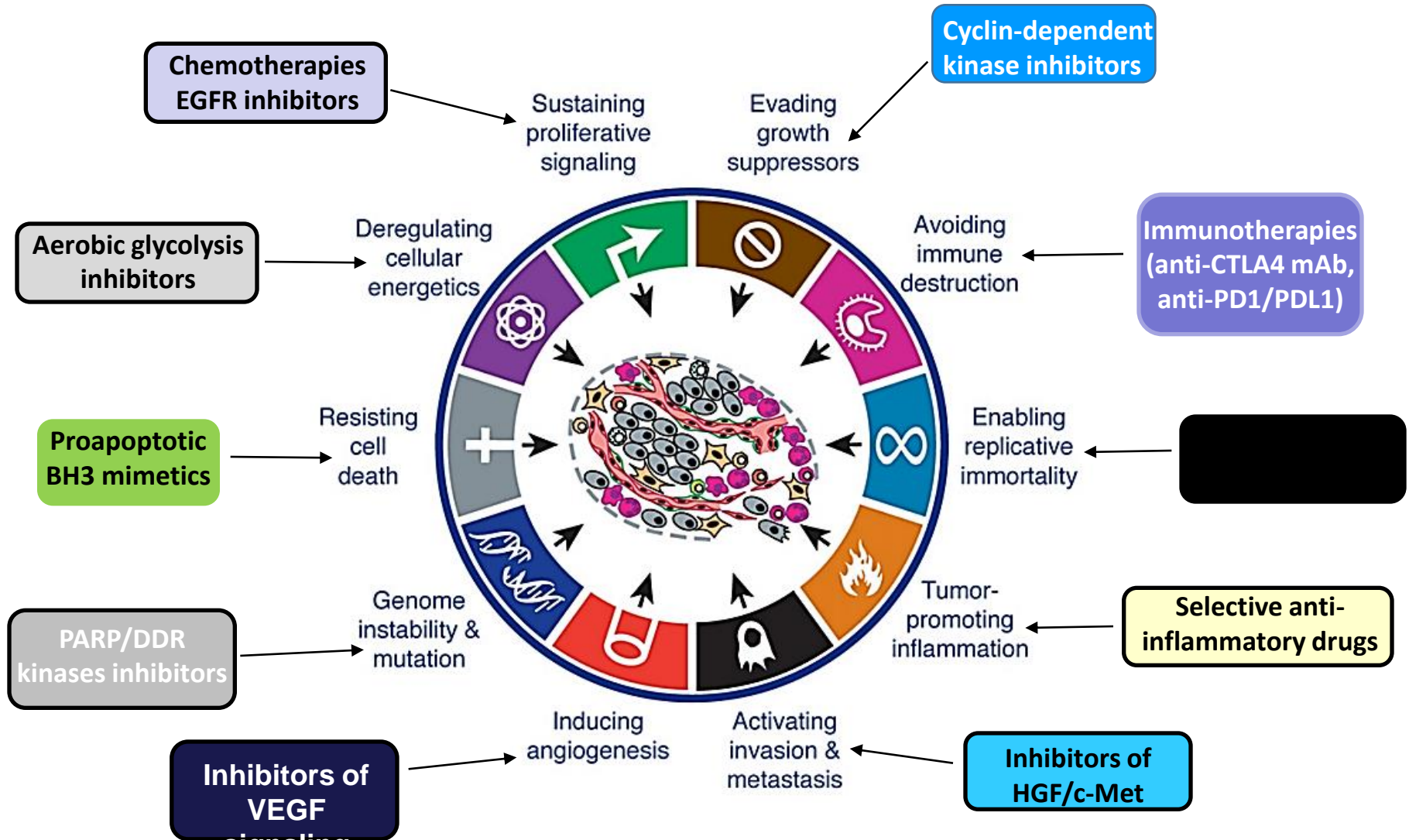


Become an eco warrior

Environmental pollution of air, water and soil with cancer-causing chemicals accounts for **1-4%** of all cancers.

Cancer, epidemiological data and strategies

➤ Development of new drugs to fight cancer :



Cancer, epidemiological data and strategies

- 5-years survival rate remains very low for a large number of cancers

Factors related to the host
(*biotransformation,*
bioavailability, toxicity, ...)

Cellular factors
(*i.e. intrinsic or acquired resistances,*
lack of apoptosis, ...)

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graph TD; A[Factors related to the host] --> D; B[Cellular factors] --> D; C[Factors related to the tumor microenvironment] --> D; D([Treatment failure: 90% of patients with metastatic cancer]);
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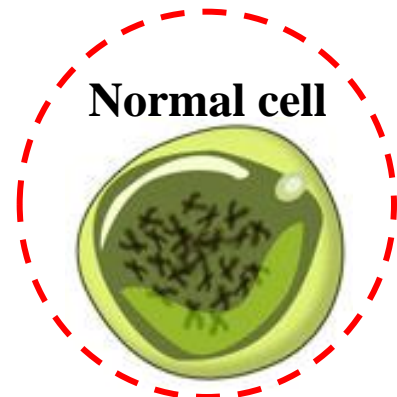
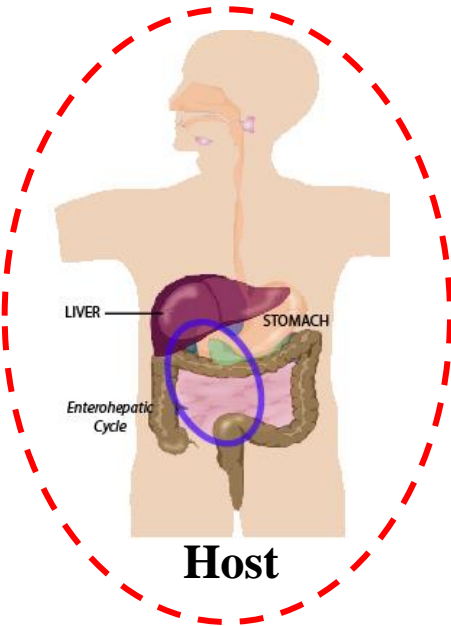
Treatment failure:
90% of patients with
metastatic cancer

Factors related to the tumor microenvironment
(*i.e. angiogenesis, membran fluidity, metabolism, ...*)

Need to develop new therapeutic approaches that
could be described as multifactorial

Cancer, epidemiological data and strategies

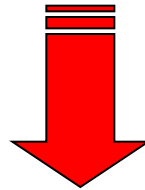
➤ The concept of therapeutic adjuvant



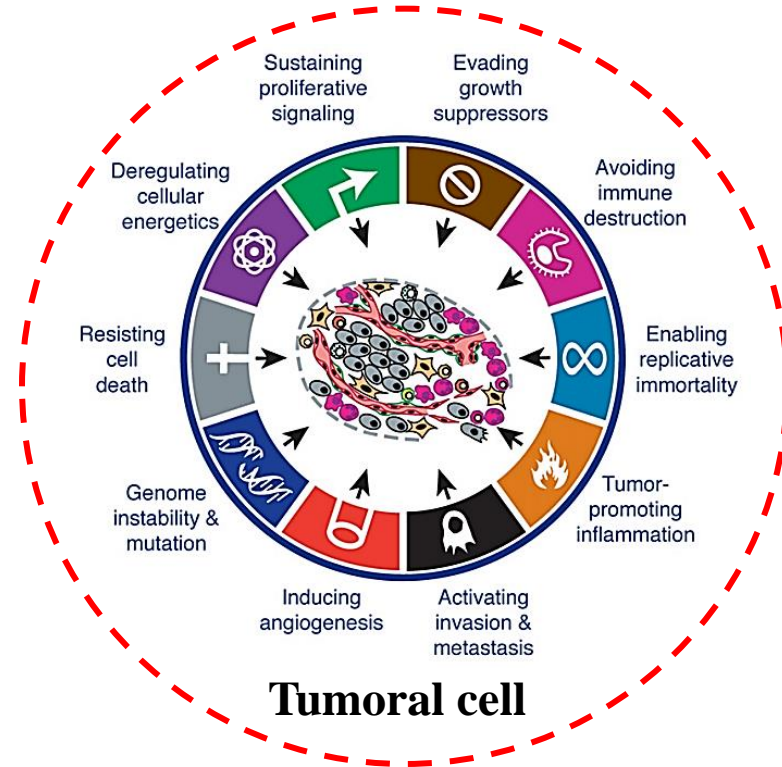
**Antitumoral
drugs**

+

**Therapeutic
adjuvant**



**Synergy to kill
tumoral cells**



Cancer, epidemiological data and strategies

➤ The concept of therapeutic adjuvant

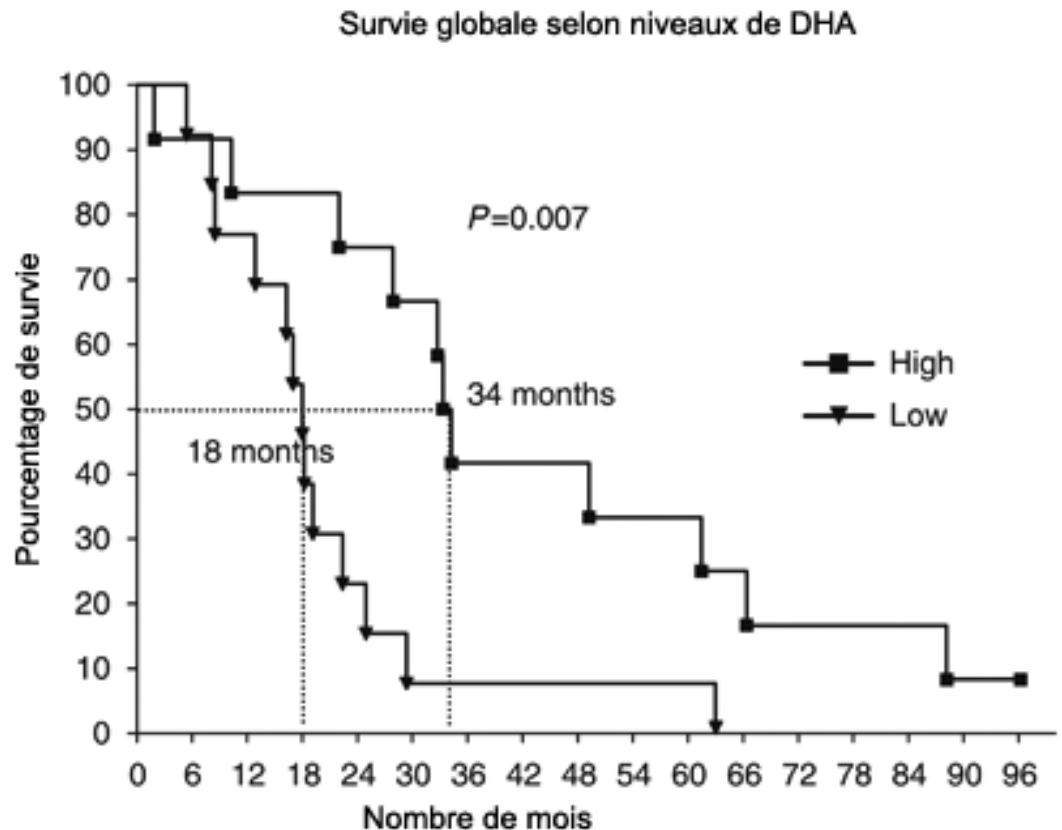


Omega-3

DHA during chemotherapy was devoid of adverse side effects and can improve the outcome of chemotherapy when highly incorporated.

DHA has a potential to specifically chemosensitise tumours.

DHA was administered from inclusion before initiation of chemotherapy (a 7–10-day loading period) and then for the 5 months of chemotherapy.



Cancer, epidemiological data and strategies

➤ The concept of therapeutic adjuvant



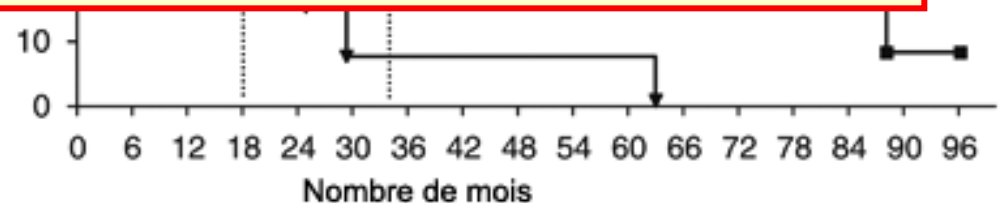
DHA was administered from inclusion before initiation of chemotherapy (a 7–10-day loading period) and then for the 5 months of chemotherapy.

Survie globale selon niveaux de DHA

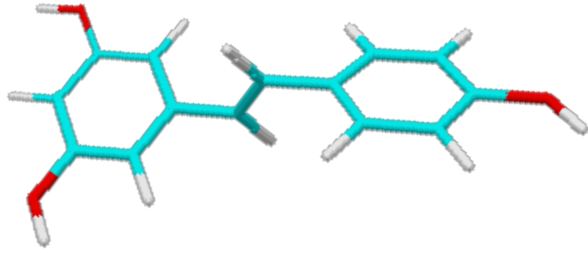
Polyphenols, especially Resveratrol, could present therapeutic properties and / or be used as chemotherapeutic adjuvant in cancer ?

DH
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inco

DHA has a potential to specifically chemosensitise tumours.



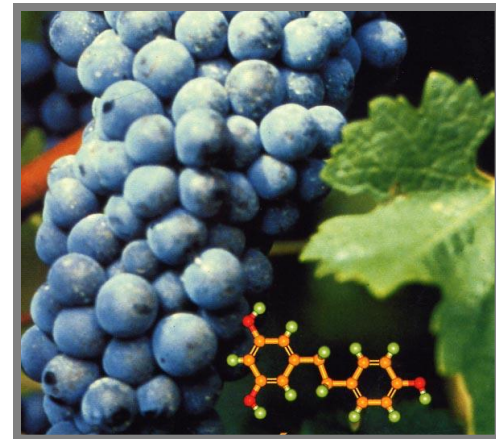
Resveratrol, a safe molecule with health benefits



Trans-3,5,4'-trihydroxystilbene

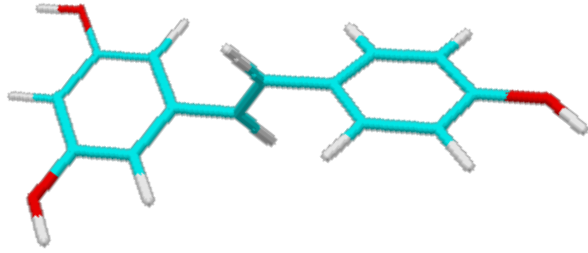
Sources :

- *Polygonum cuspidatum*,
- Peanuts,
- Grapes red wine,
- Blackberries, ...

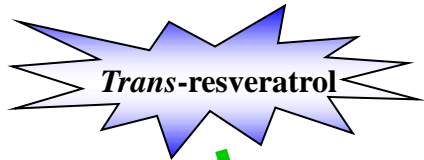


Resveratrol, a phytoalexin of grapewine

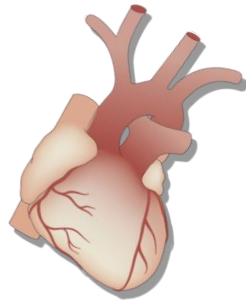
Resveratrol, a safe molecule with health benefits



***Trans*-3,5,4'-trihydroxystilbene**



**Cardiovascular
diseases**



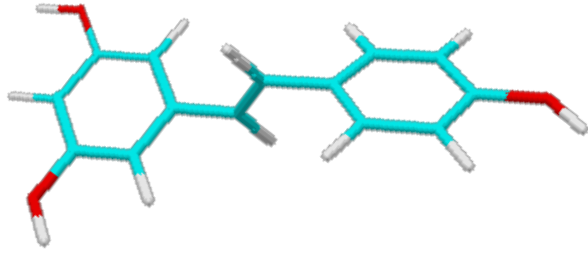
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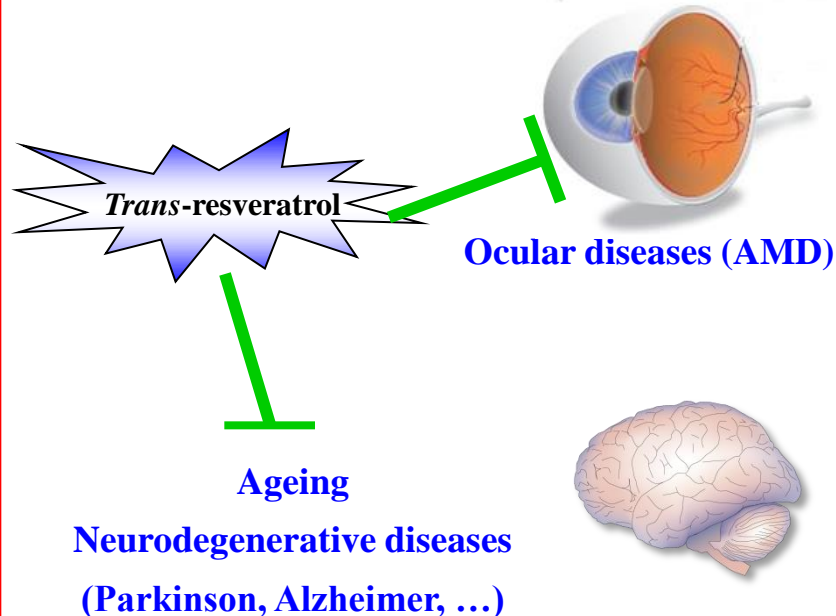
Preventing properties against pathology processess :

- Oxidative stress,
- Atherosclerosis,
- Foam cells formation,
- Cytokines production,
- Platelet aggregation,

Resveratrol, a safe molecule with health benefits



Trans-3,5,4'-trihydroxystilbene



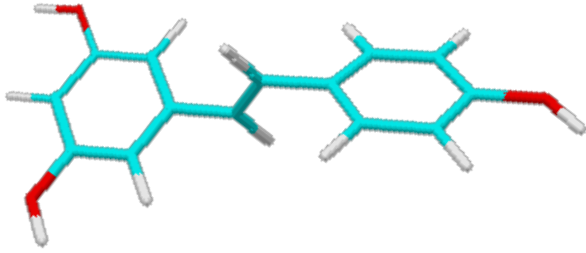
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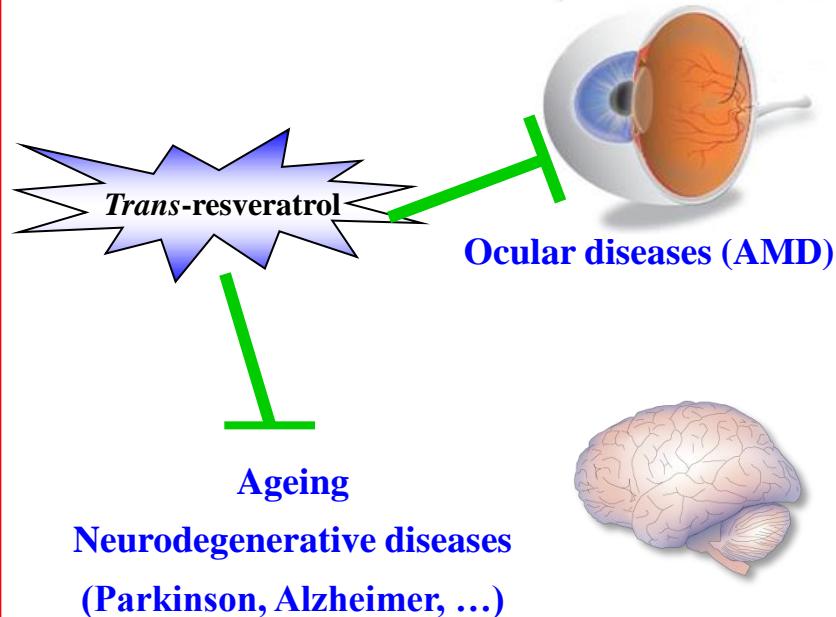
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Resveratrol, a safe molecule with health benefits



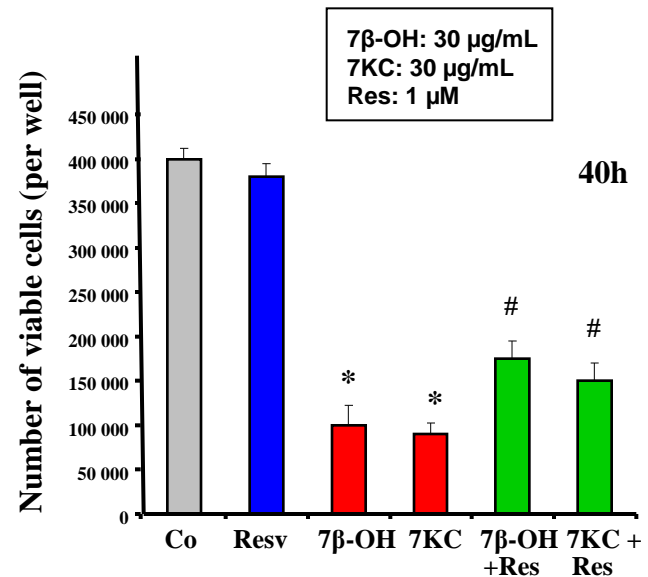
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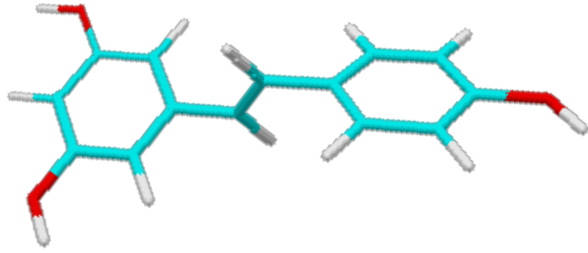
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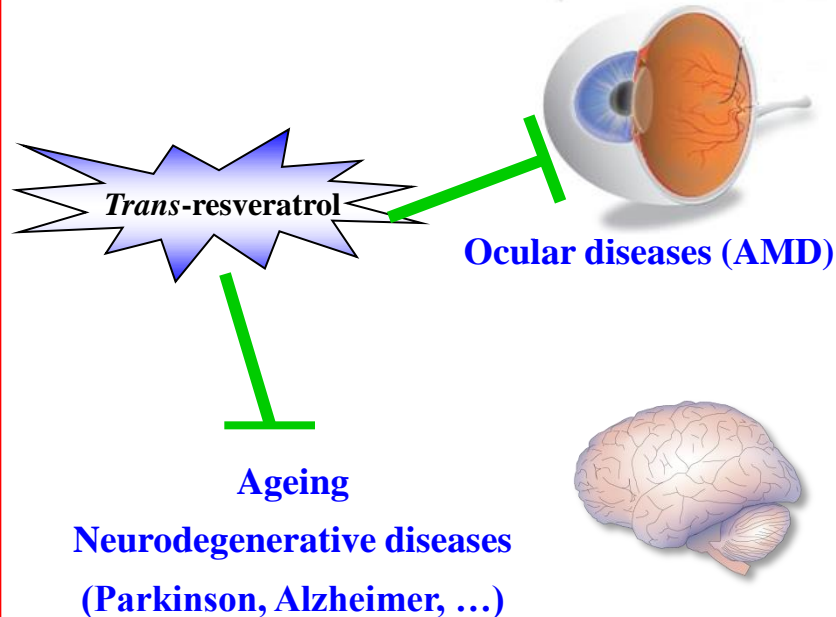


Dugas et al. Eur J Nutr (2010)

Resveratrol, a safe molecule with health benefits



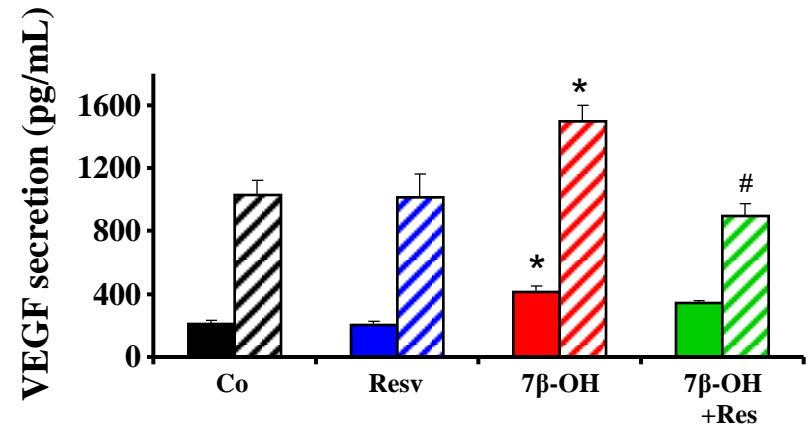
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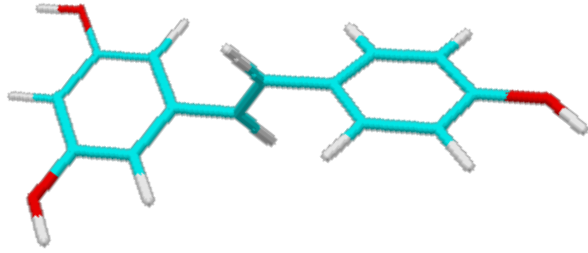
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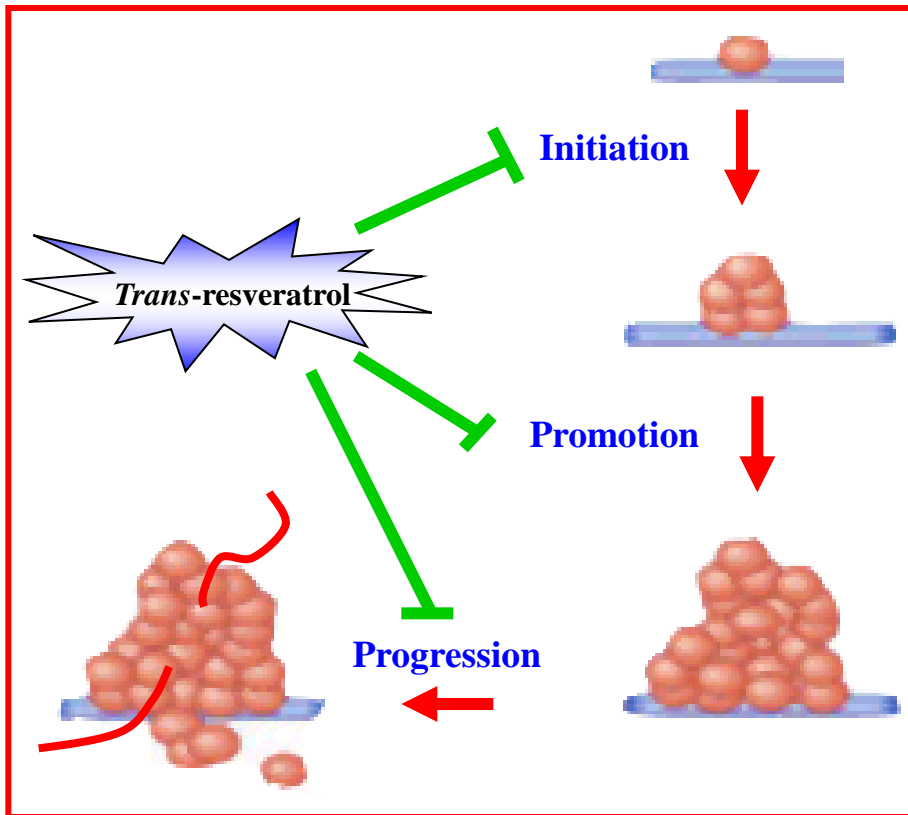
Preventing properties against pathology processess :



Resveratrol, a safe molecule with health benefits



Trans-3,5,4'-trihydroxystilbene



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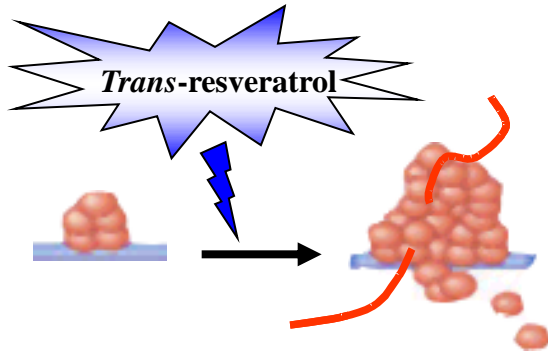
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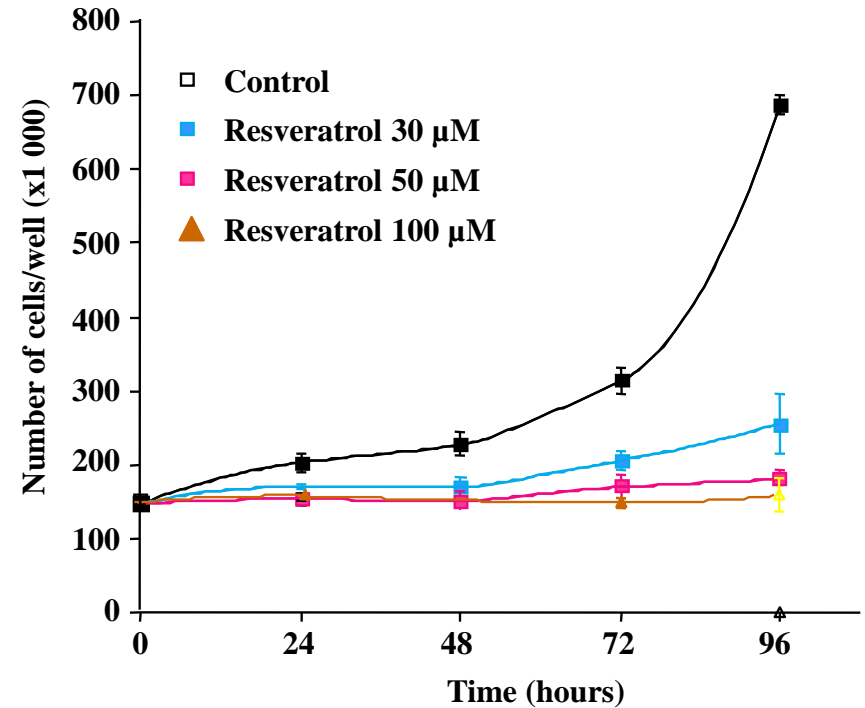
- Oxidative stress,
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- Foam cells formation,
- Cytokines production,
- Platelet aggregation,
- Age-related degenerescence,
- Carcinogenesis, ...

Resveratrol, a safe molecule with health benefits

1- Resveratrol: an inhibitor of tumoral proliferation



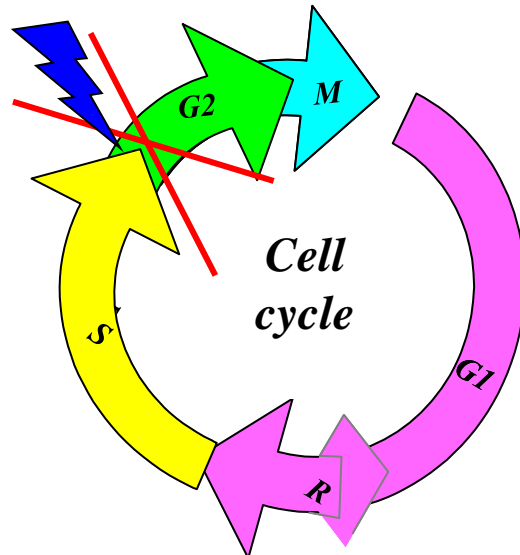
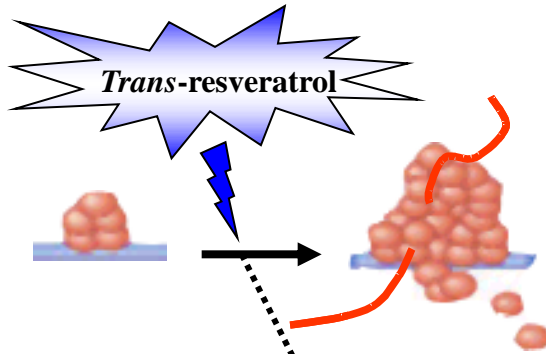
■ Resveratrol inhibits colon and hepatic cancer cell proliferation



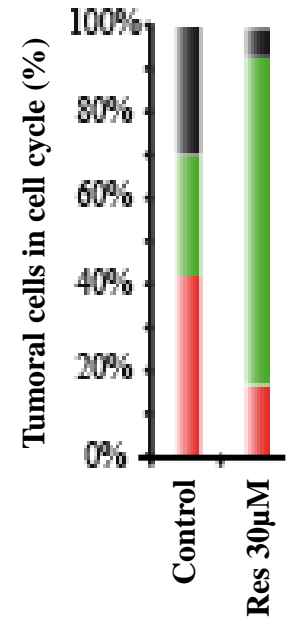
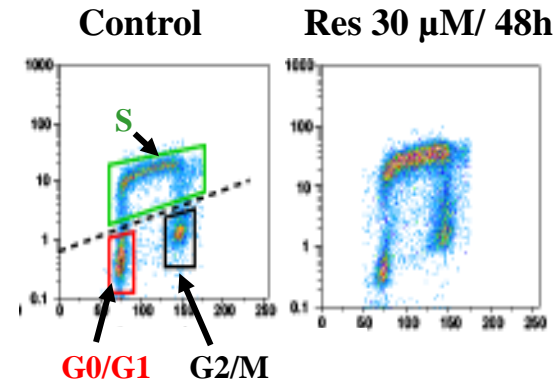
Delmas et al. Oncol. Report (2000); Delmas et al. Int. J. Mol. Med. (2002); Marel et al. Mol. Nut. Food Res. (2008); Colin et al. Int. J. Cancer (2009)

Resveratrol, a safe molecule with health benefits

2- Resveratrol: a disruptors of cell cycle



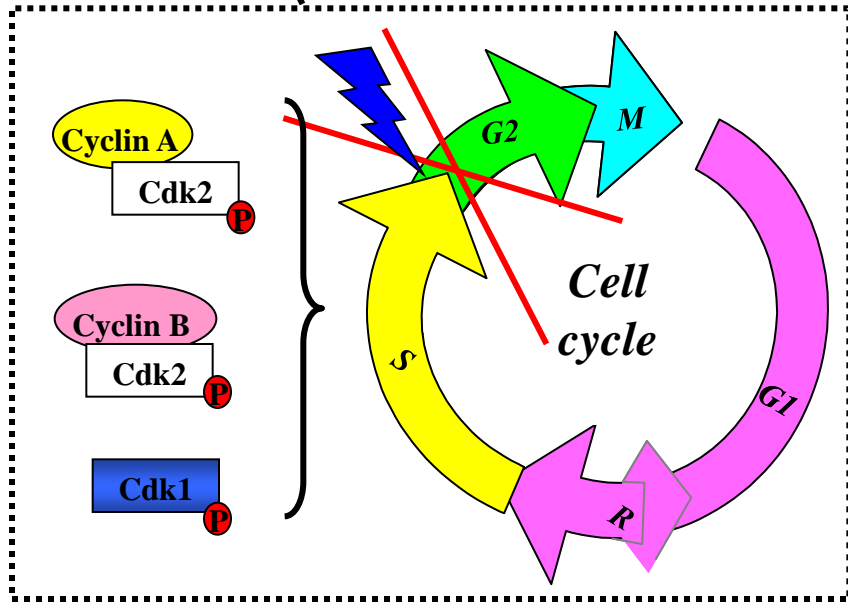
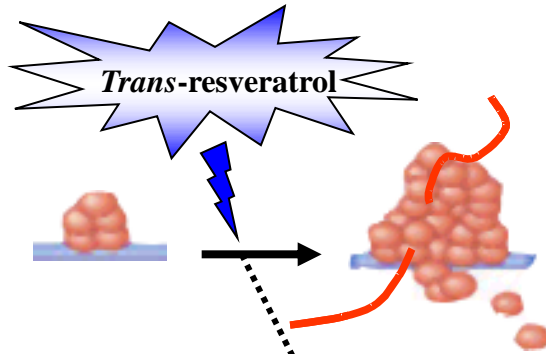
- Resveratrol inhibits colon and hepatic cancer cell proliferation
- Resveratrol blocks the cell cycle in S phase



Delmas et al. Oncol. Report (2000); Delmas et al. Int. J. Mol. Med. (2002); Marel et al. Mol. Nut. Food Res. (2008); Colin et al. Int. J. Cancer (2009)

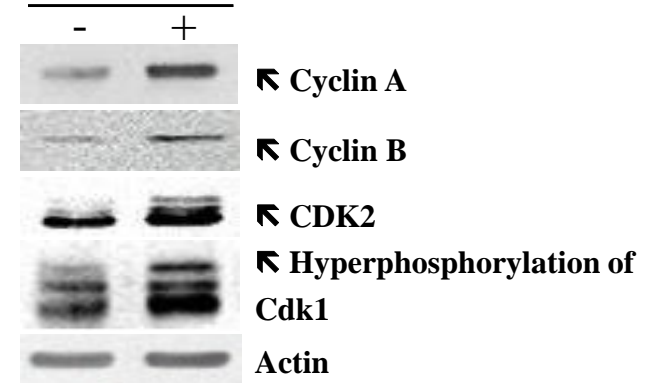
Resveratrol, a safe molecule with health benefits

2- Resveratrol: a disruptors of cell cycle



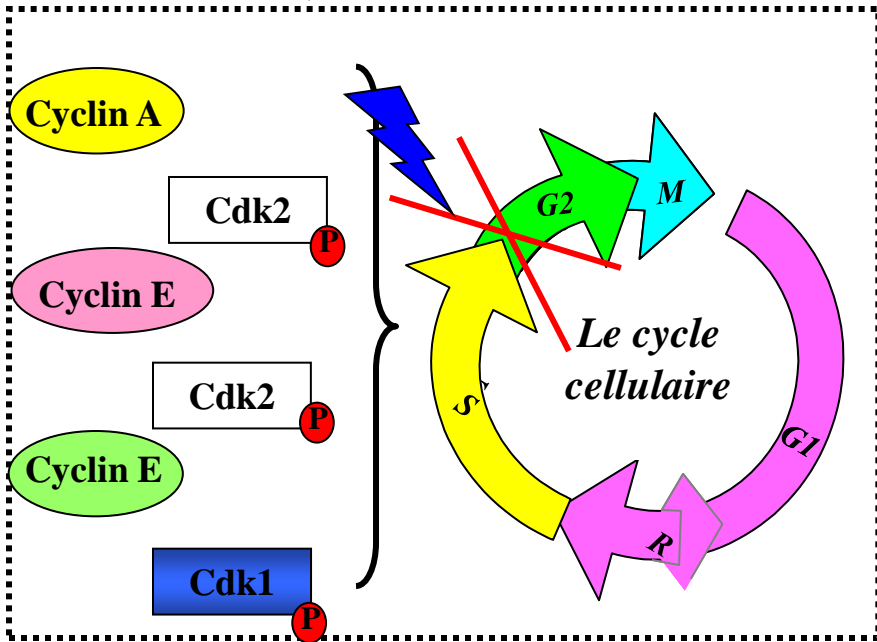
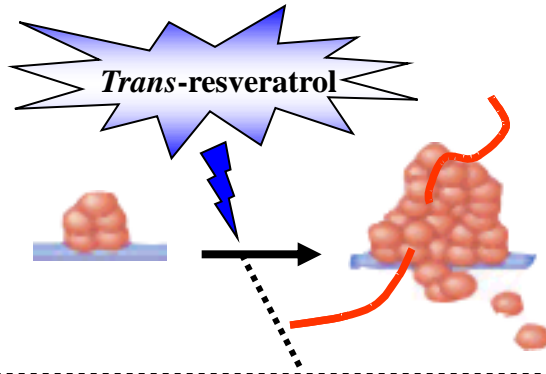
- Resveratrol inhibits colon and hepatic cancer cell proliferation
- Resveratrol blocks the cell cycle in S phase
- Resveratrol induces the accumulation and the phosphorylation of key regulators of the cell cycle

Res 30 μ M/48h

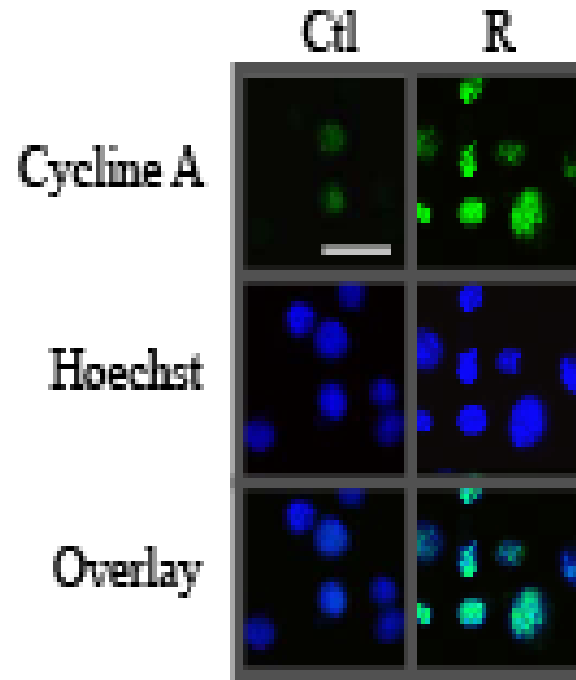


Resveratrol, a safe molecule with health benefits

2- Resveratrol: a disruptors of cell cycle

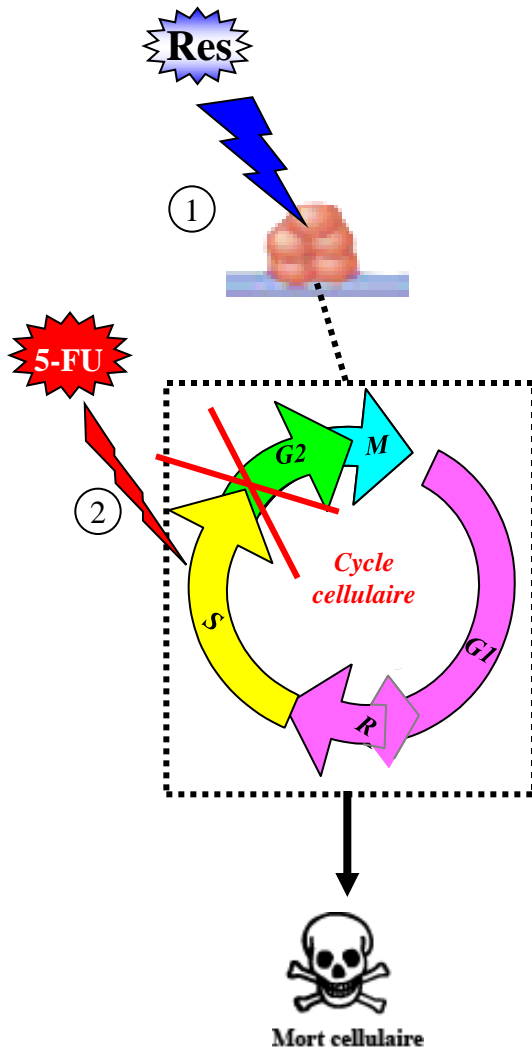


- Resveratrol induces accumulation and nuclear relocalisation of cyclin A during early S phase of cell cycle

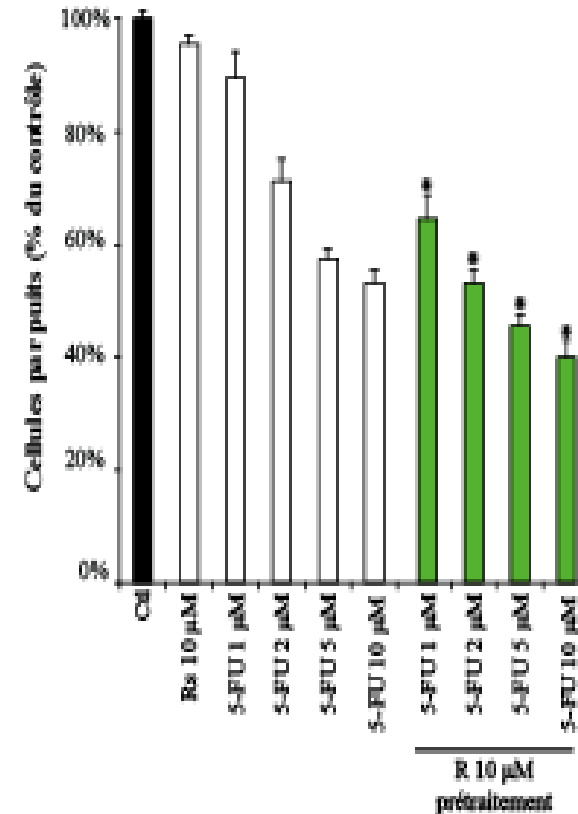


Resveratrol, a safe molecule with health benefits

3- Resveratrol: a chemosensitizer agent to drugs targeting cell cycle

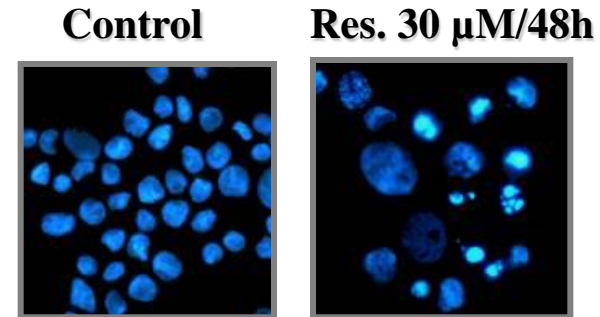
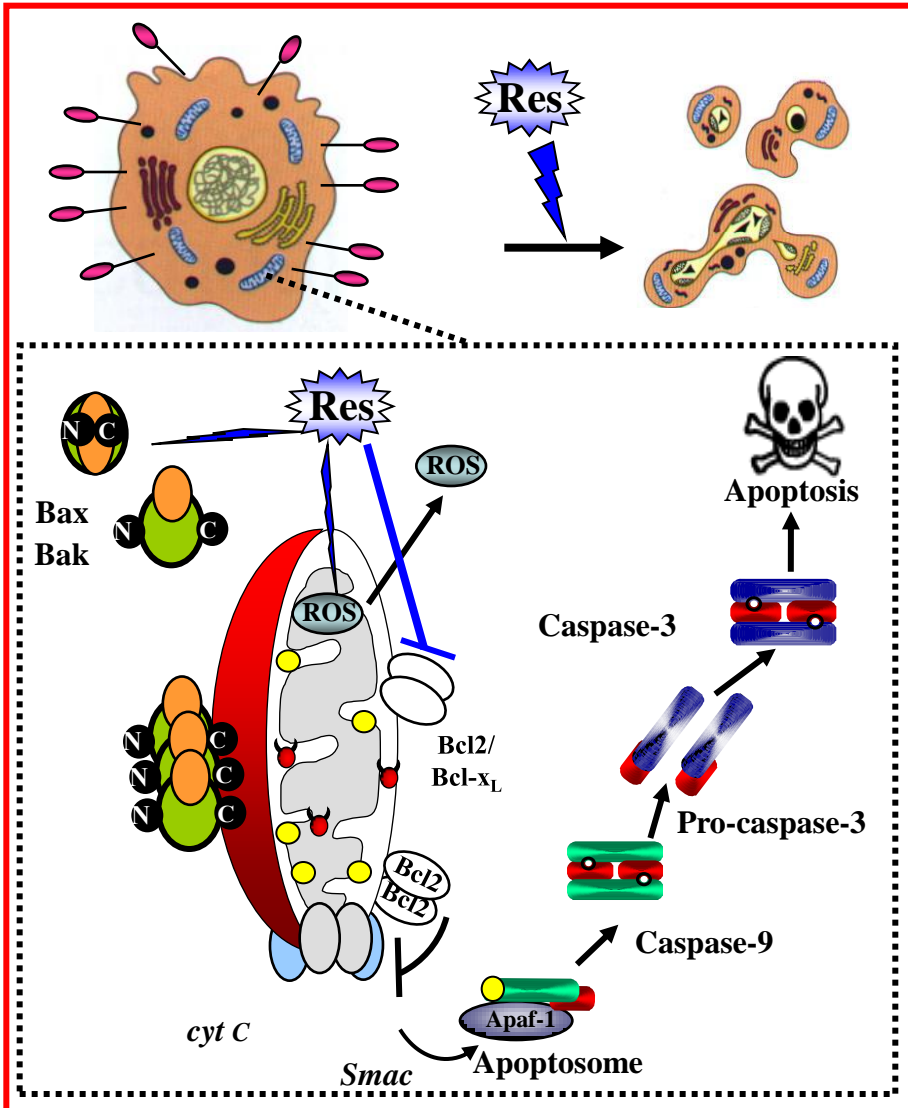


■ Synergic effect of Resveratrol with 5-FU (5-Fluoro-uracil) on colon carcinoma cells

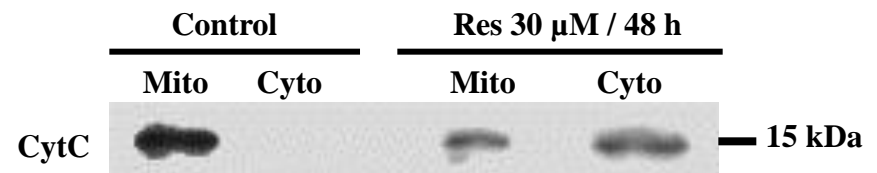
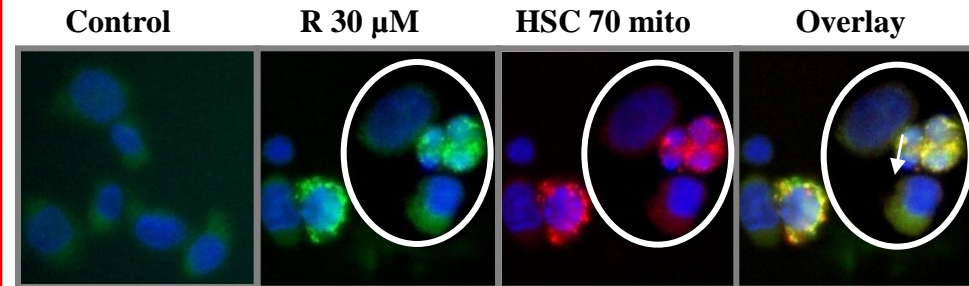


Resveratrol, a safe molecule with health benefits

4- Resveratrol: an inducer of apoptosis



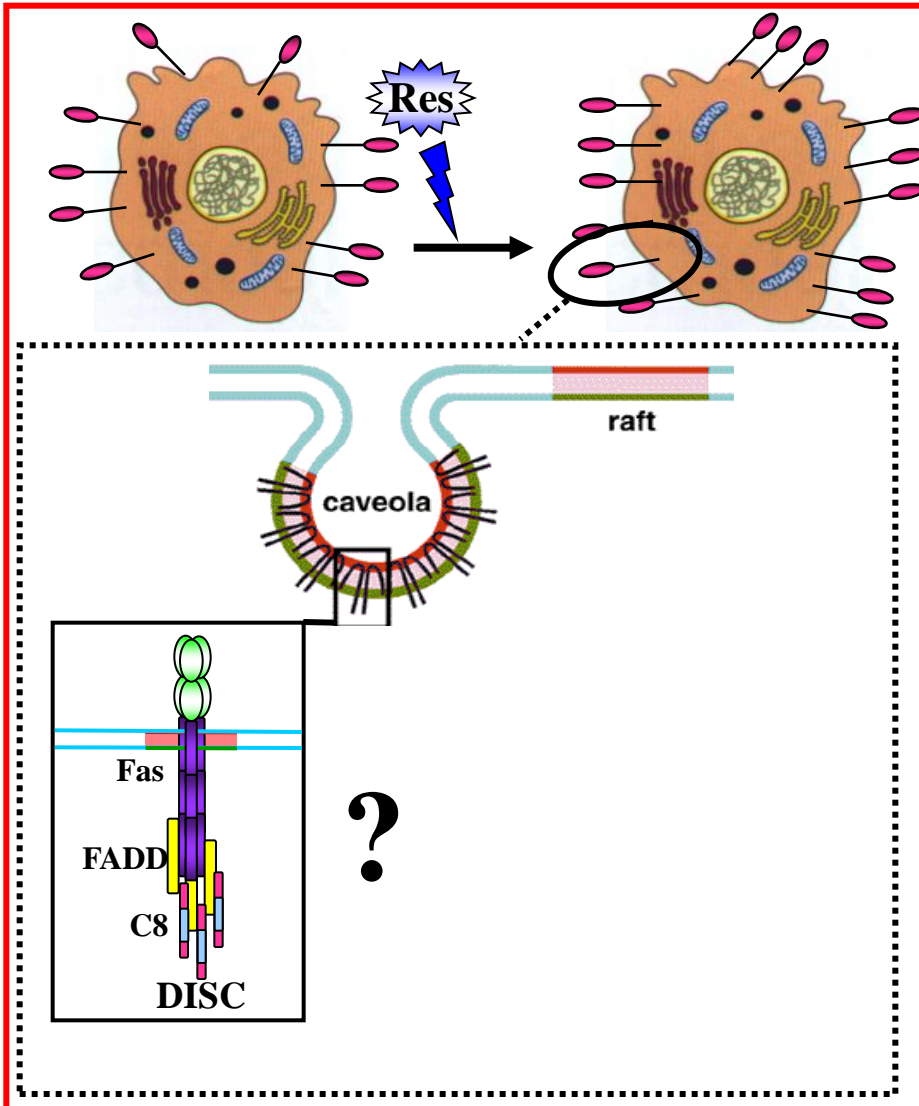
■ Resveratrol induces apoptosis of tumoral cells *via* a mitochondrial pathway



Delmas et al. J. Biol Chem (2003)

Resveratrol, a safe molecule with health benefits

4- Resveratrol: an inducer of apoptosis



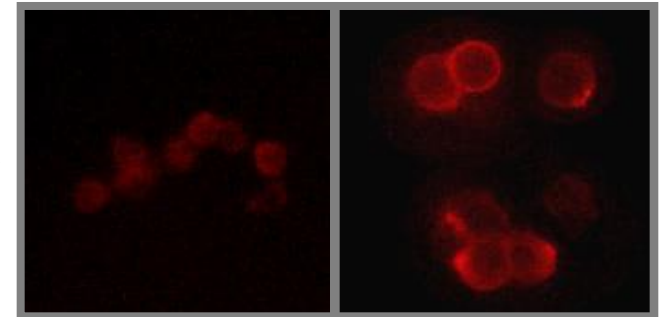
■ Resveratrol induces:

- trimérisation
- redistribution of death receptors into lipid microdomains ?

Control

R 30 μ M / 48h

Fas

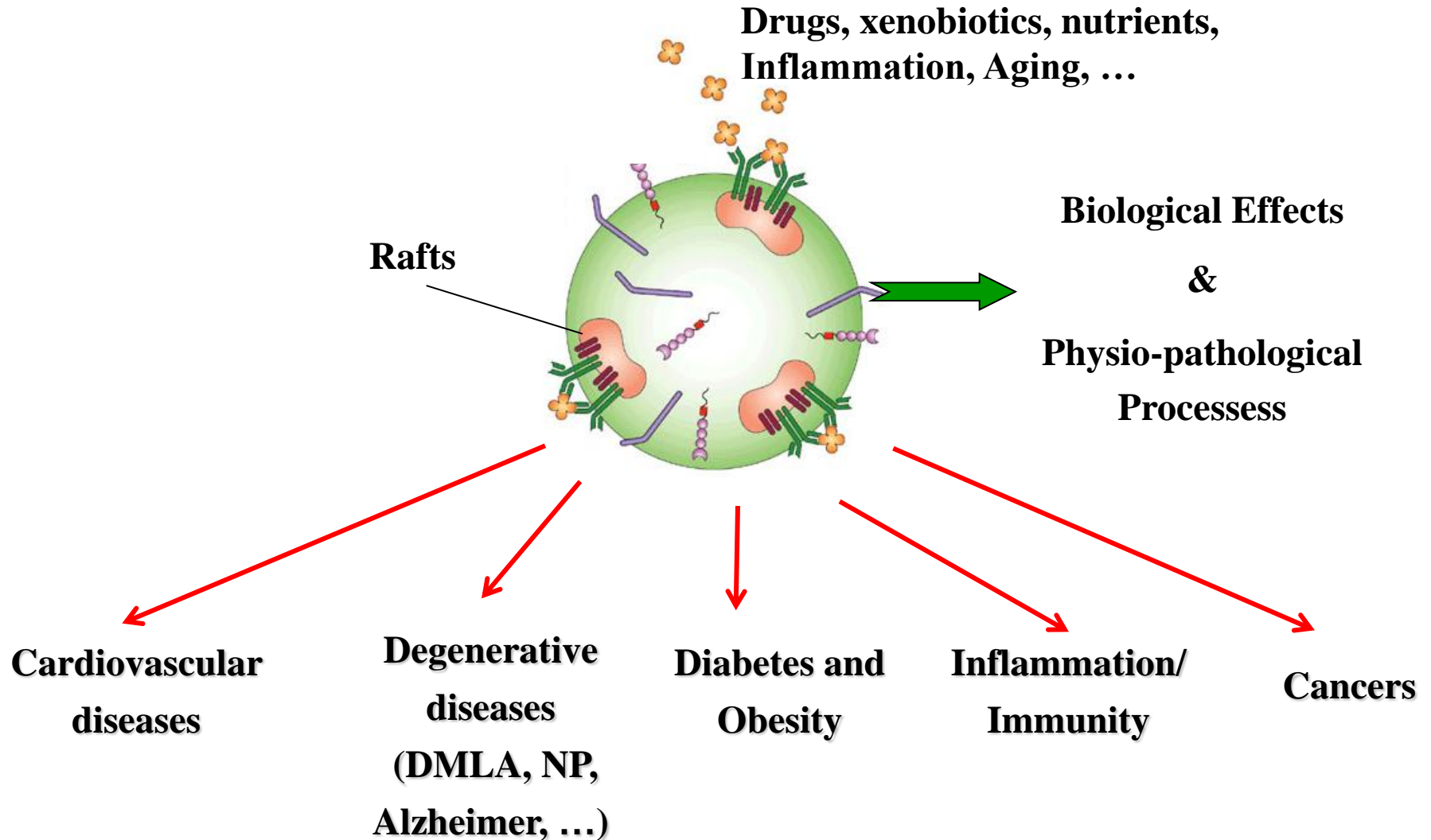


Delmas et al. J. Biol Chem (2003)

Delmas et al. Oncogene (2004)

Resveratrol, a safe molecule with health benefits

➤ Why lipid rafts ?



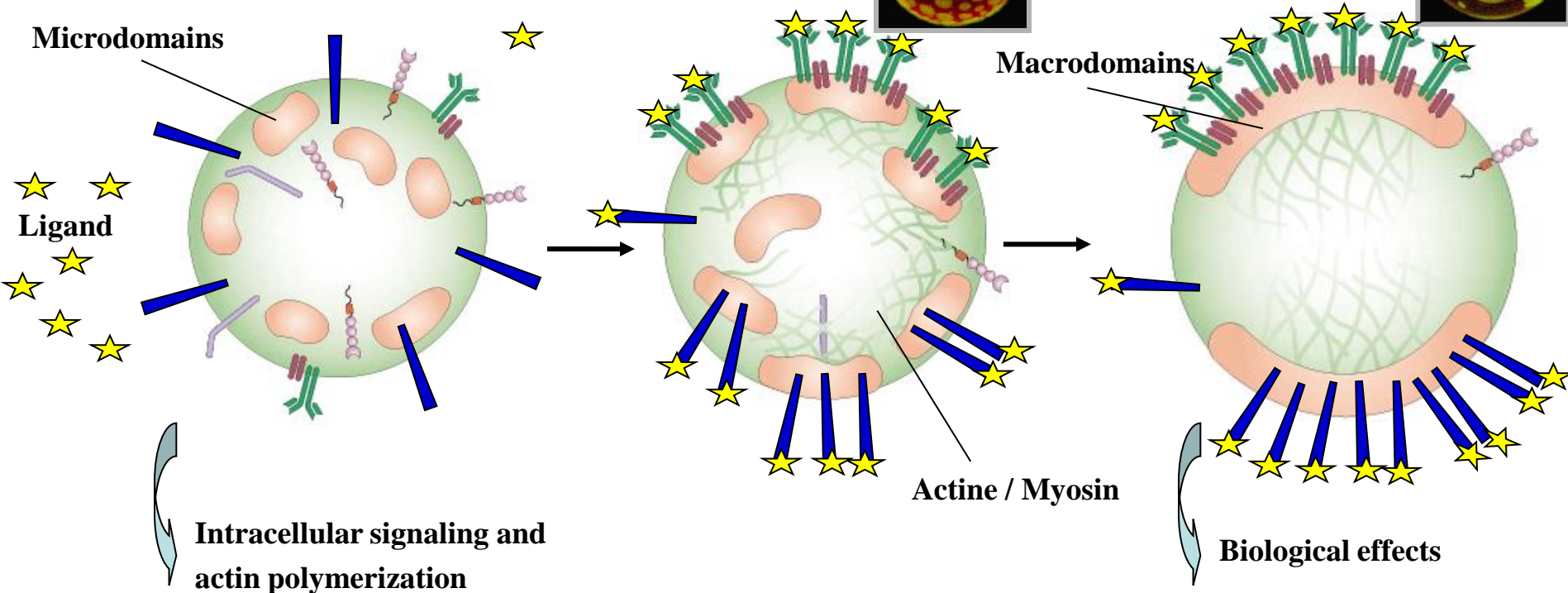
Resveratrol, a safe molecule with health benefits

➤ Lipid rafts as dynamic platforms

Ligand-Receptor
Interactions

Microdomains
migration

Signal pathways
amplification



Lipid macrodomains functions:

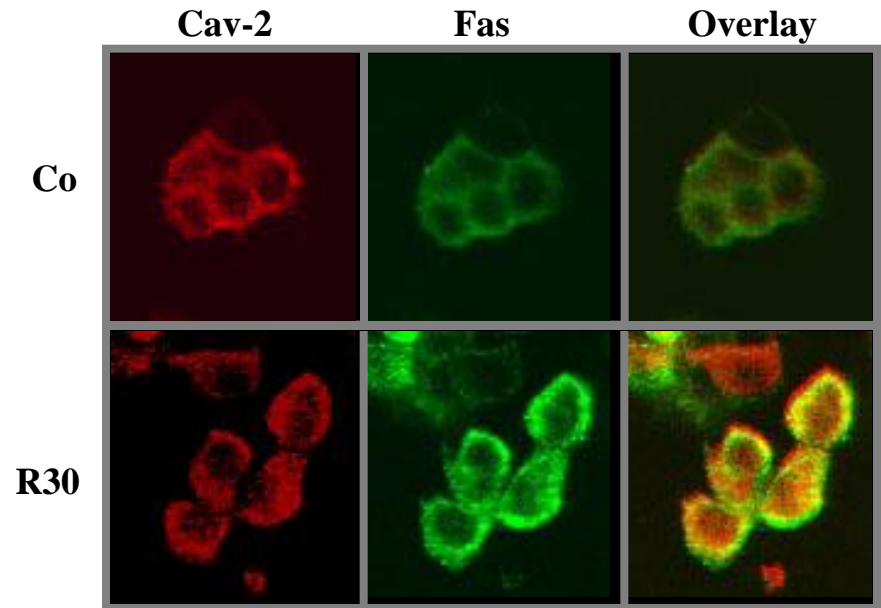
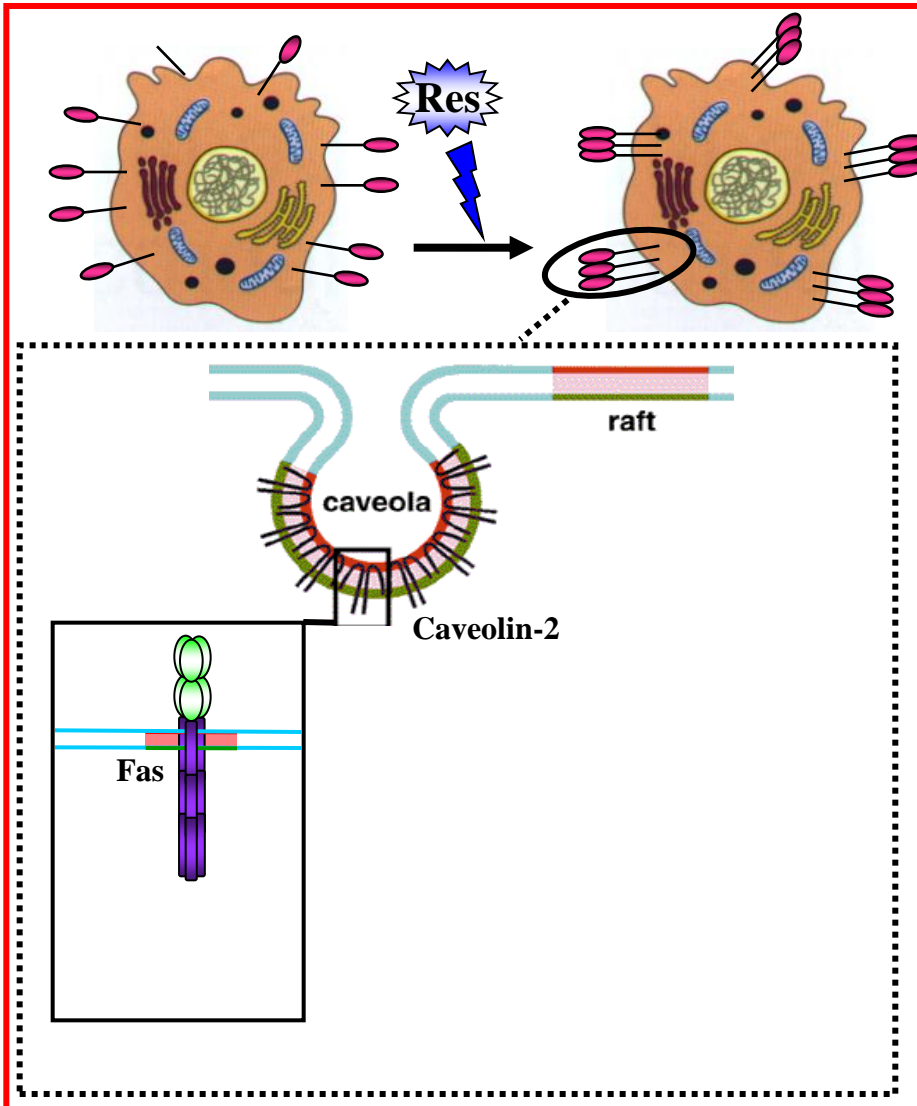
- amplification of protein-protein interactions ;
- amplification of initial signal ;
- increases of rafts recruitment and signaling proteins.

(adapted from Susan K. Pierce, *Nat Rev Immunol*, 2002)

Resveratrol, a safe molecule with health benefits

4- Resveratrol: an inducer of apoptosis

- Resveratrol induces death receptors redistribution into lipid rafts

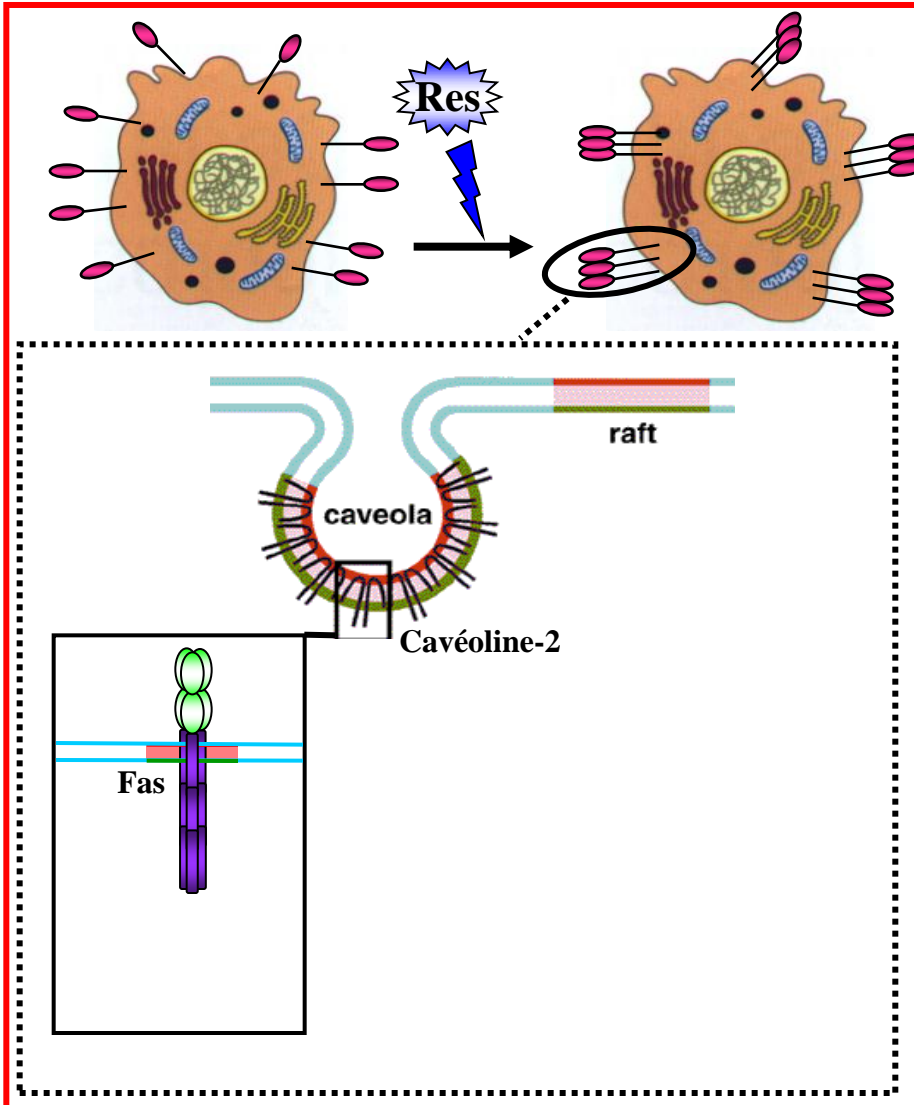


Delmas et al. J. Biol Chem (2003)

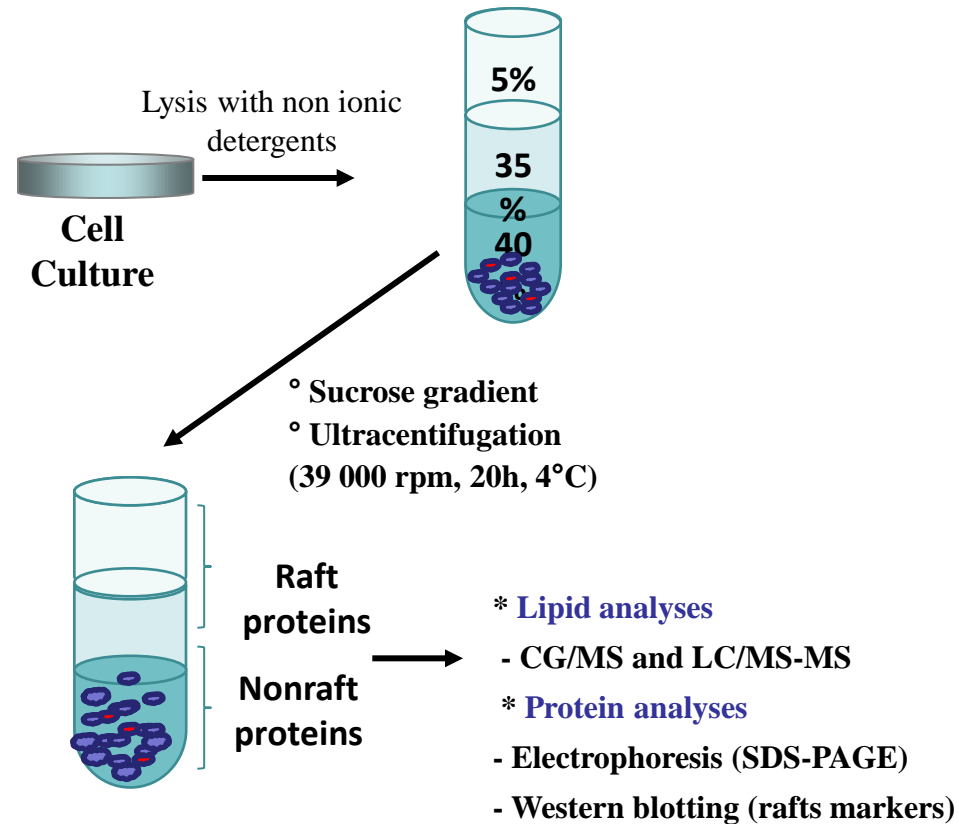
Delmas et al. Oncogene (2004)

Resveratrol, a safe molecule with health benefits

4- Resveratrol: an inducer of apoptosis

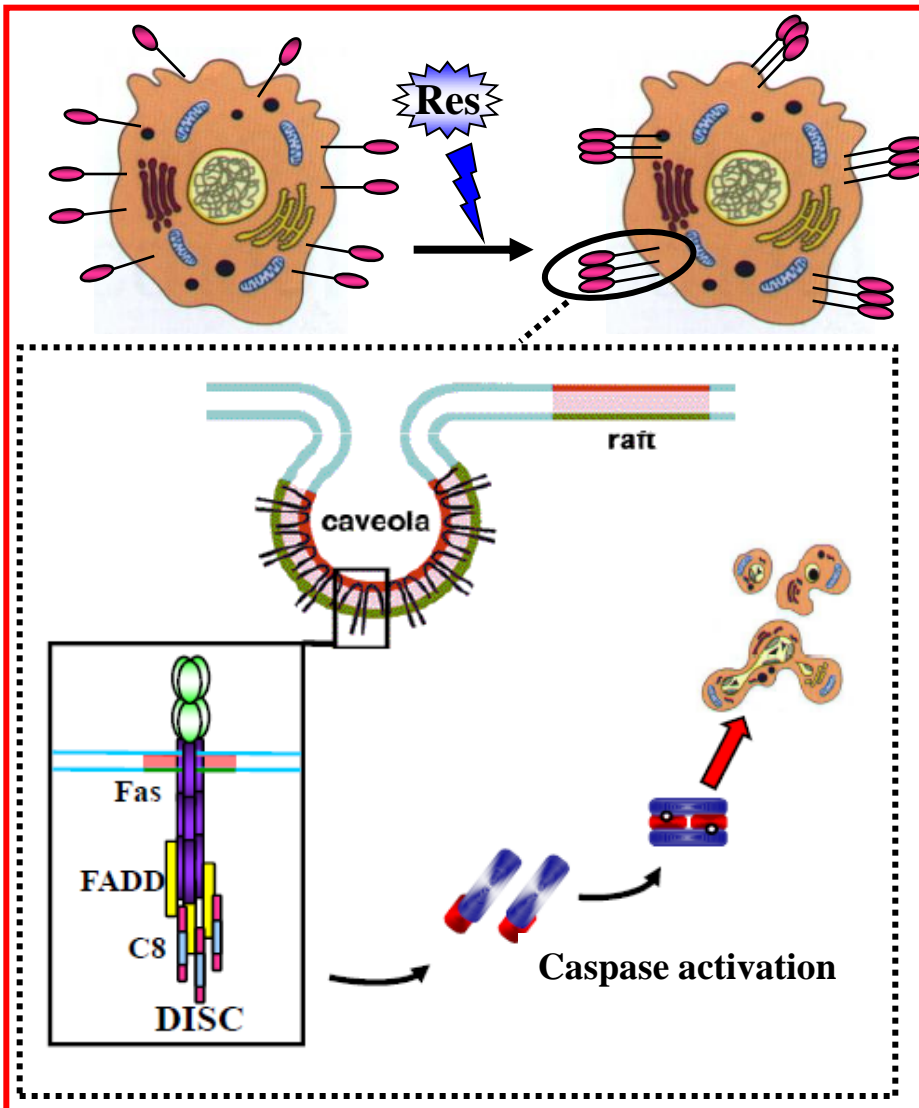


- Resveratrol induces death receptors redistribution into lipid rafts

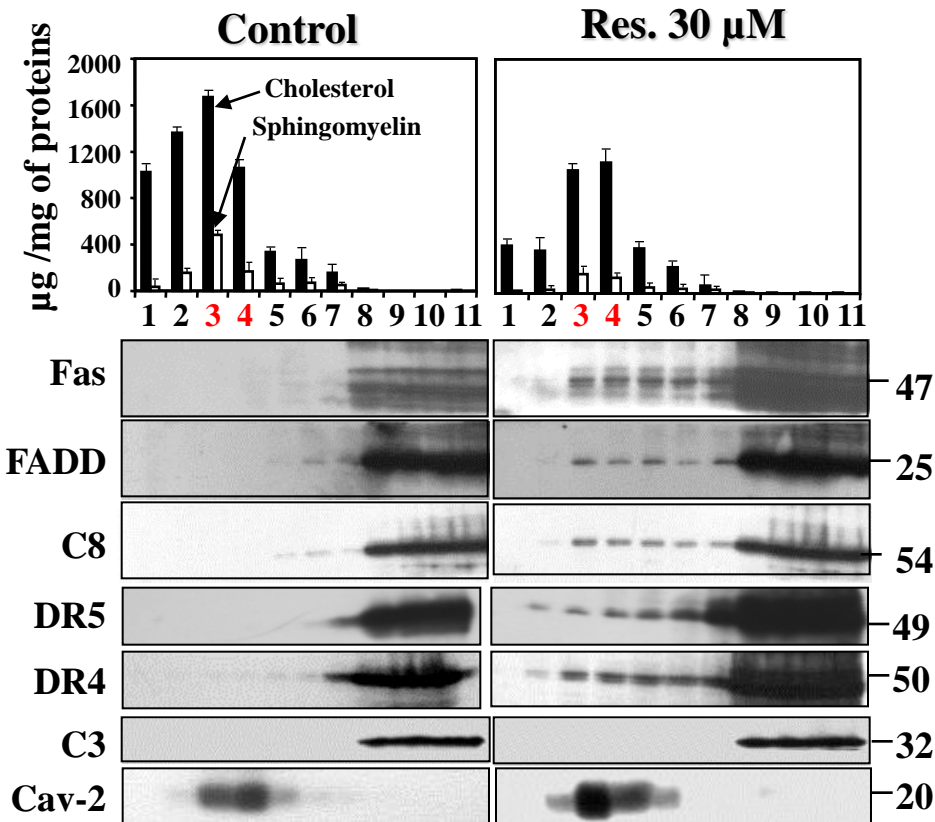


Resveratrol, a safe molecule with health benefits

4- Resveratrol: an inducer of apoptosis



■ Resveratrol induces DISC proteins redistribution into rafts

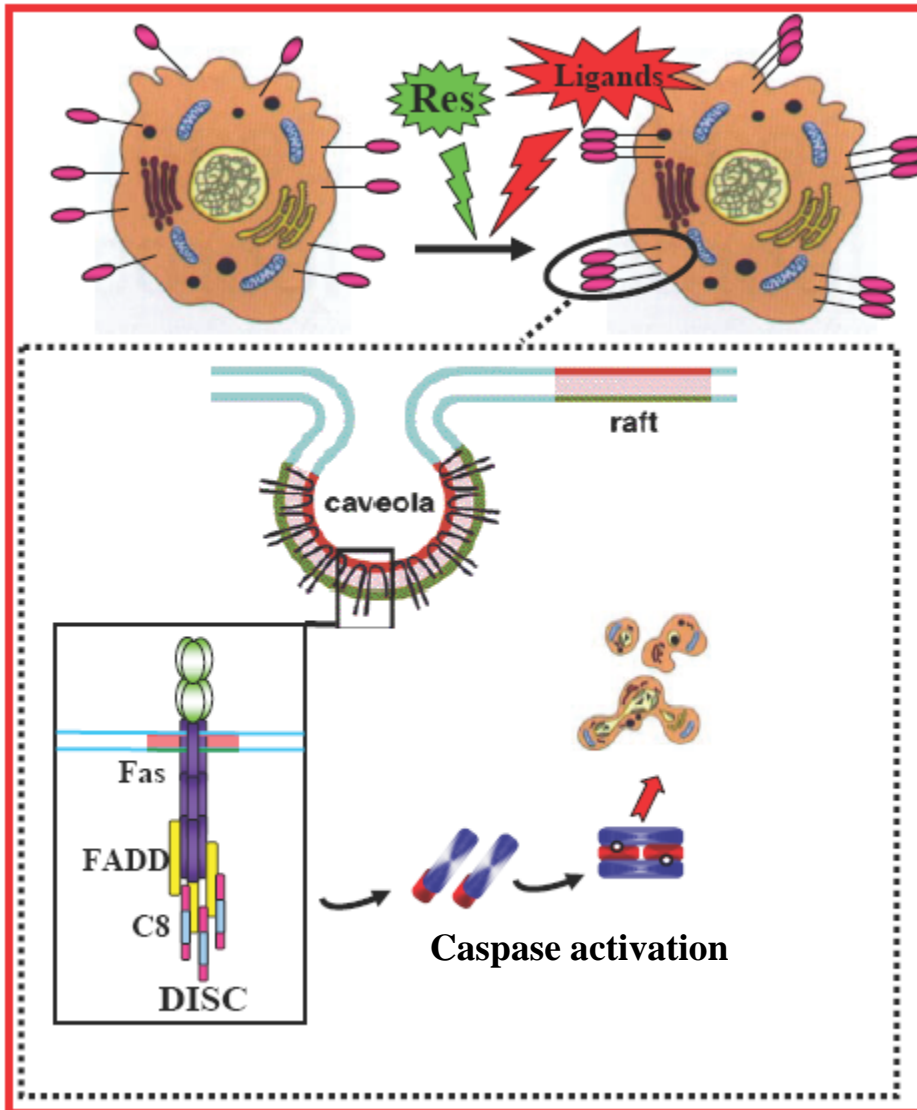


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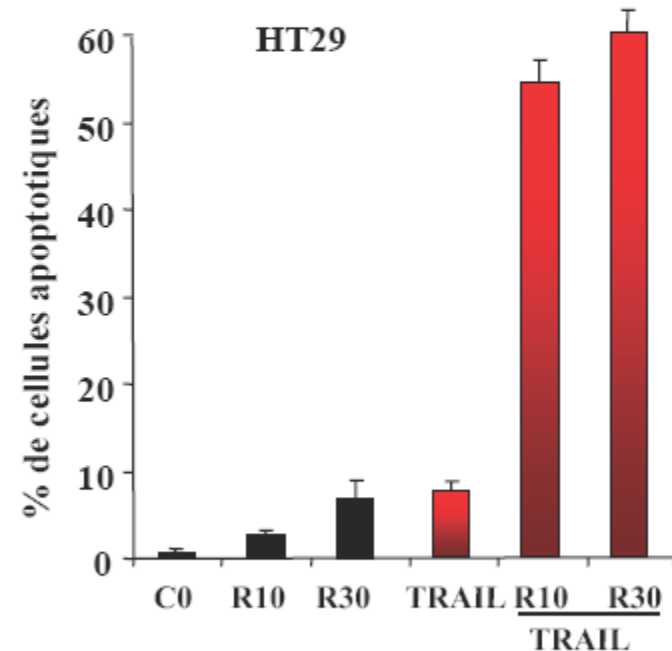
Delmas et al. Oncogene (2004)

Resveratrol, a safe molecule with health benefits

5- Resveratrol: a chemosensitizer *via* lipid rafts

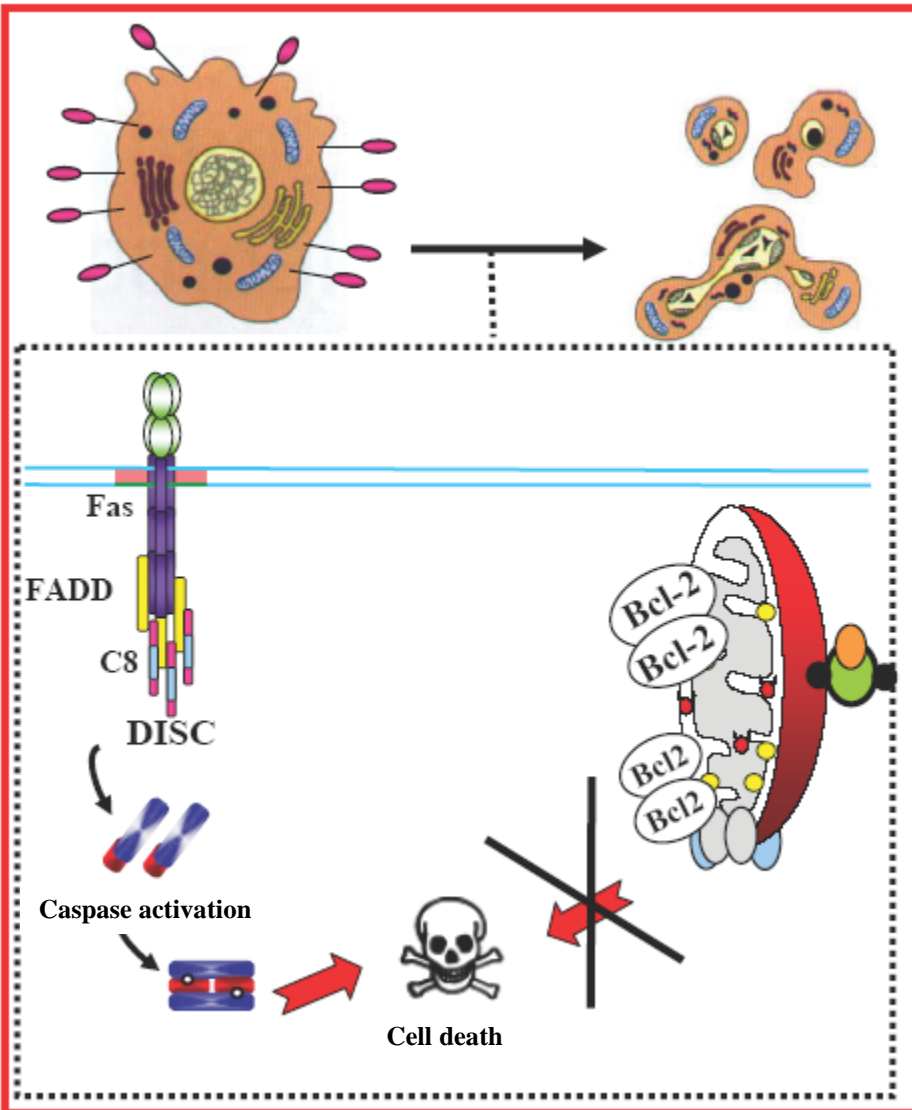


- Resveratrol sensitizes colon cancer cells to death receptor agonists-mediated apoptosis

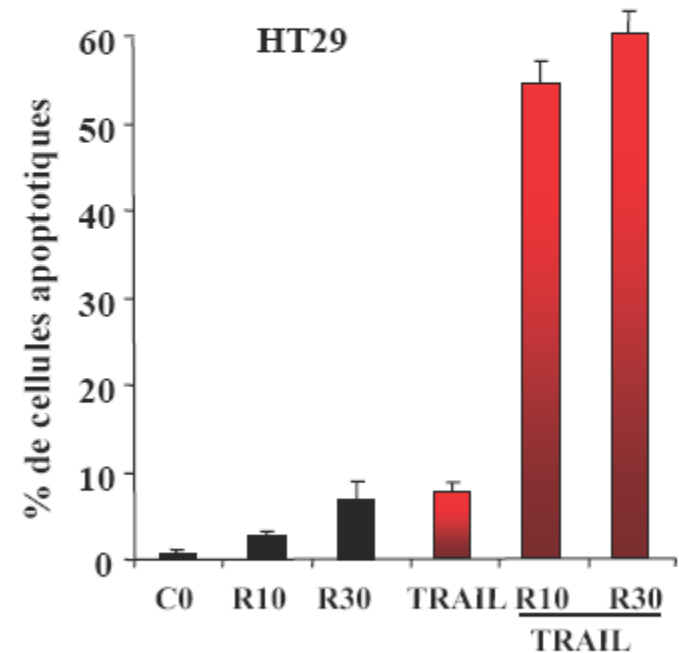


Resveratrol, a safe molecule with health benefits

5- Resveratrol: a chemosensitizer *via* lipid rafts



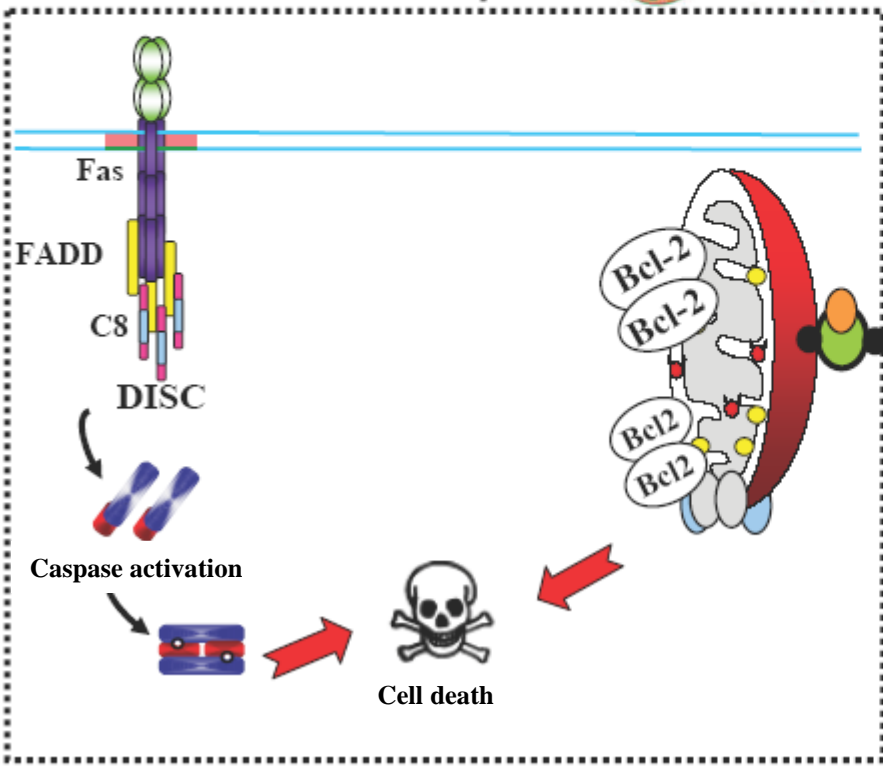
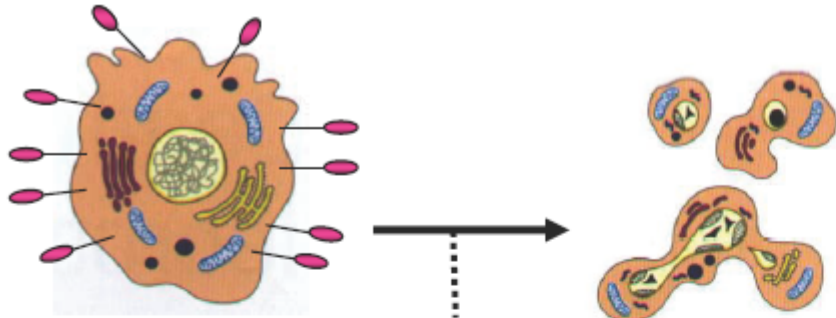
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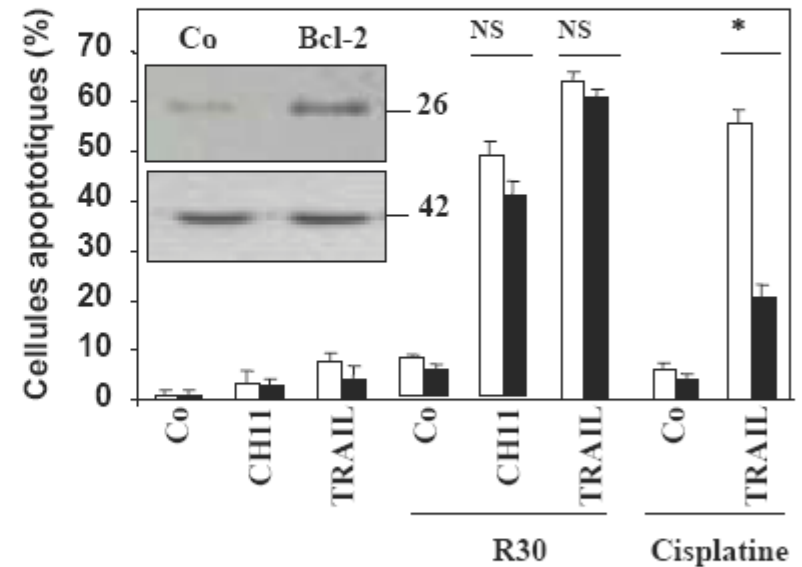
Delmas et al. Oncogene (2004)

Resveratrol, a safe molecule with health benefits

5- Resveratrol: a chemosensitizer *via* lipid rafts

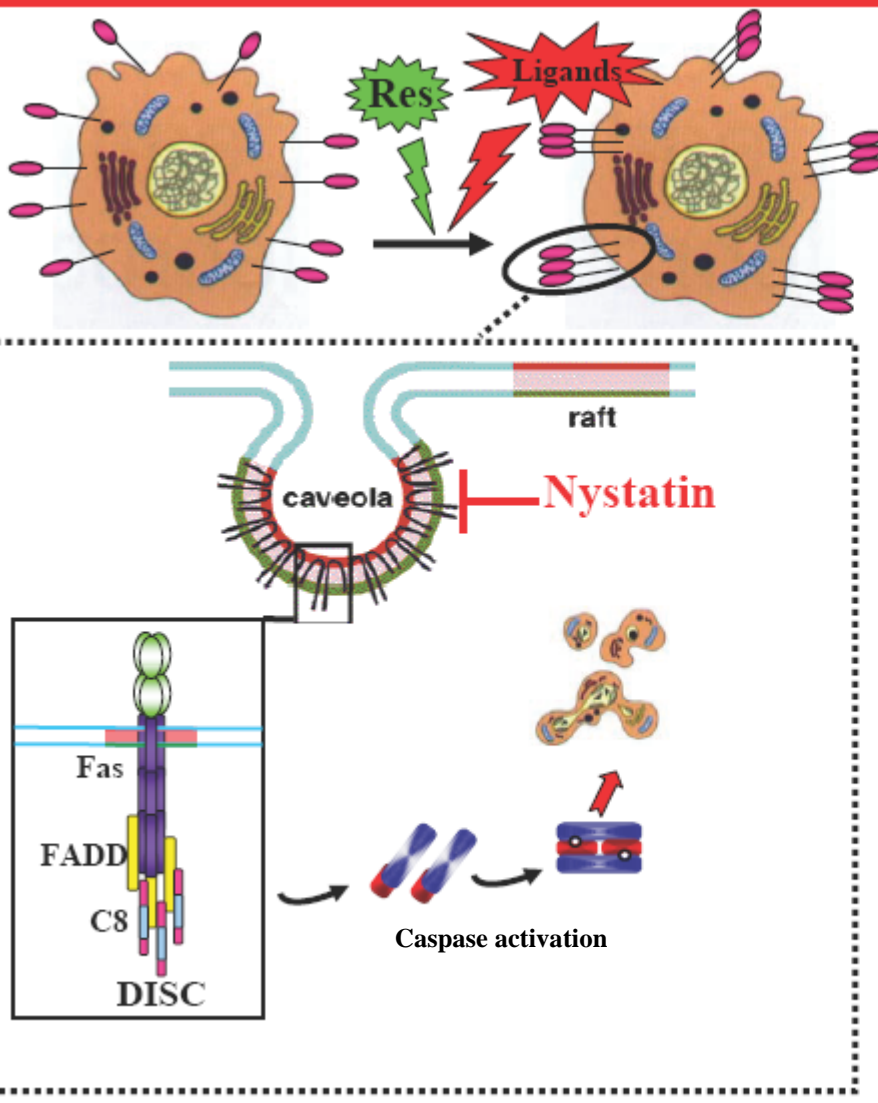


- Resveratrol / death receptor agonists combination overcome Bcl-2 resistance in colon cancer cells

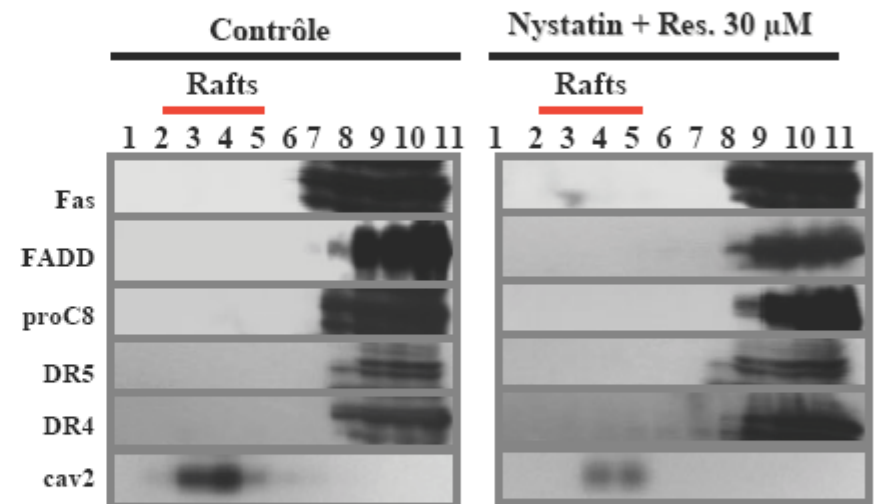


Resveratrol, a safe molecule with health benefits

5- Resveratrol: a chemosensitizer *via* lipid rafts

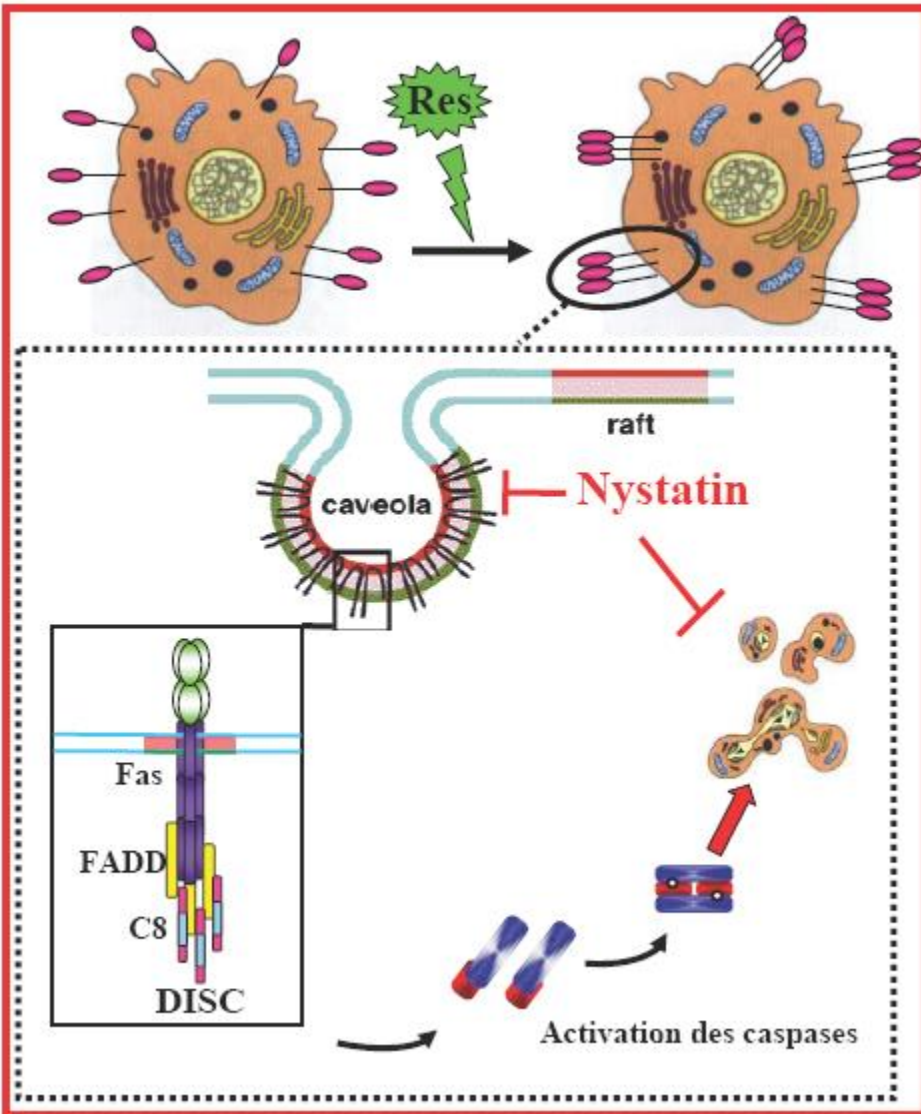


- Nystatin prevents death receptors redistribution into rafts and resveratrol-induced apoptosis

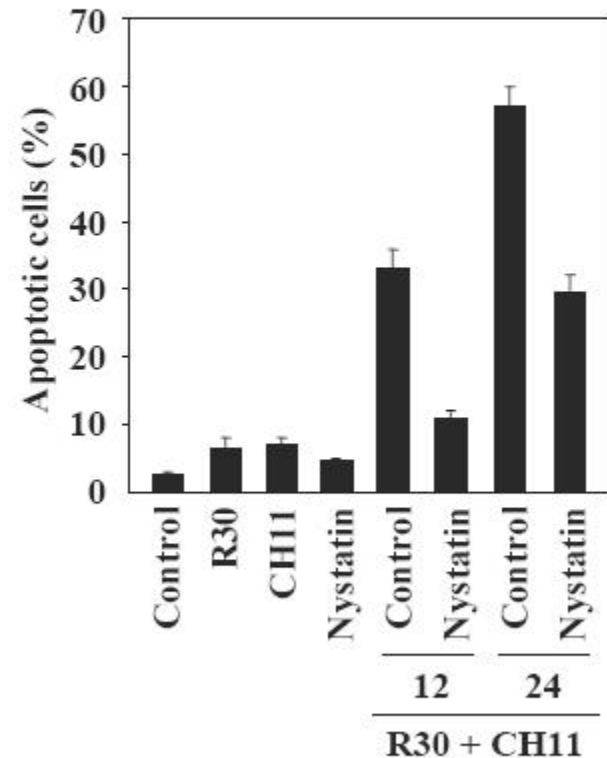


Resveratrol, a safe molecule with health benefits

5- Resveratrol: a chemosensitizer *via* lipid rafts



- Nystatin prevents death receptors redistribution into rafts and resveratrol-induced apoptosis

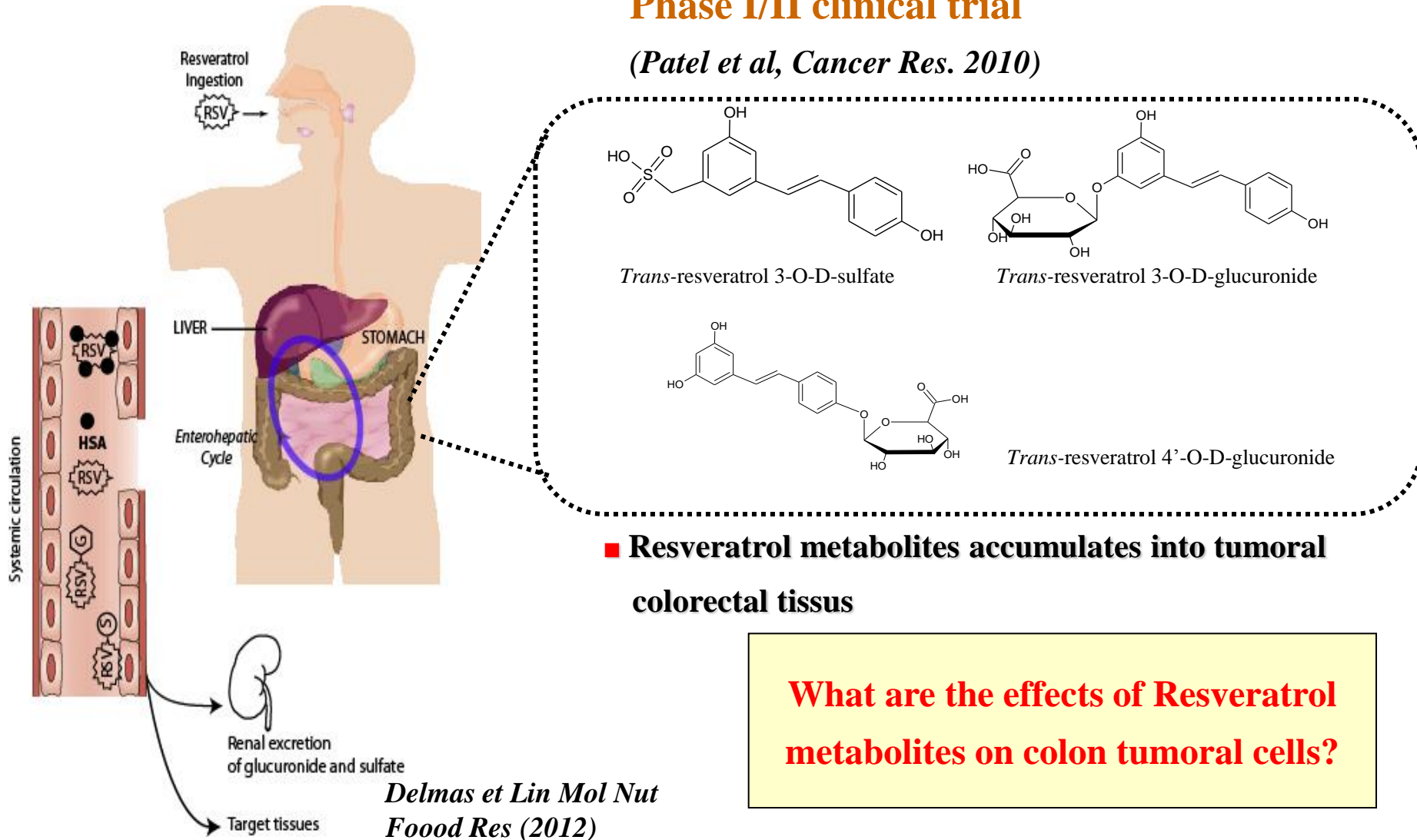


Resveratrol, a safe molecule with health benefits

6- Pharmacology of Resveratrol and clinical trials

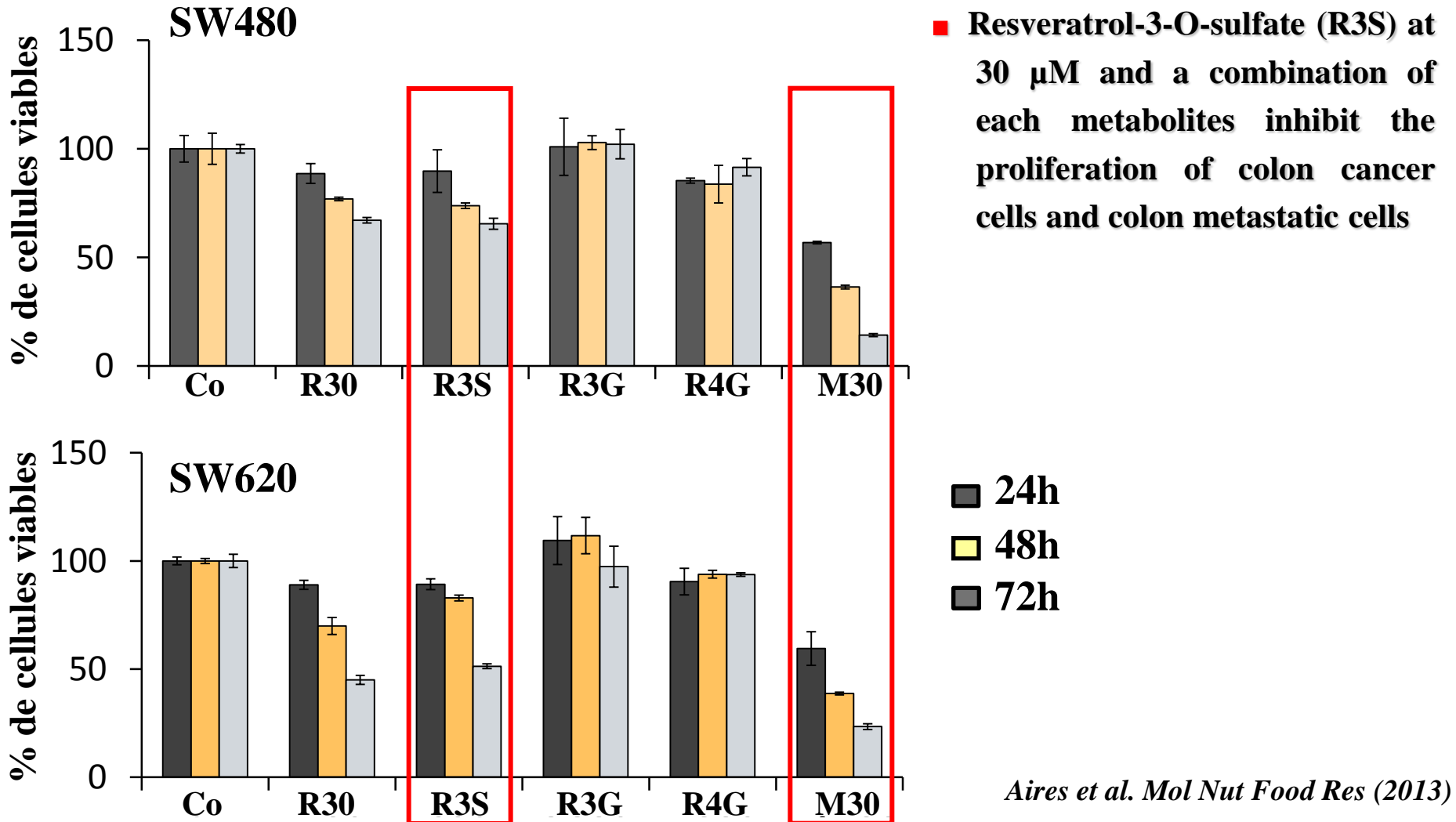
Phase I/II clinical trial

(Patel et al, Cancer Res. 2010)



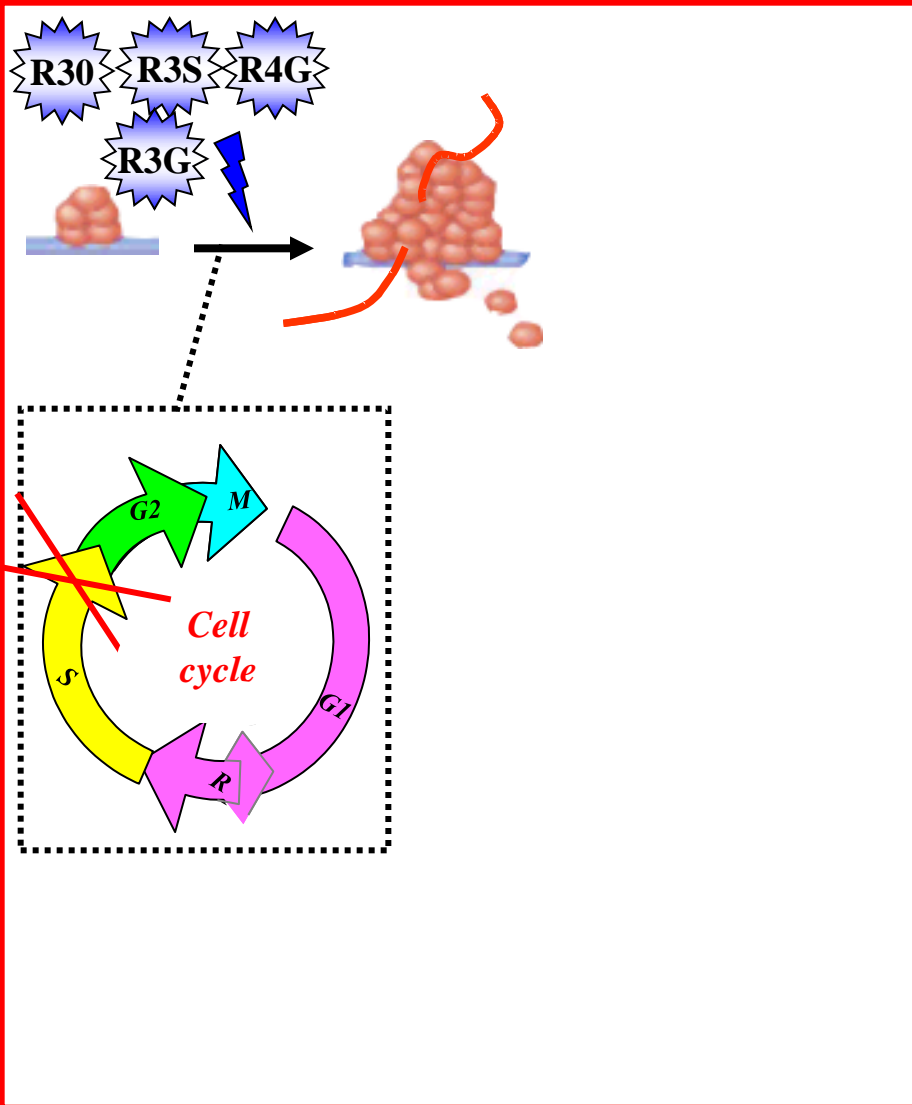
Resveratrol, a safe molecule with health benefits

7- Resveratrol & metabolites: inducers of DNA damages

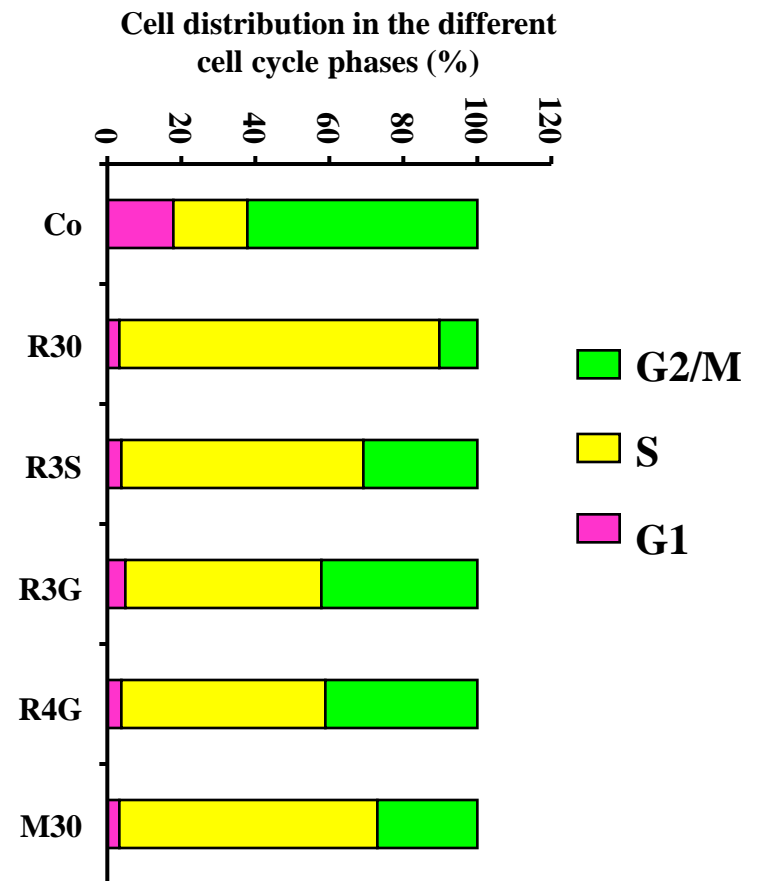


Resveratrol, a safe molecule with health benefits

7- Resveratrol & metabolites: inducers of DNA damages



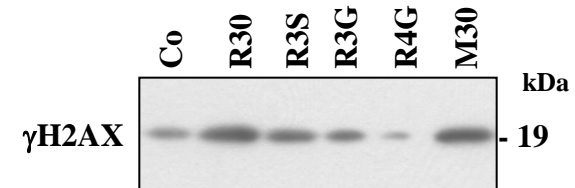
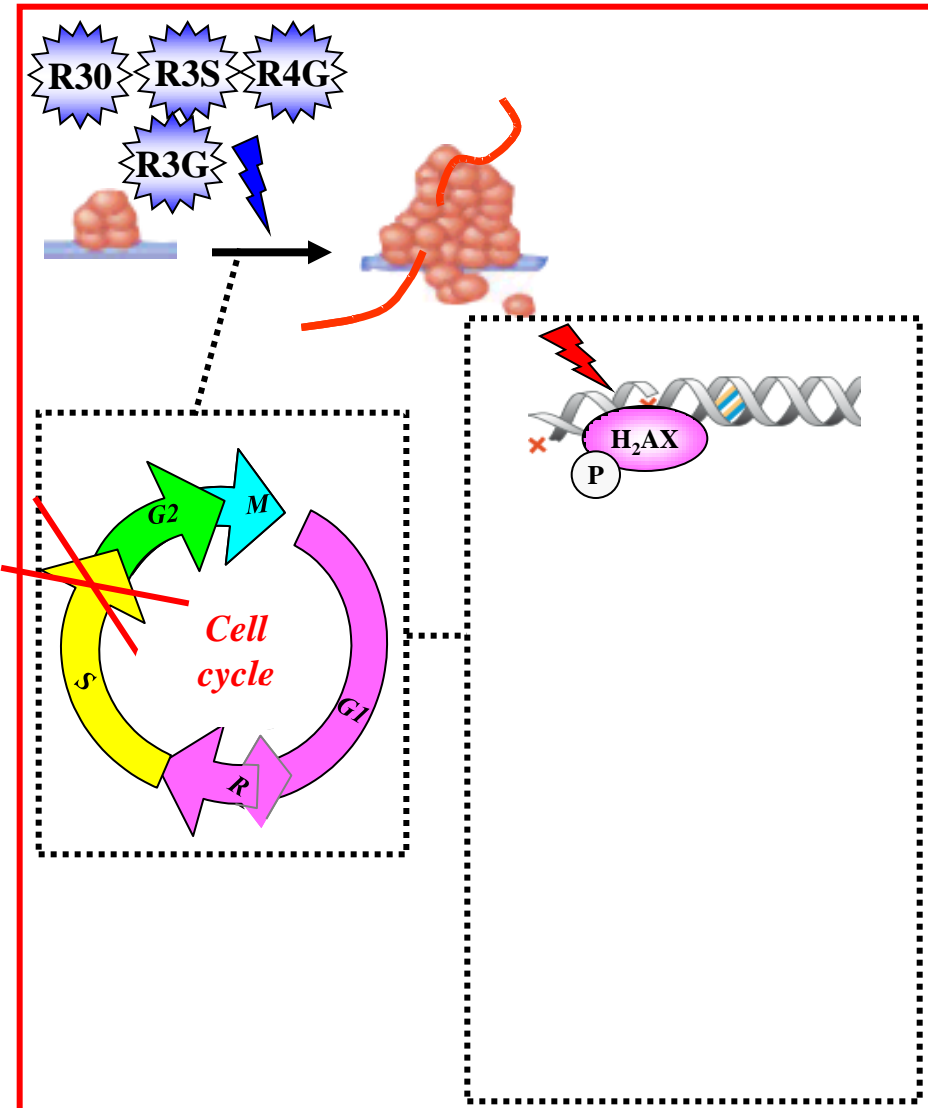
- Resveratrol metabolites accumulate colon cancer cells in S phase of the cell cycle



Resveratrol, a safe molecule with health benefits

7- Resveratrol & metabolites: inducers of DNA damages

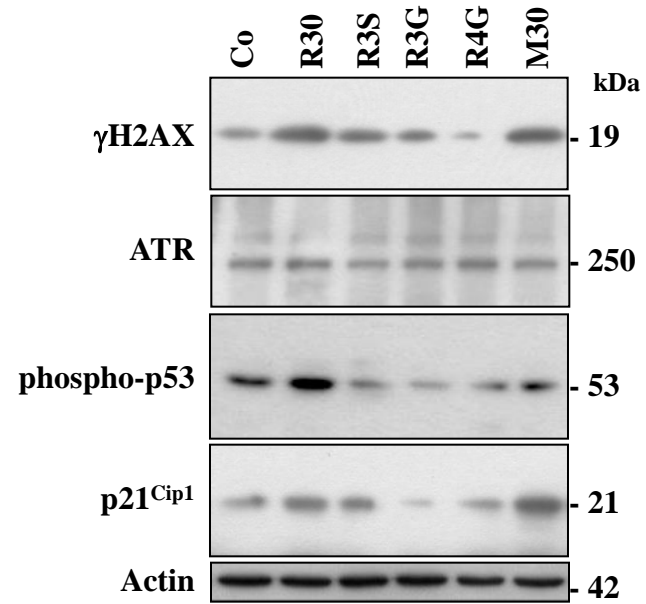
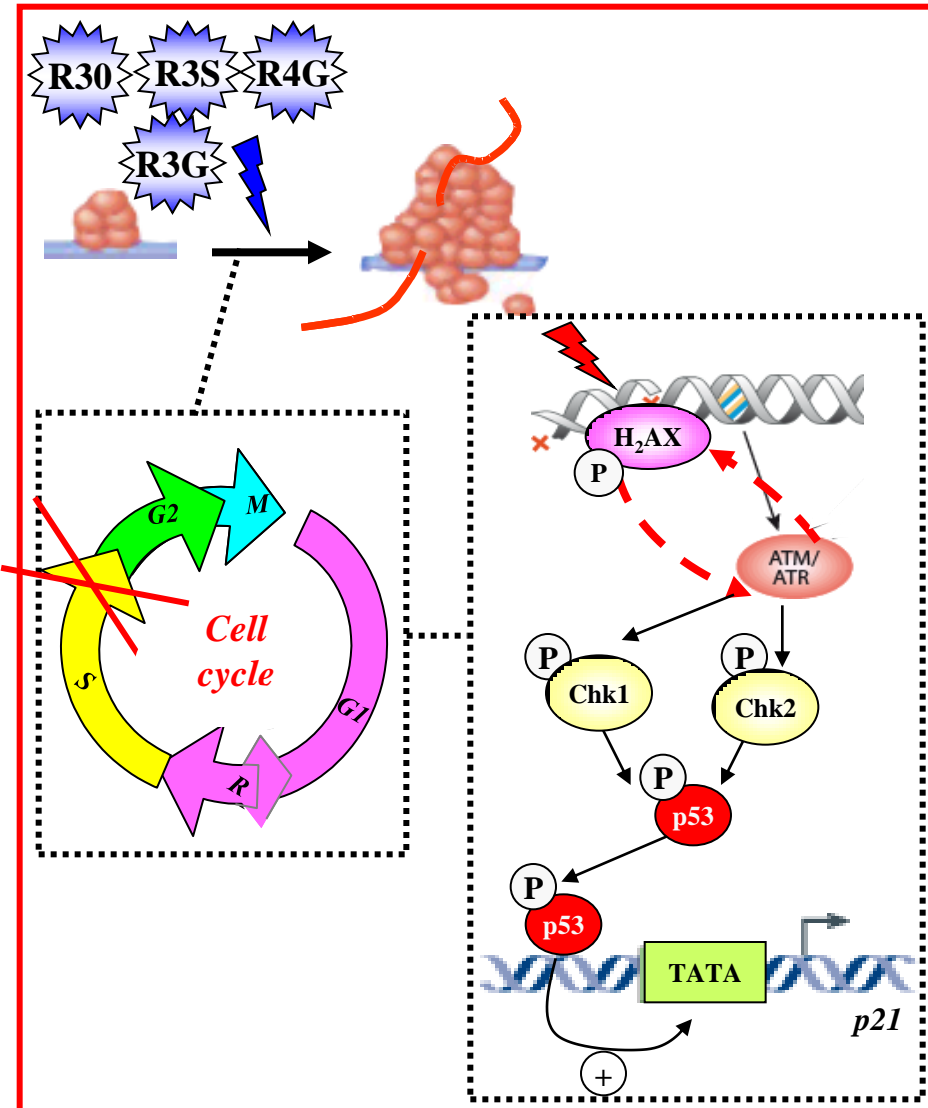
- Resveratrol sulfate and the combination of each metabolites induce DNA damages in colon cancer cells



Resveratrol, a safe molecule with health benefits

7- Resveratrol & metabolites: inducers of DNA damages

- Resveratrol sulfate and the combination of each metabolites induce DNA damages in colon cancer cells

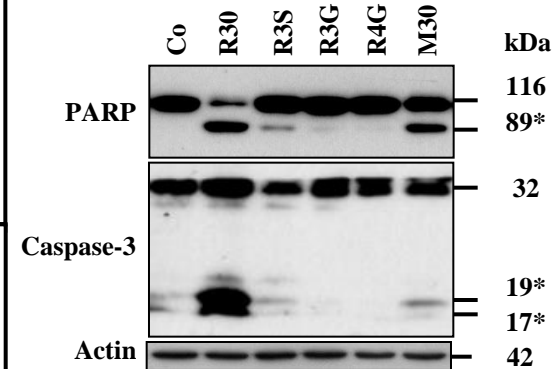
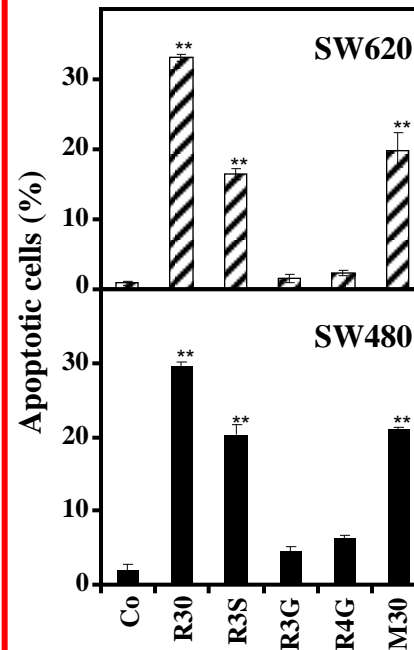
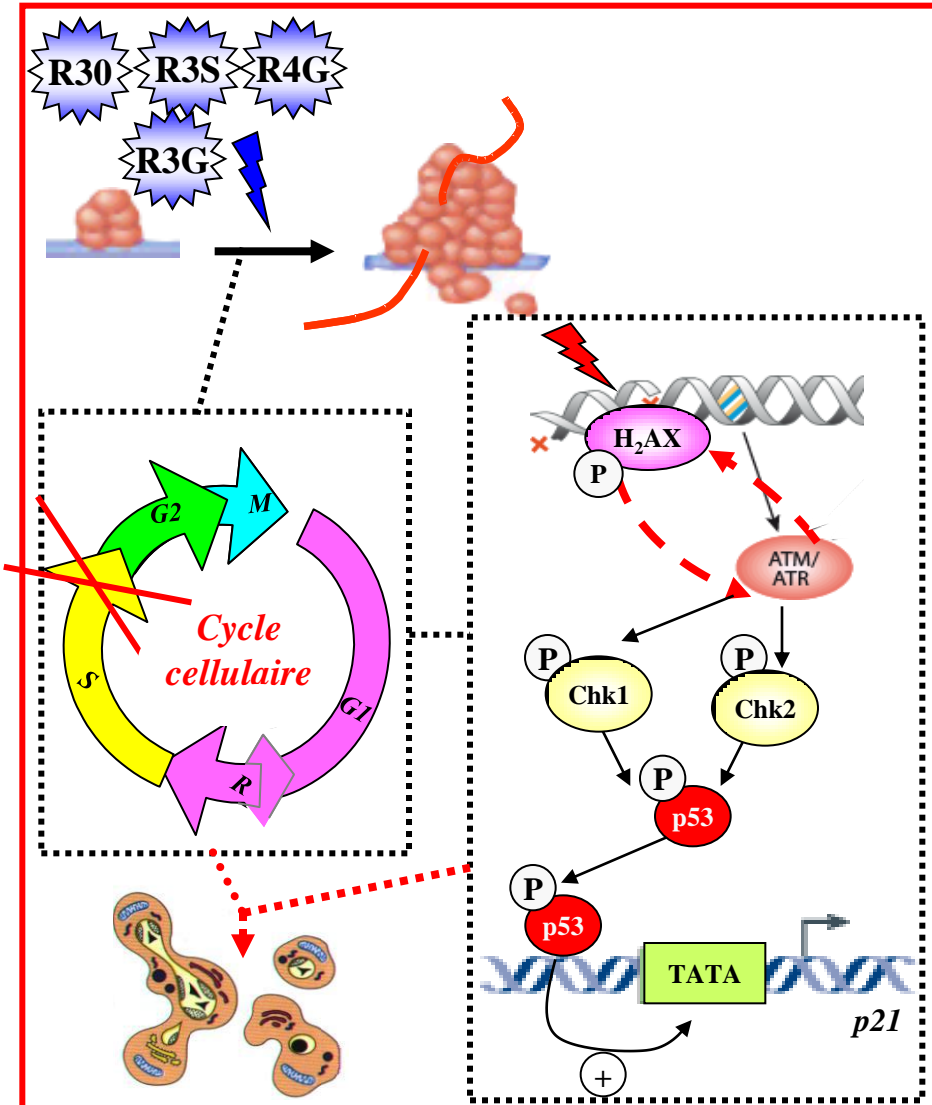


Aires et al. Mol Nut Food Res (2013)
Colin et al. Cell Death & Diseases (2014)

Resveratrol, a safe molecule with health benefits

7- Resveratrol & metabolites: inducers of DNA damages

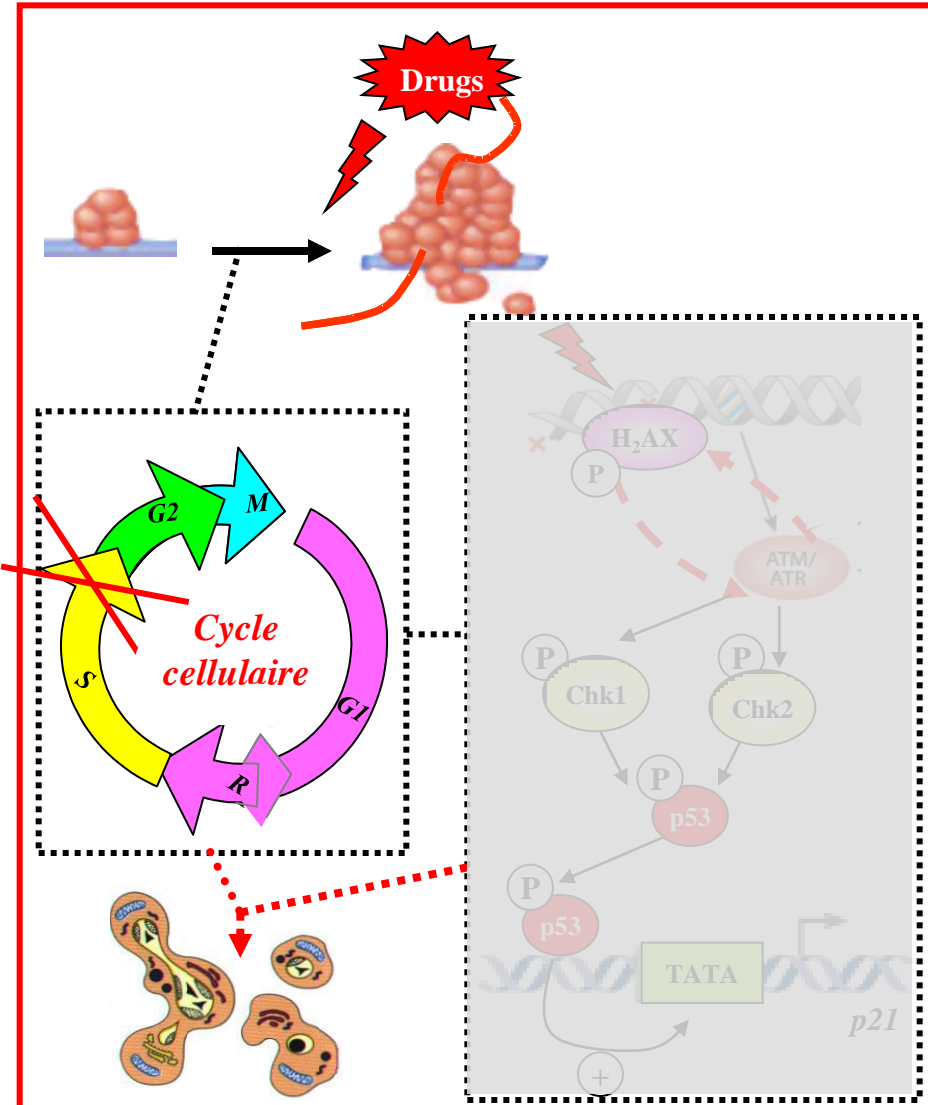
- Resveratrol sulfate and the combination of each metabolites induce apoptosis of colon tumoral cells



Aires et al. Mol Nut Food Res (2013)
Colin et al. Cell Death & Diseases (2014)

Resveratrol, a safe molecule with health benefits

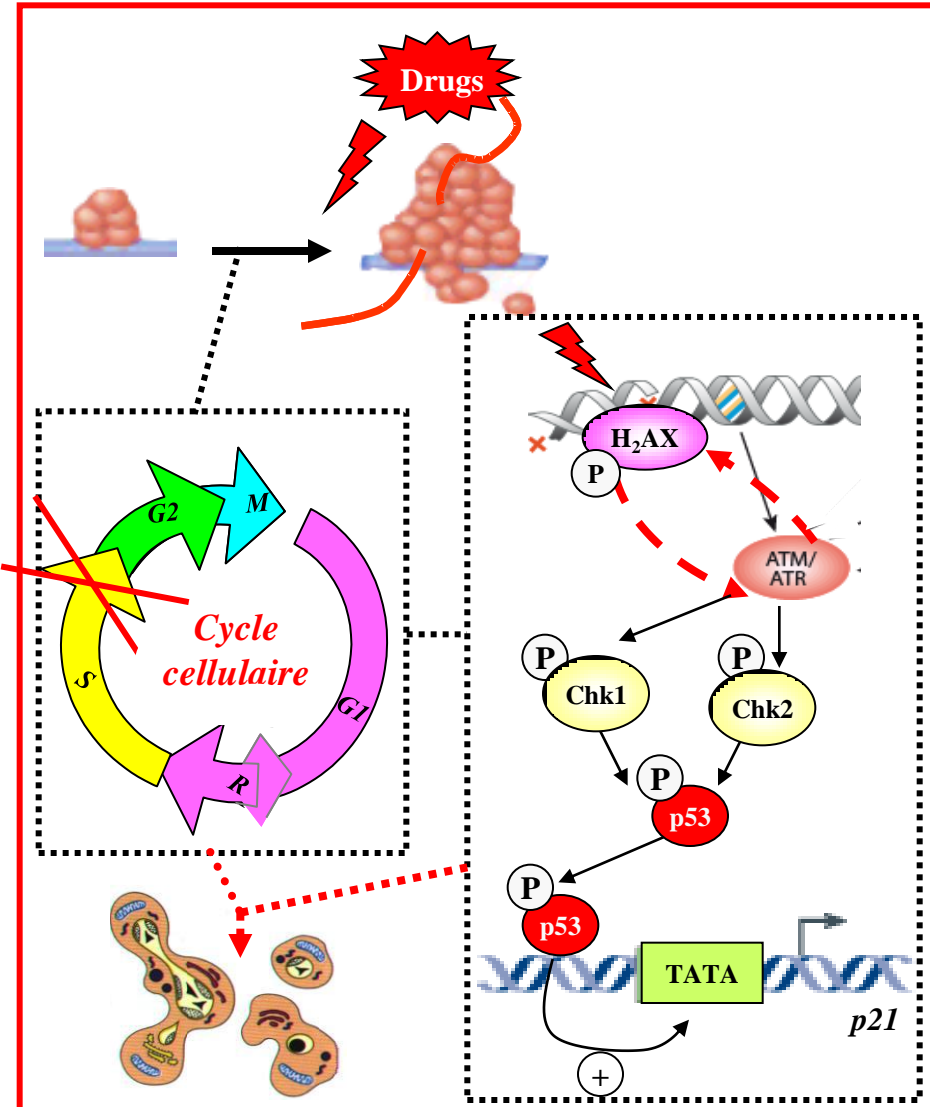
8- Resveratrol & metabolites: chemosensitizers *via* DNA damage pathway



- Colon cancer cells, especially, metastatic cells, present a huge reduction of DNA double strand breaks formation compared to sensitive cells

Resveratrol, a safe molecule with health benefits

8- Resveratrol & metabolites: chemosensitizers *via* DNA damage pathway

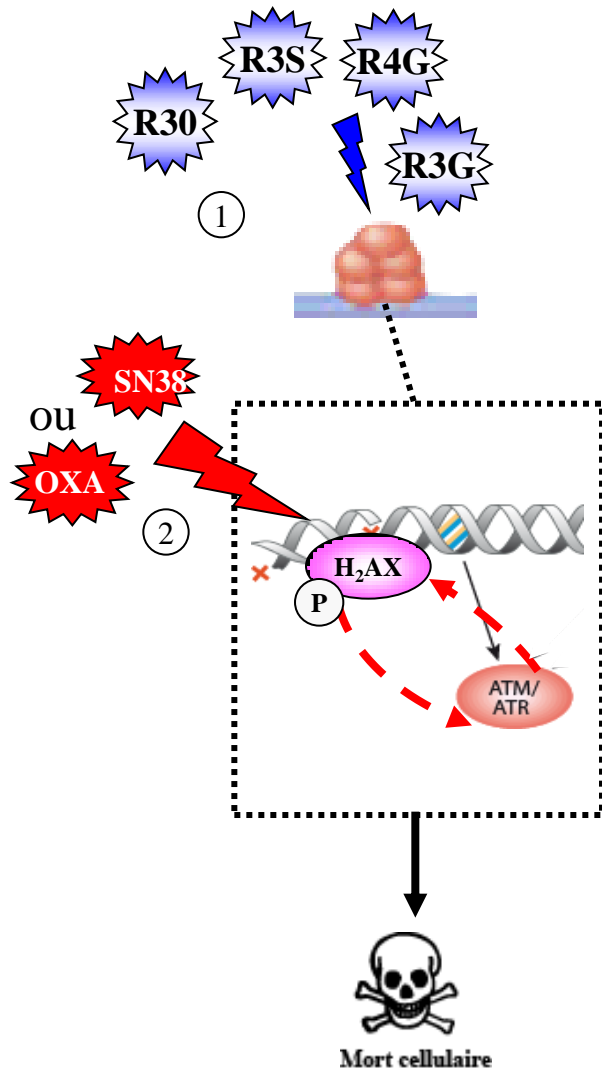


- Colon cancer cells, especially, metastatic cells, present a huge reduction of DNA double strand breaks formation compared to sensitive cells

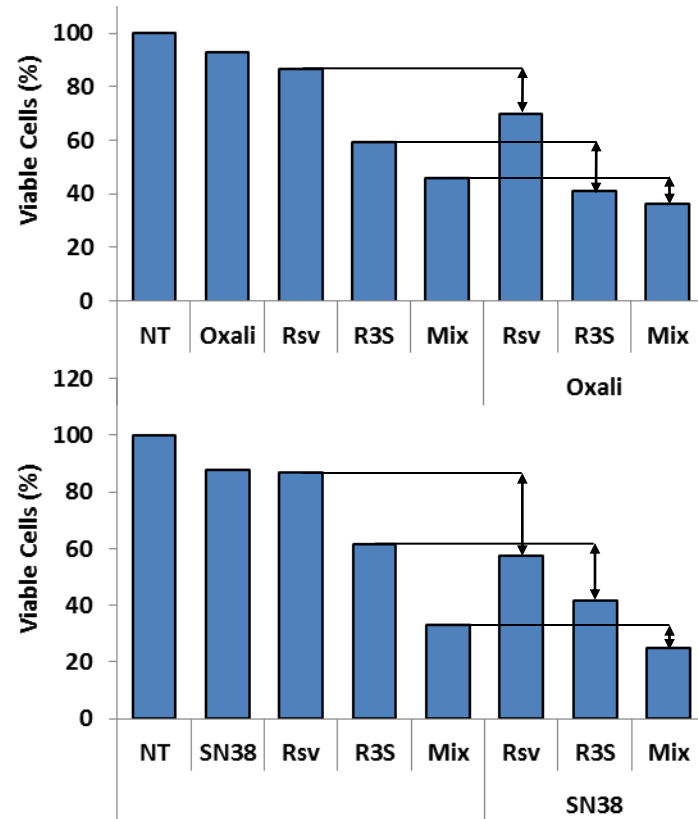
Resveratrol metabolites could sensitize colon metastatic cells to anticancer agents inducing DNA damages ?

Resveratrol, a safe molecule with health benefits

8- Resveratrol & metabolites: chemosensitizers *via* DNA damage pathway



- Resveratrol metabolites sensitize colon metastatic cells to death induced by SN38 and oxaliplatin



Resveratrol, a safe molecule with health benefits

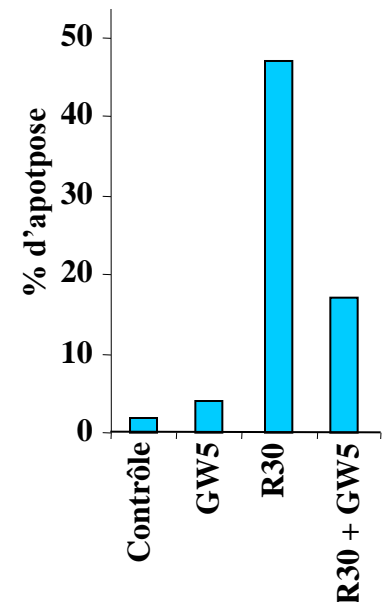
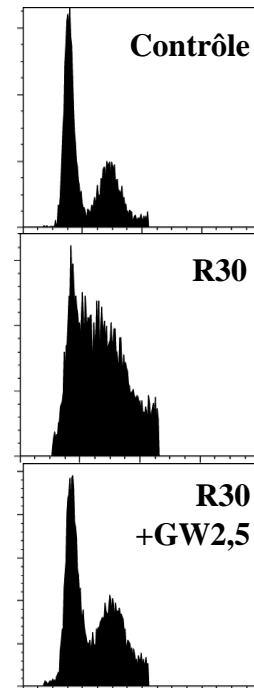
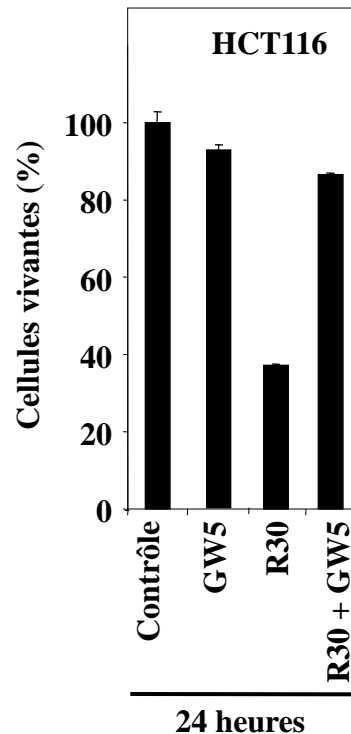
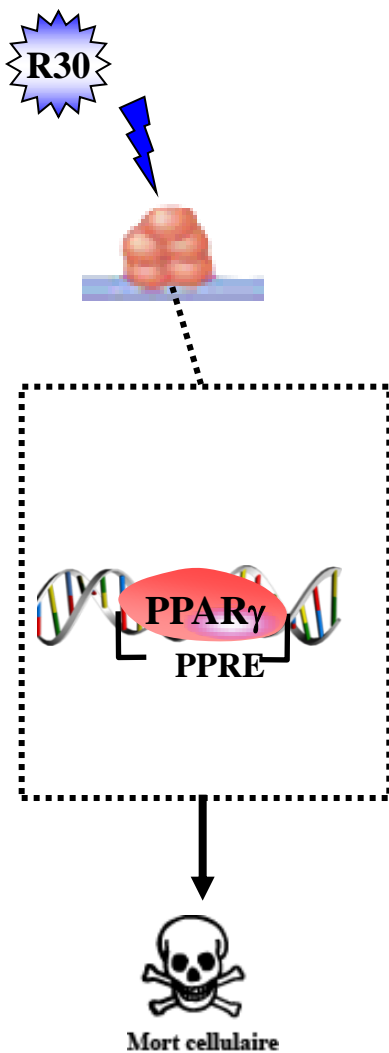
9- Resveratrol: an agonist of Peroxisome Proliferator Activated Receptor ($\text{PPAR}\gamma$)

■ GW a $\text{PPAR}\gamma$ antagonist decreases resveratrol effects:

- restoration of cell proliferation

- prevents cell cycle disruption

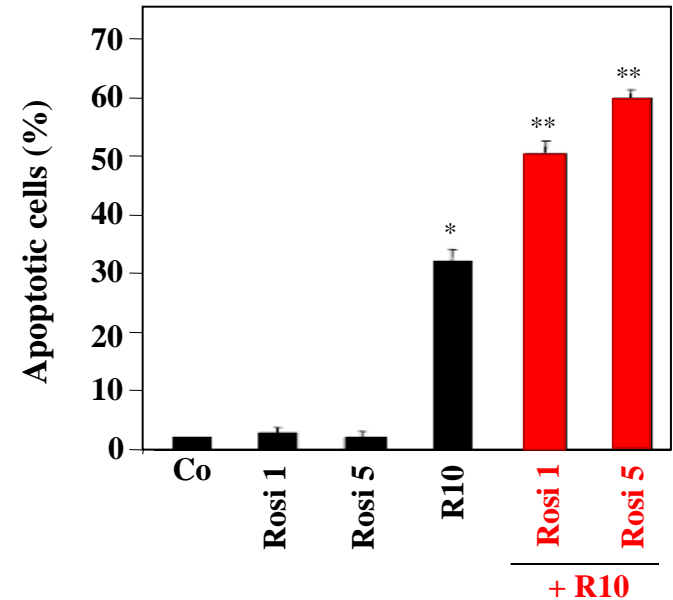
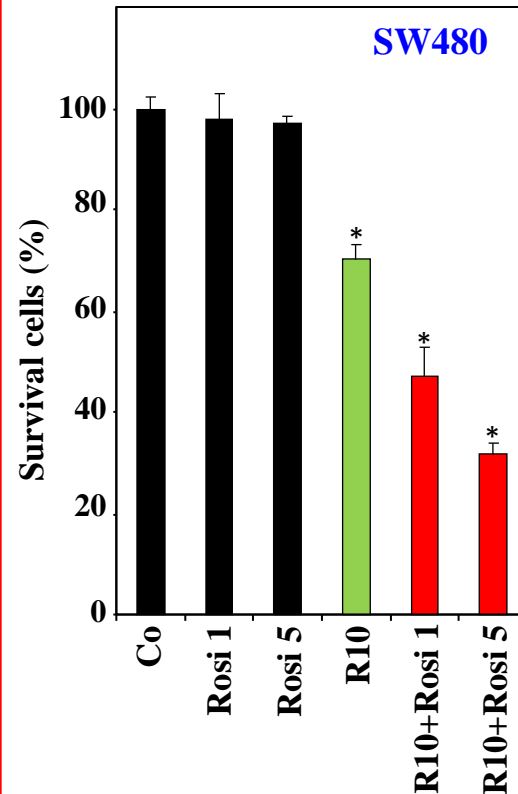
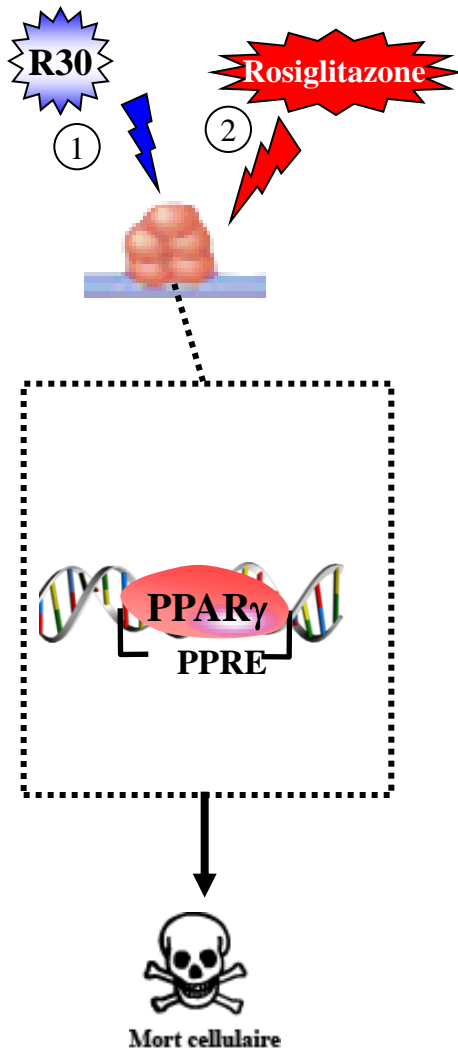
- prevents apoptosis induction



Resveratrol, a safe molecule with health benefits

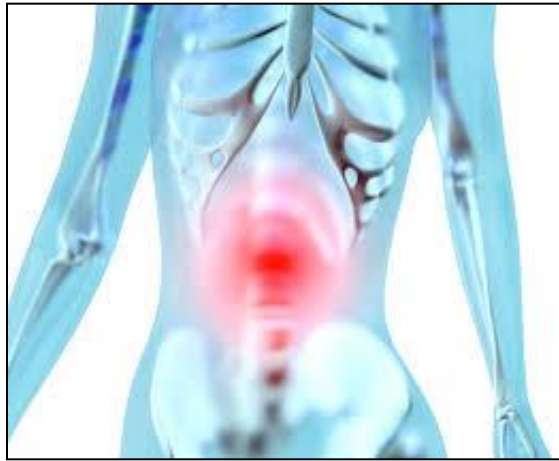
10- Resveratrol: a chemosensitizer with an agonist of PPAR γ

■ Resveratrol synergizes with Rosiglitazone to kill tumoral cells



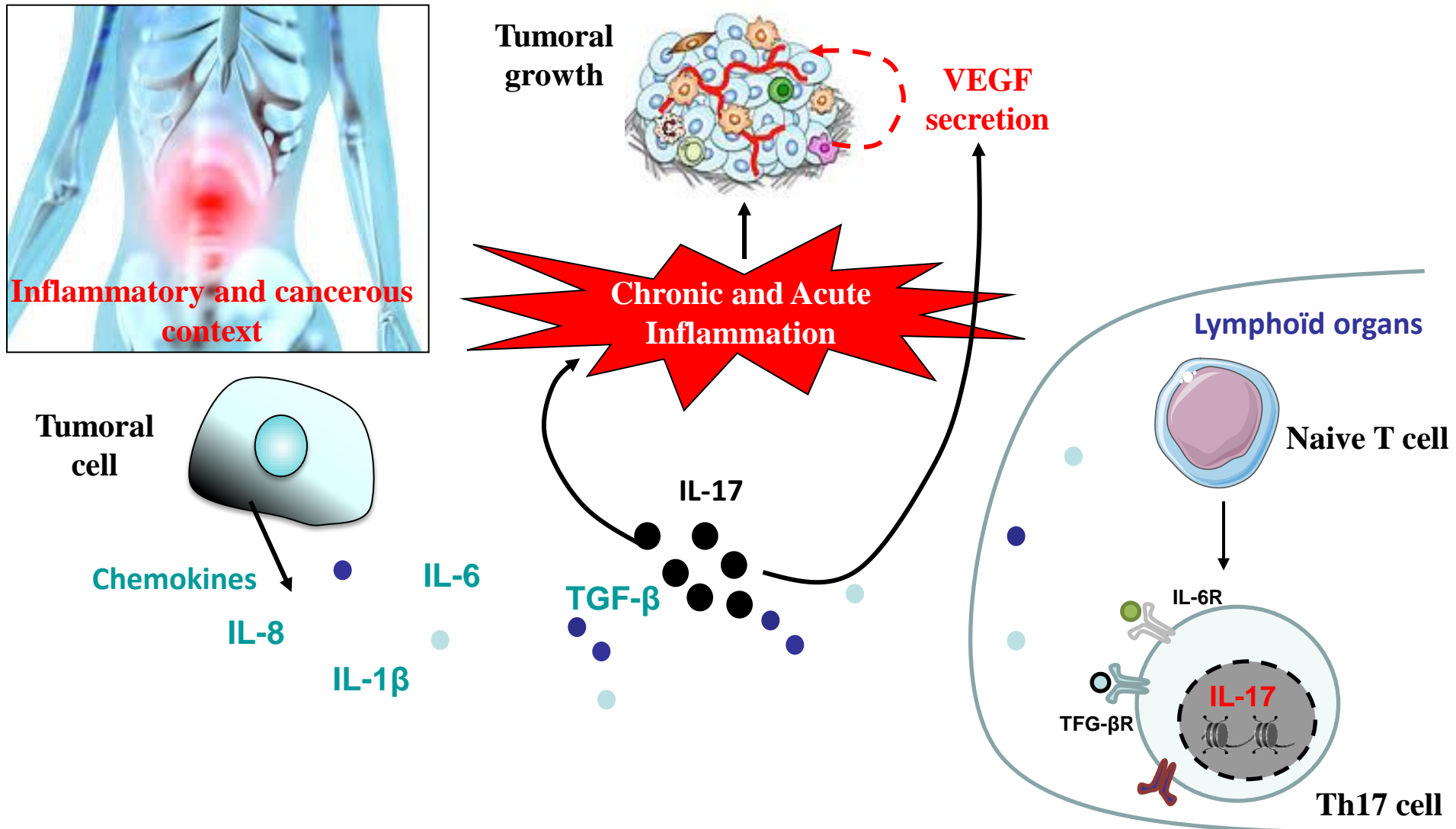
Resveratrol, a safe molecule with health benefits

11- Resveratrol: a modulator of the immune system



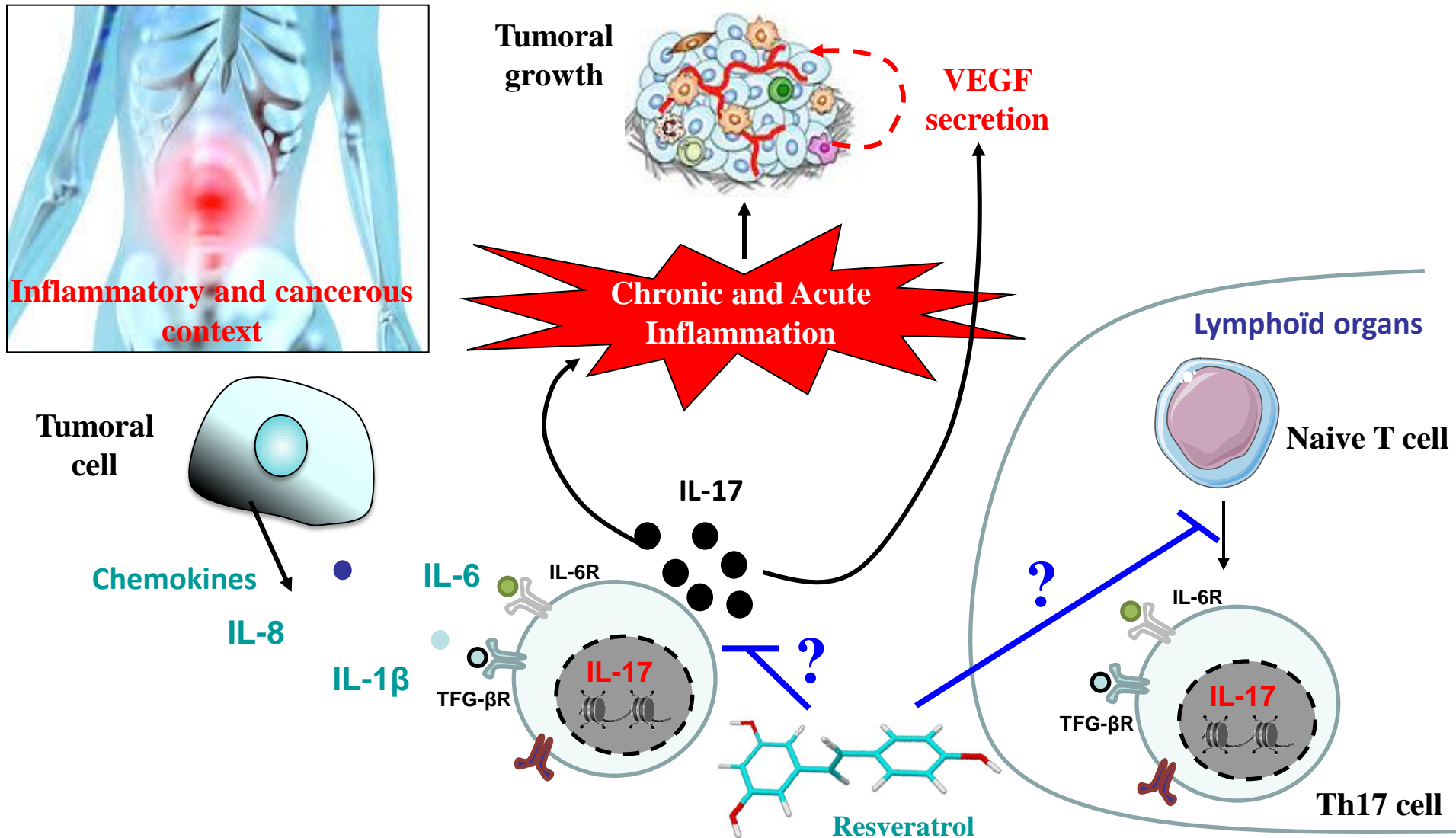
Resveratrol, a safe molecule with health benefits

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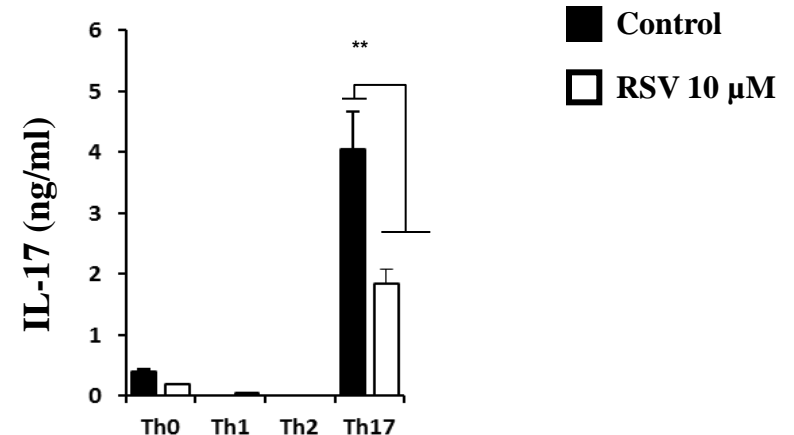
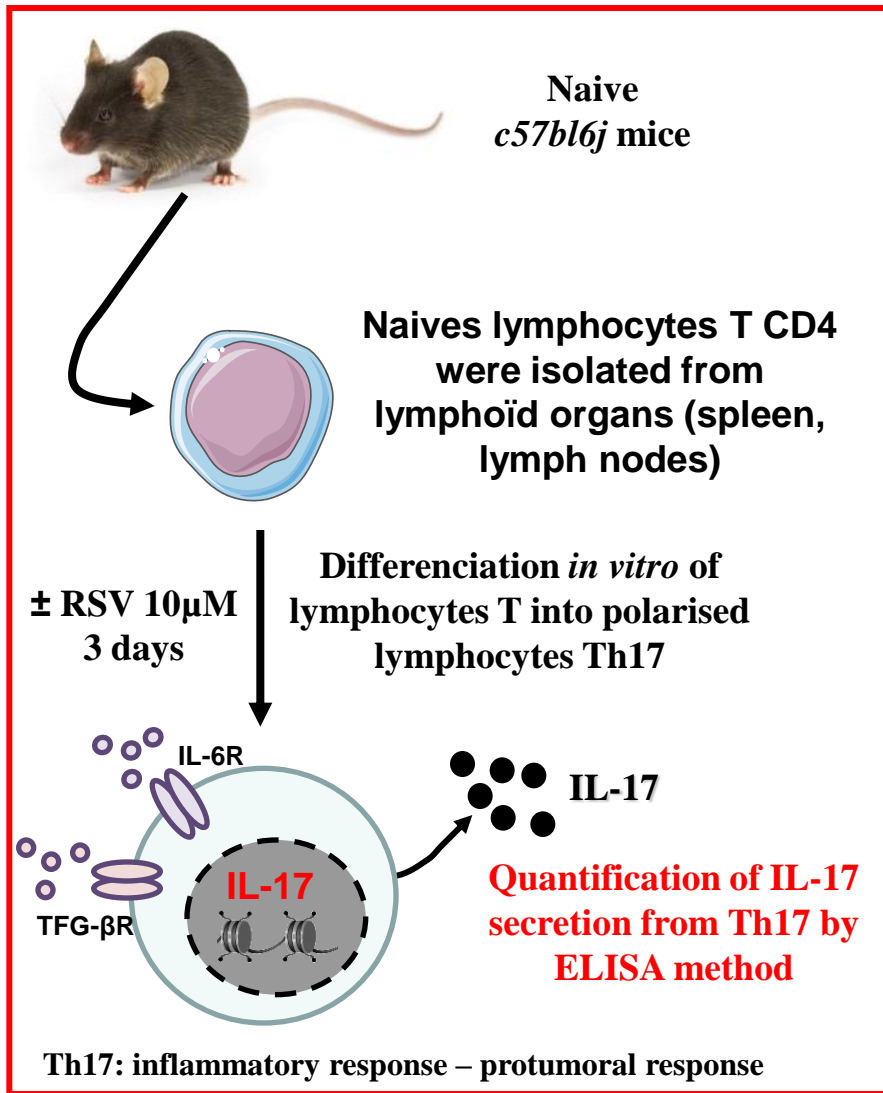
11- Resveratrol: a modulator of the immune system



Resveratrol, a safe molecule with health benefits

11- Resveratrol: a modulator of the immune system

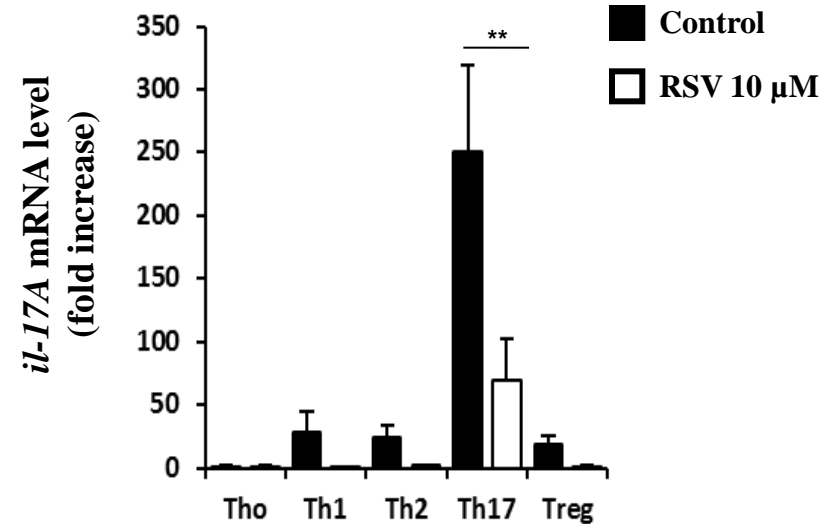
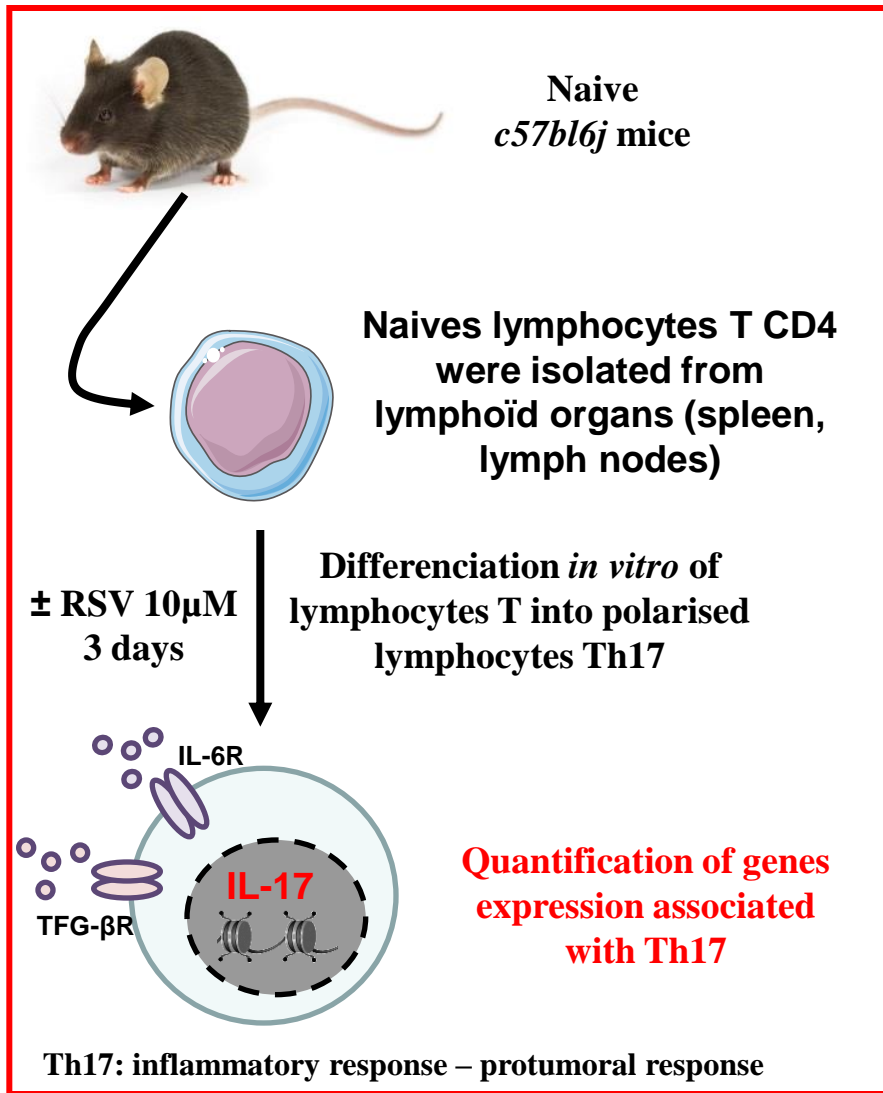
- Resveratrol (RSV) decreases IL-17 production from Th17 lymphocytes



Resveratrol, a safe molecule with health benefits

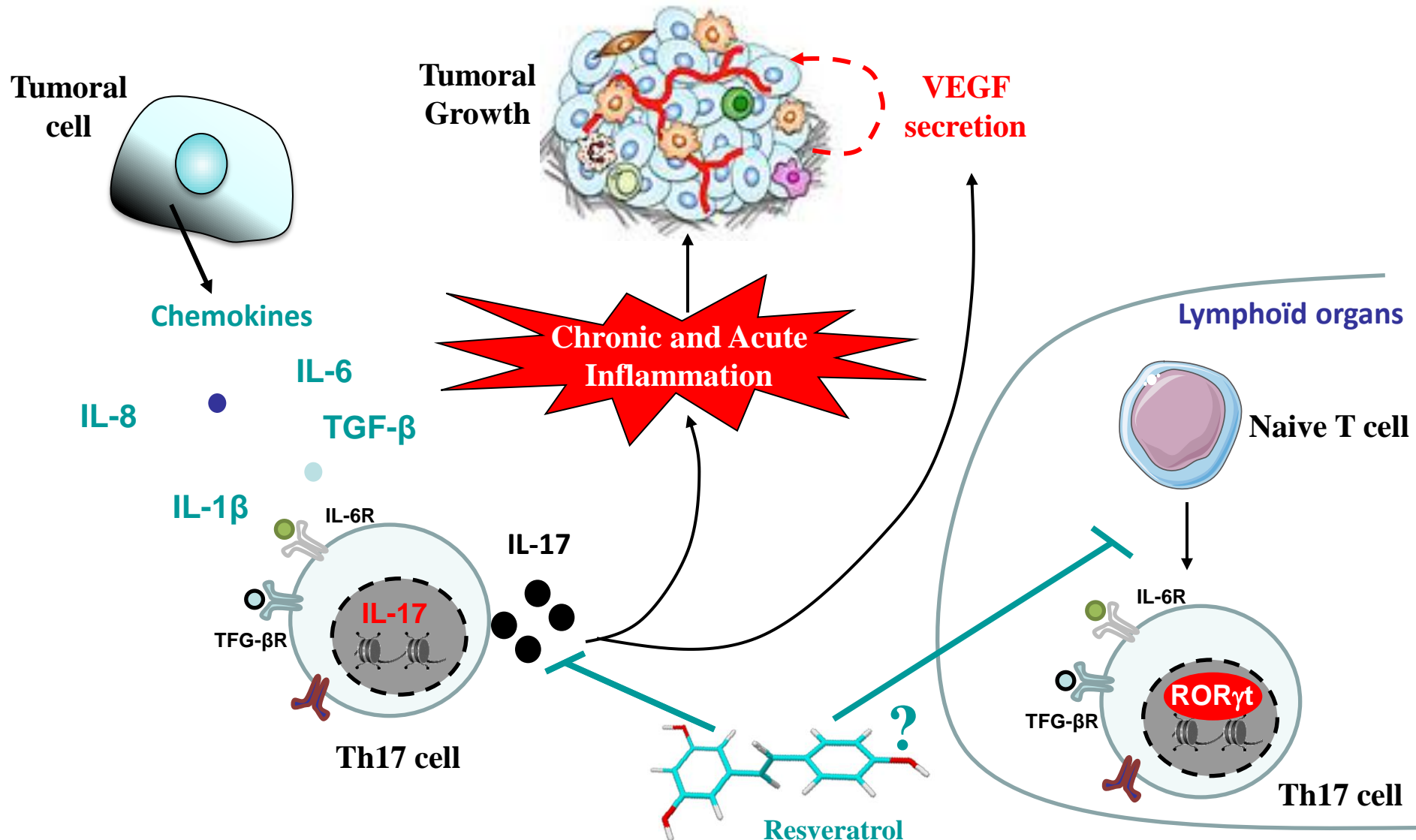
11- Resveratrol: a modulator of the immune system

- Resveratrol (RSV) decreases *il-17A* mRNA levels into Th17 lymphocytes



Resveratrol, a safe molecule with health benefits

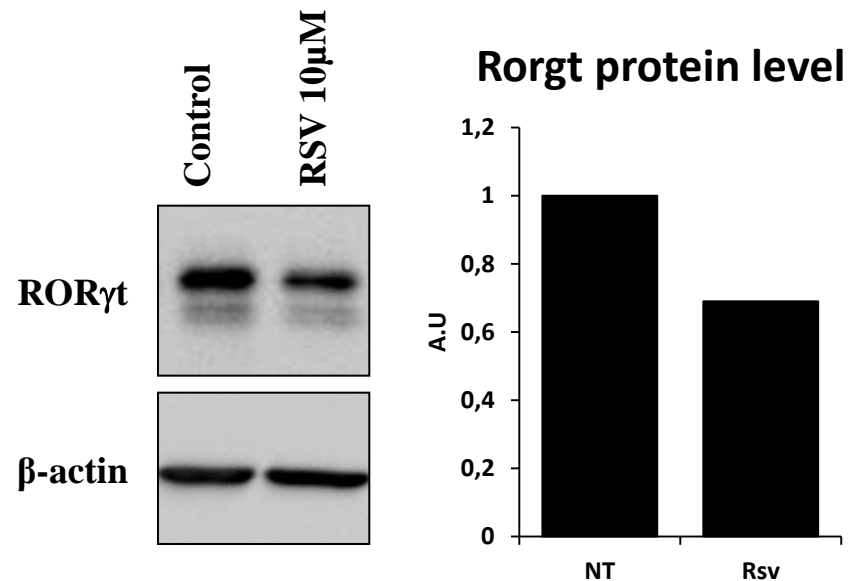
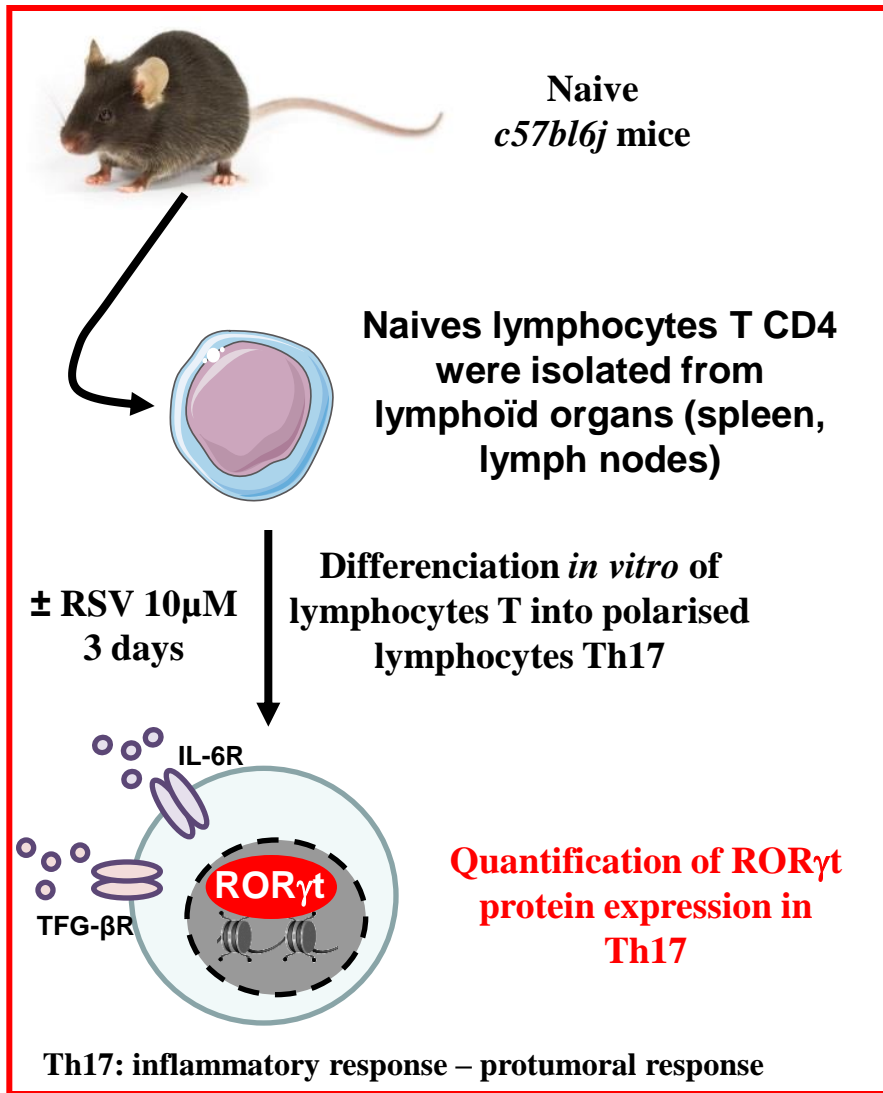
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Resveratrol, a safe molecule with health benefits

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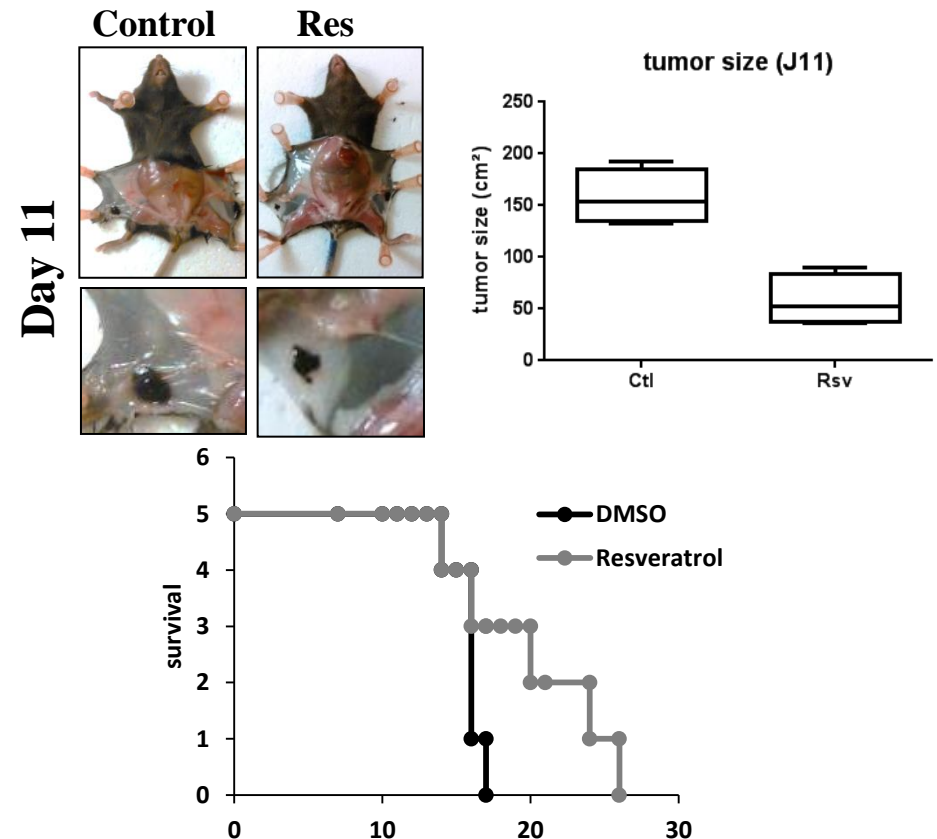
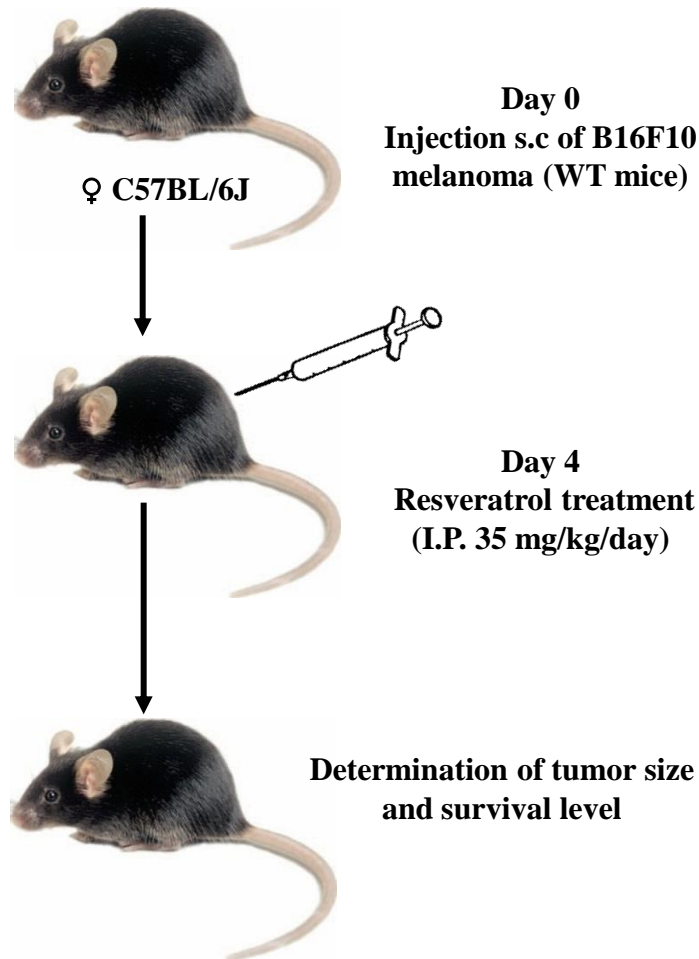
- Resveratrol (RSV) decreases ROR γ t protein expression into Th17 lymphocytes



Resveratrol, a safe molecule with health benefits

11- Resveratrol: a modulator of the immune system

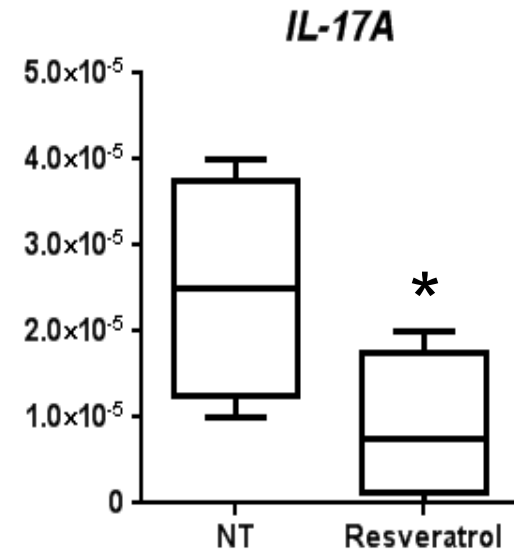
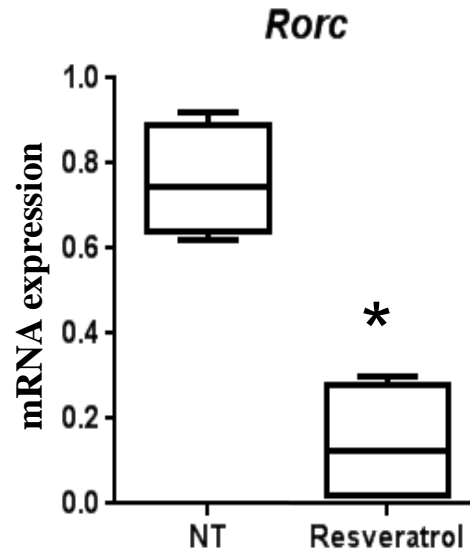
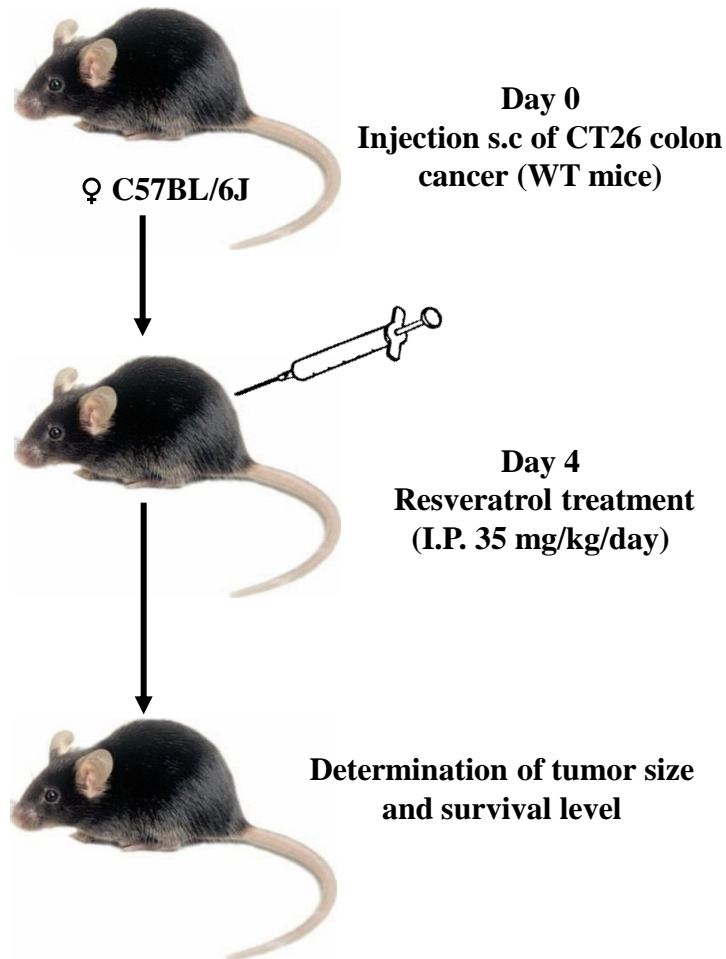
- Resveratrol (RSV) reduces tumor size of B16F10 melanoma in mice and increases survival level



Resveratrol, a safe molecule with health benefits

11- Resveratrol: a modulator of the immune system

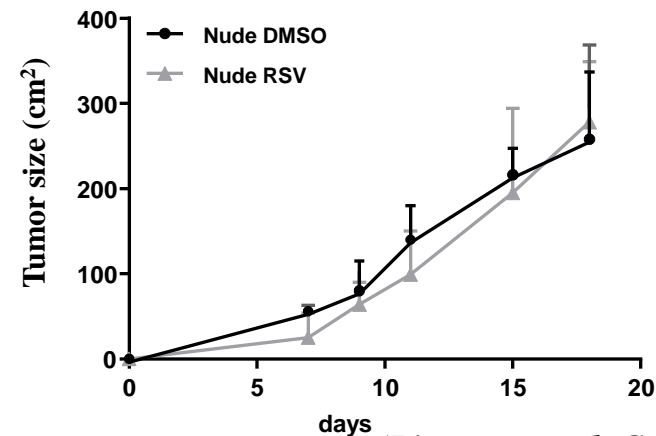
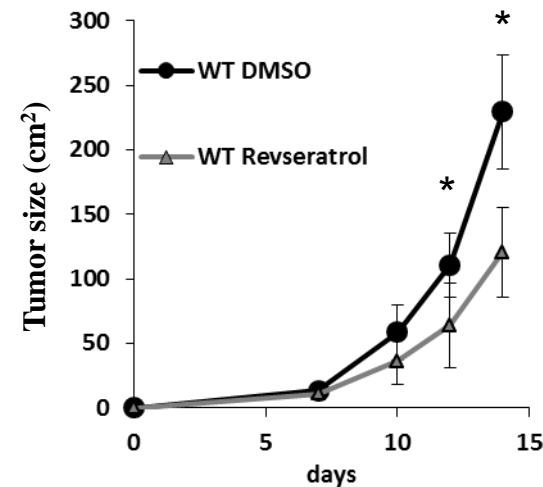
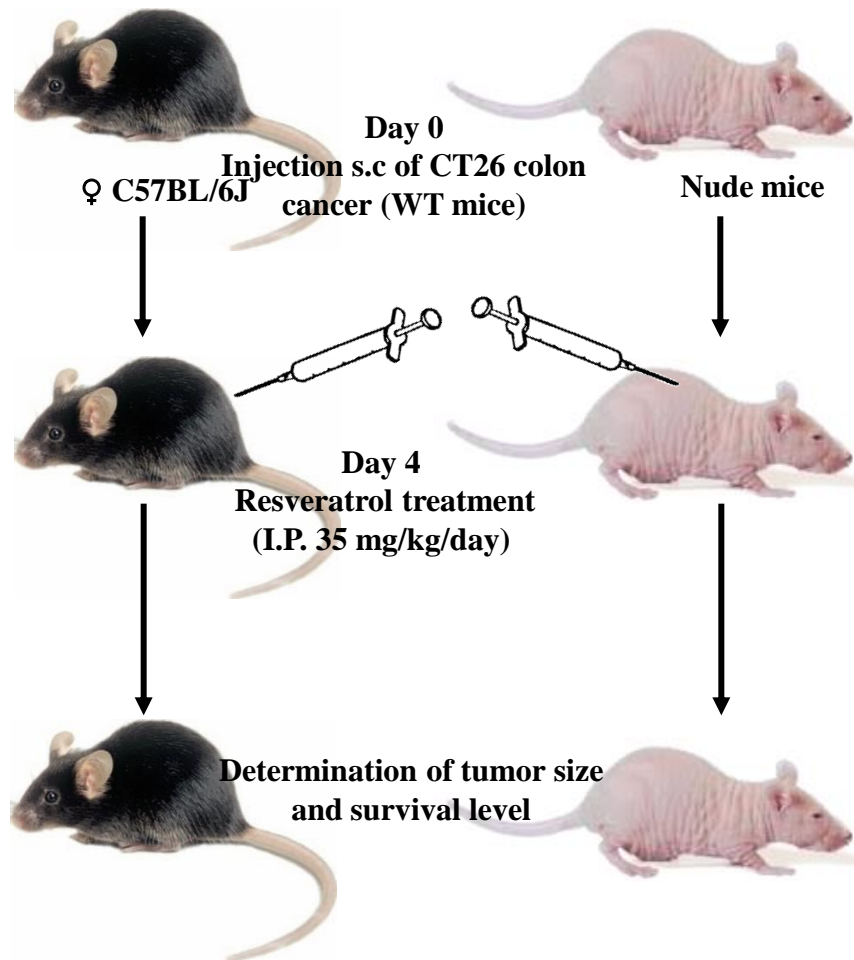
- Resveratrol (RSV) decreases il-17A and RORc in melanoma in mice



Resveratrol, a safe molecule with health benefits

11- Resveratrol: a modulator of the immune system

- Immune system is an essential player in resveratrol antitumoral activity

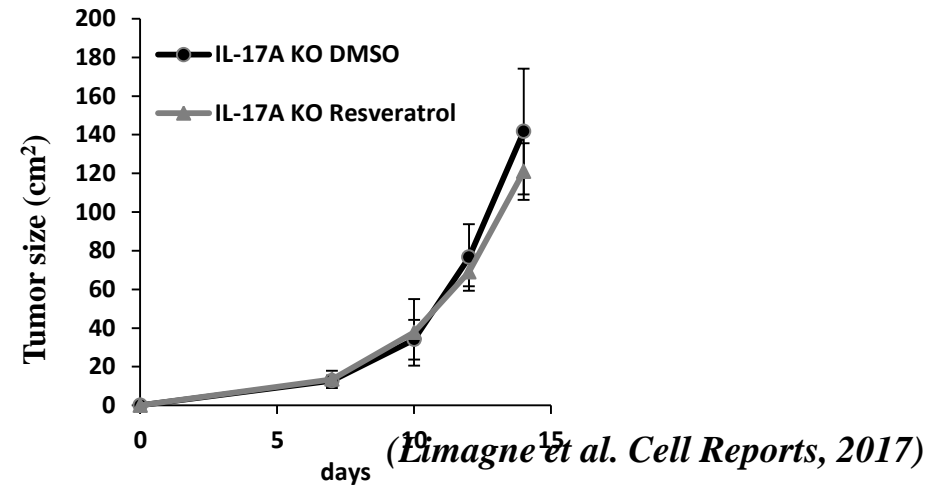
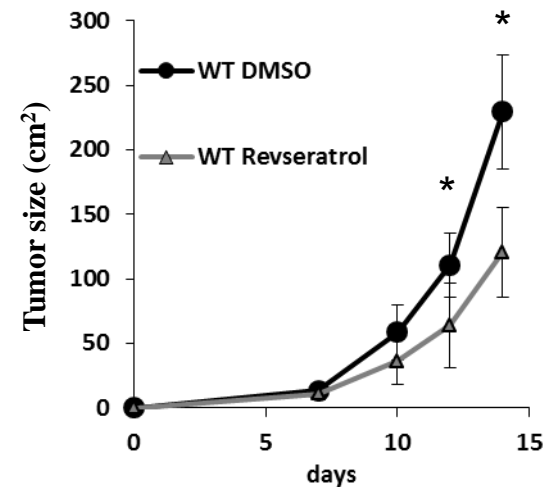
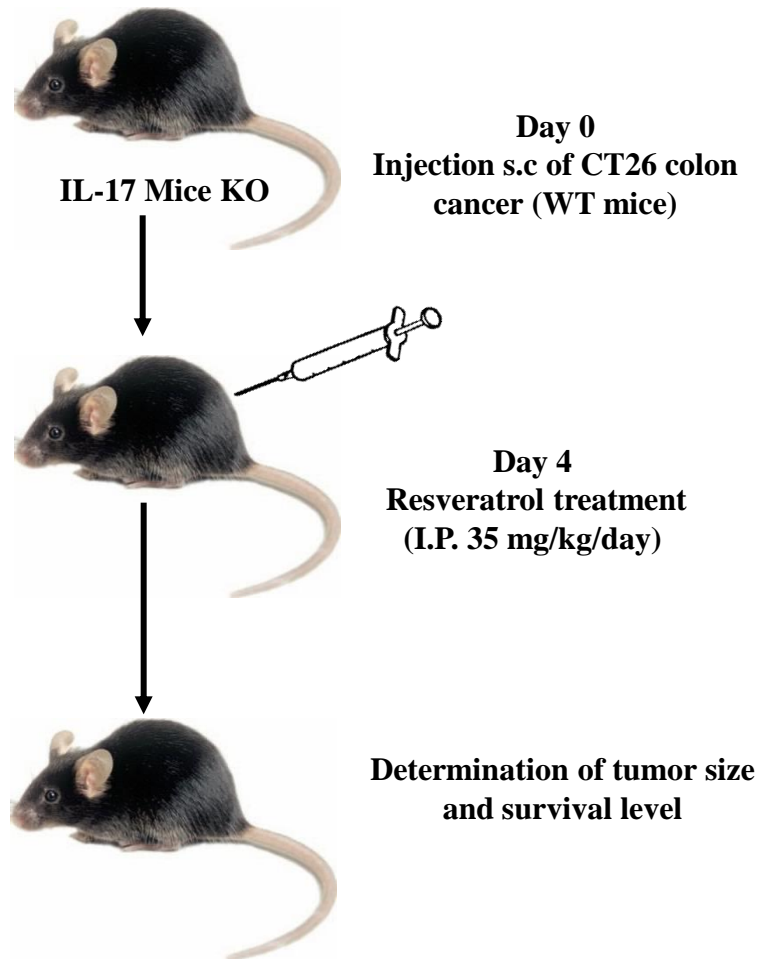


(Limagne et al. Cell Reports, 2017)

Resveratrol, a safe molecule with health benefits

11- Resveratrol: a modulator of the immune system

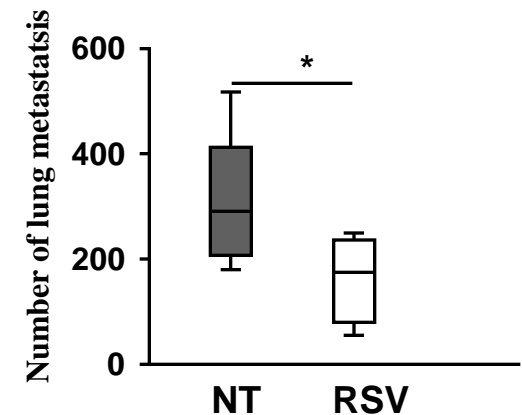
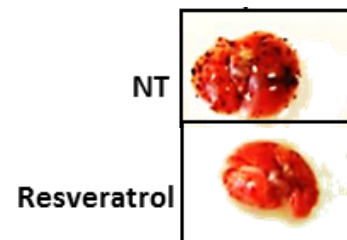
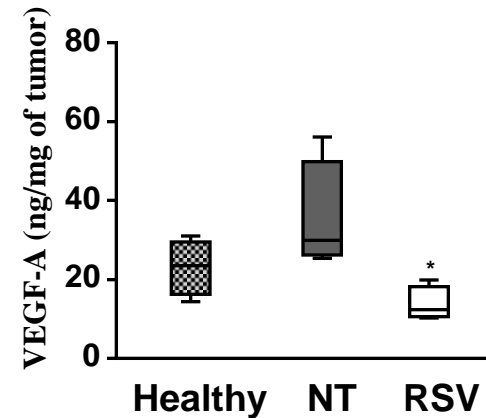
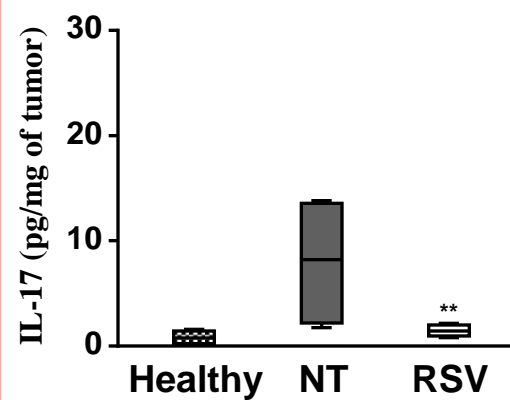
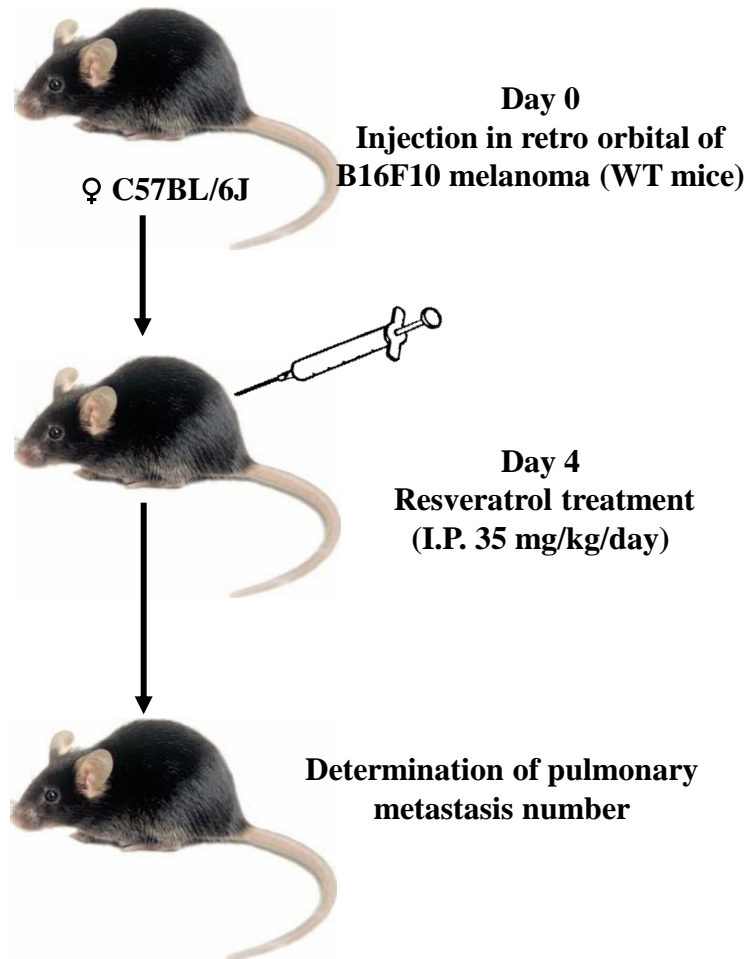
■ IL-17A is an essential player in resveratrol antitumoral activity



Resveratrol, a safe molecule with health benefits

11- Resveratrol: a modulator of the immune system

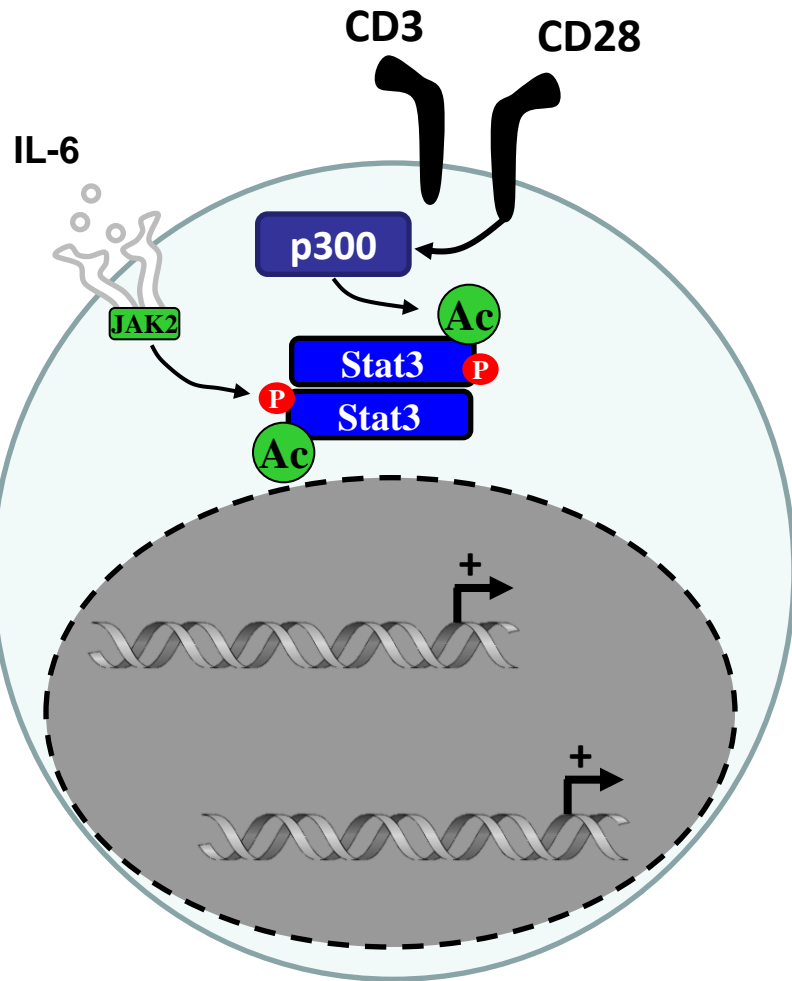
■ RSV prevents tumoral invasion and metastasis progression



(Limagne et al. Cell Reports, 2017)

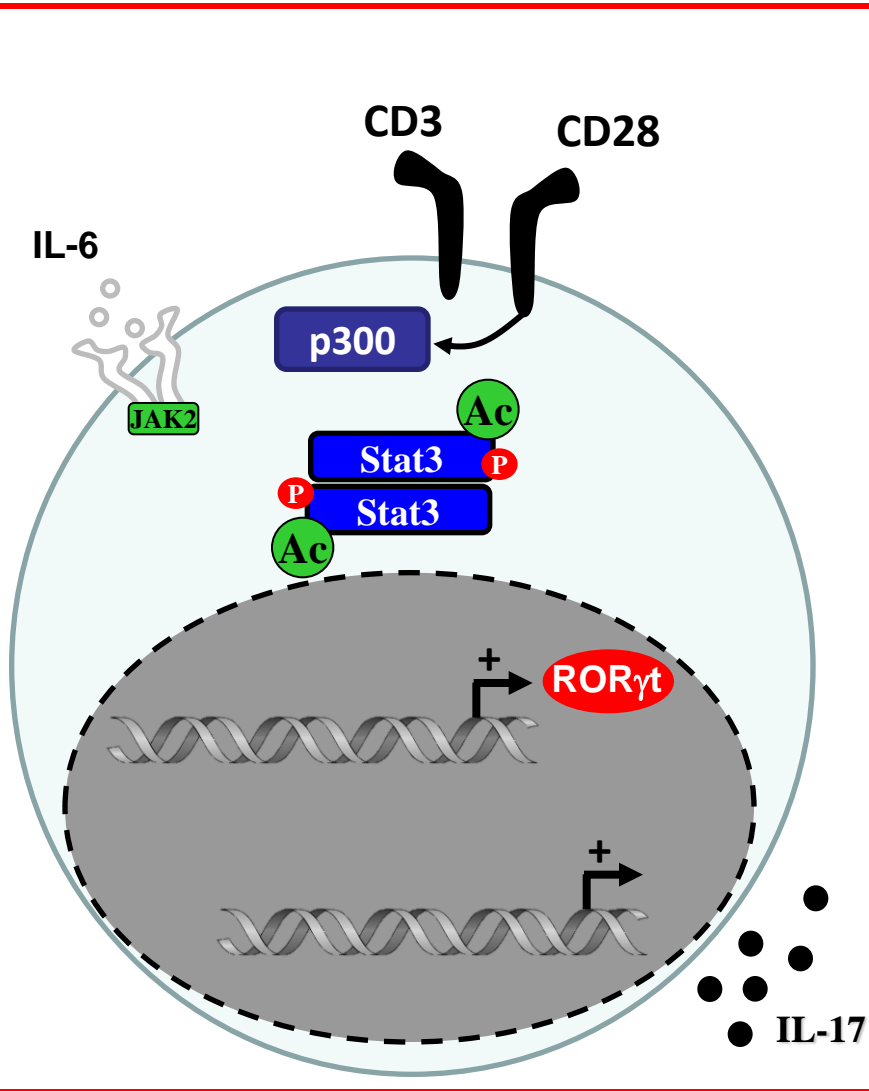
Resveratrol, a safe molecule with health benefits

11- Resveratrol: a modulator of the immune system



Resveratrol, a safe molecule with health benefits

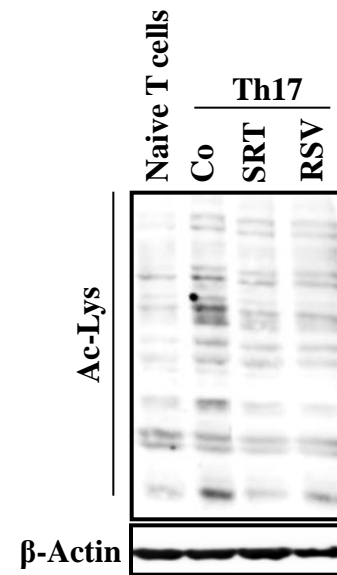
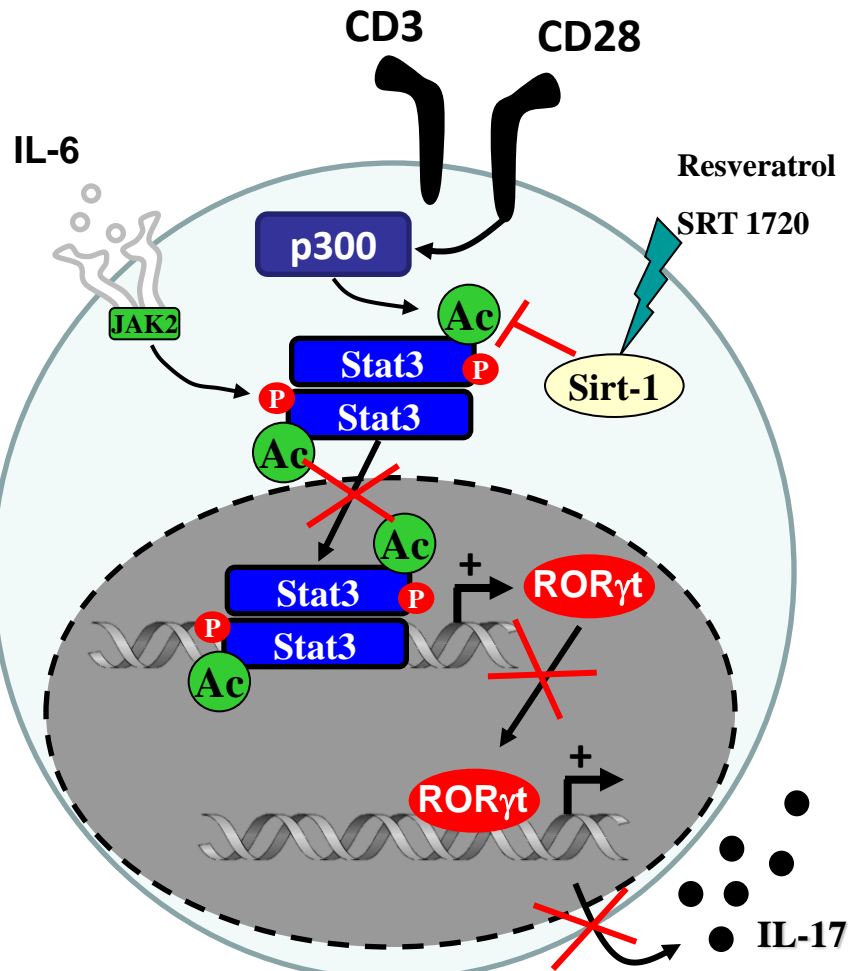
11- Resveratrol: a modulator of the immune system



Resveratrol, a safe molecule with health benefits

11- Resveratrol: a modulator of the immune system

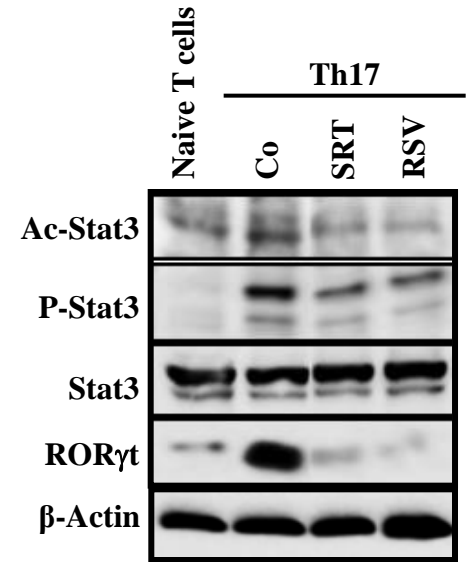
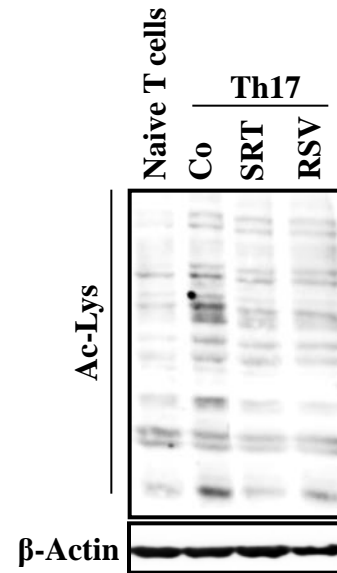
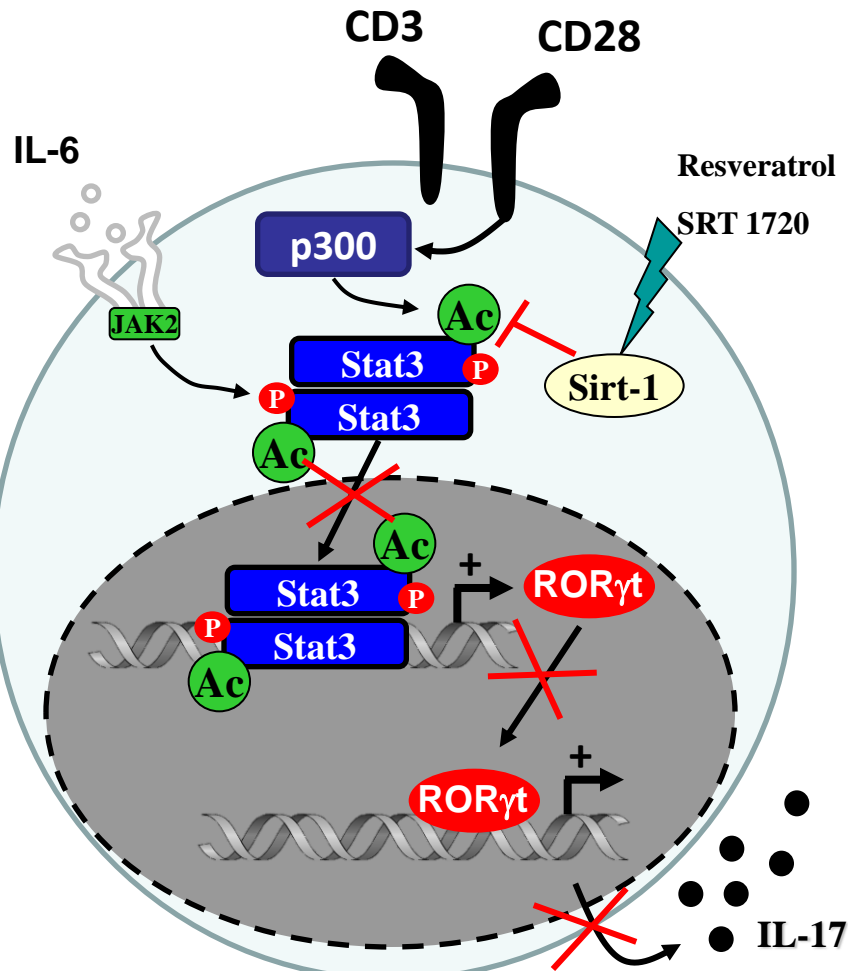
- RSV decreases proteins acetylation in Th17 cells



Resveratrol, a safe molecule with health benefits

11- Resveratrol: a modulator of the immune system

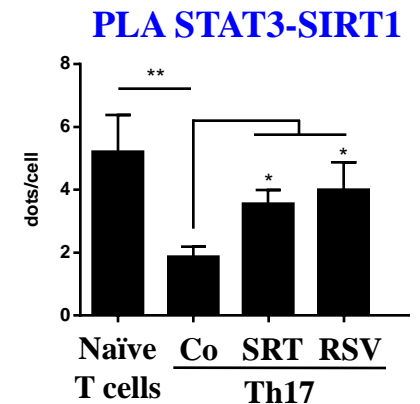
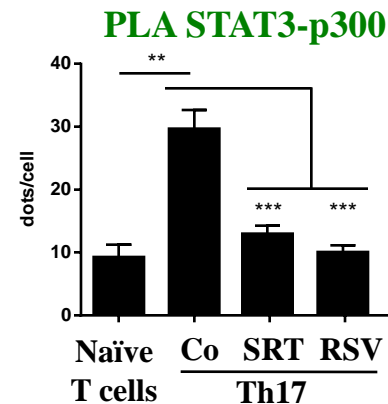
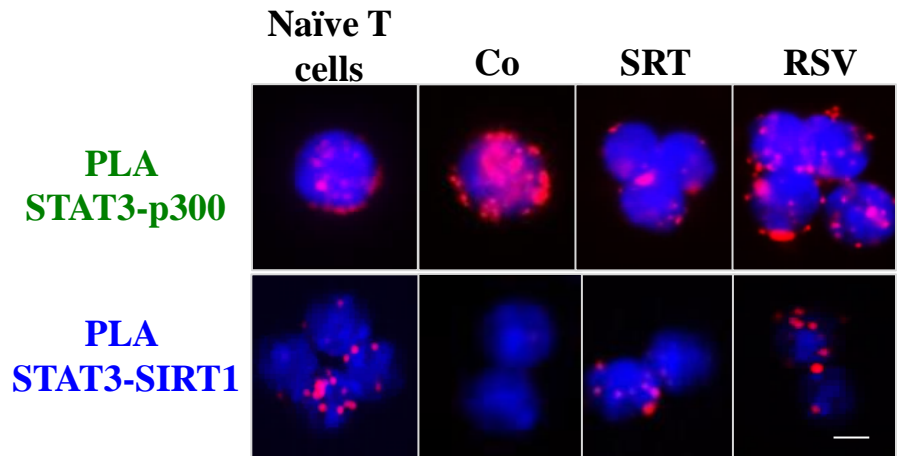
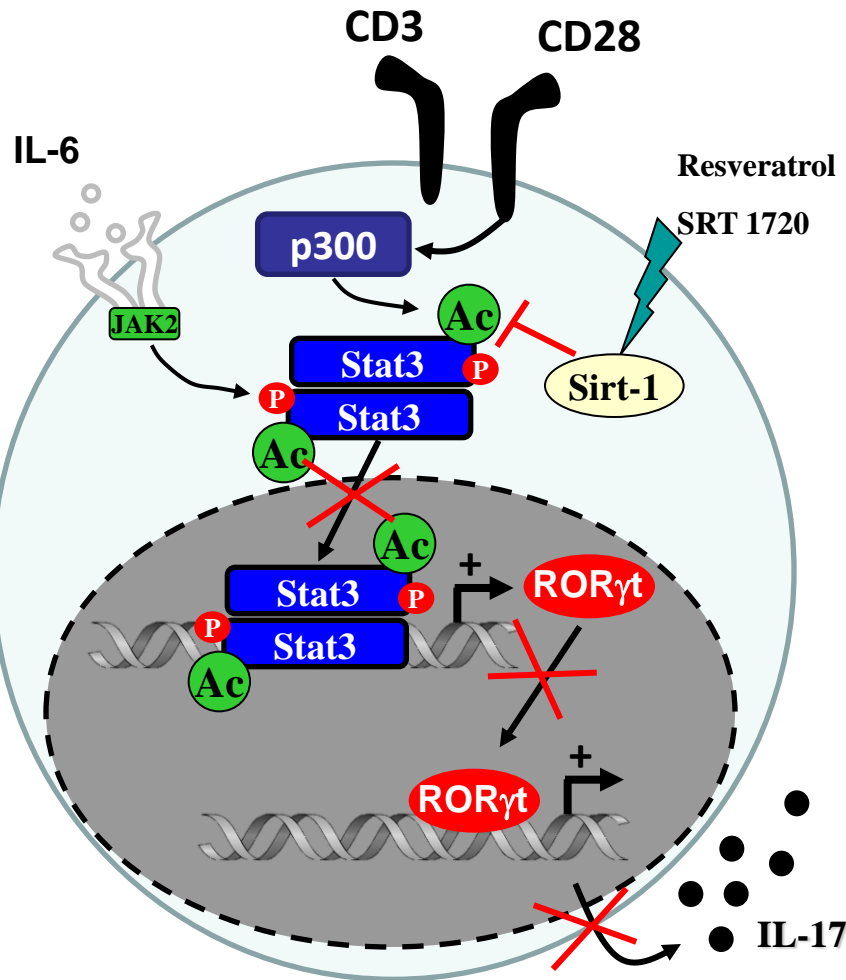
- RSV decreases proteins acetylation in Th17 cells and decreases Stat3 pathway



Resveratrol, a safe molecule with health benefits

11- Resveratrol: a modulator of the immune system

■ RSV strongly increases SIRT1-STAT3 interaction

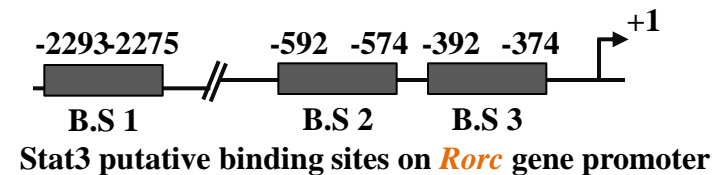
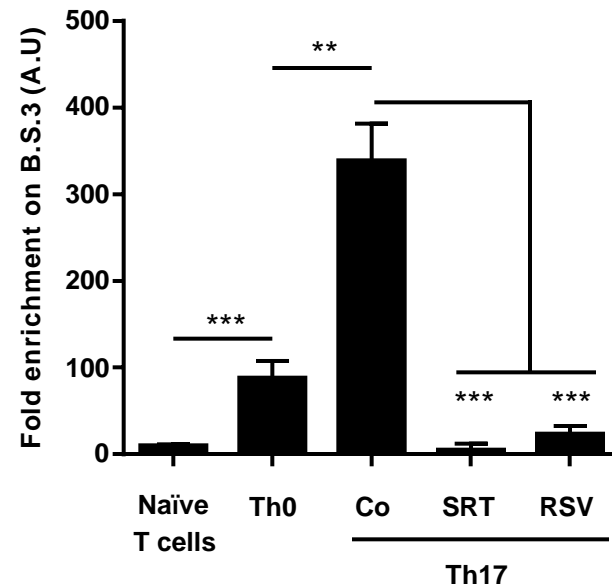
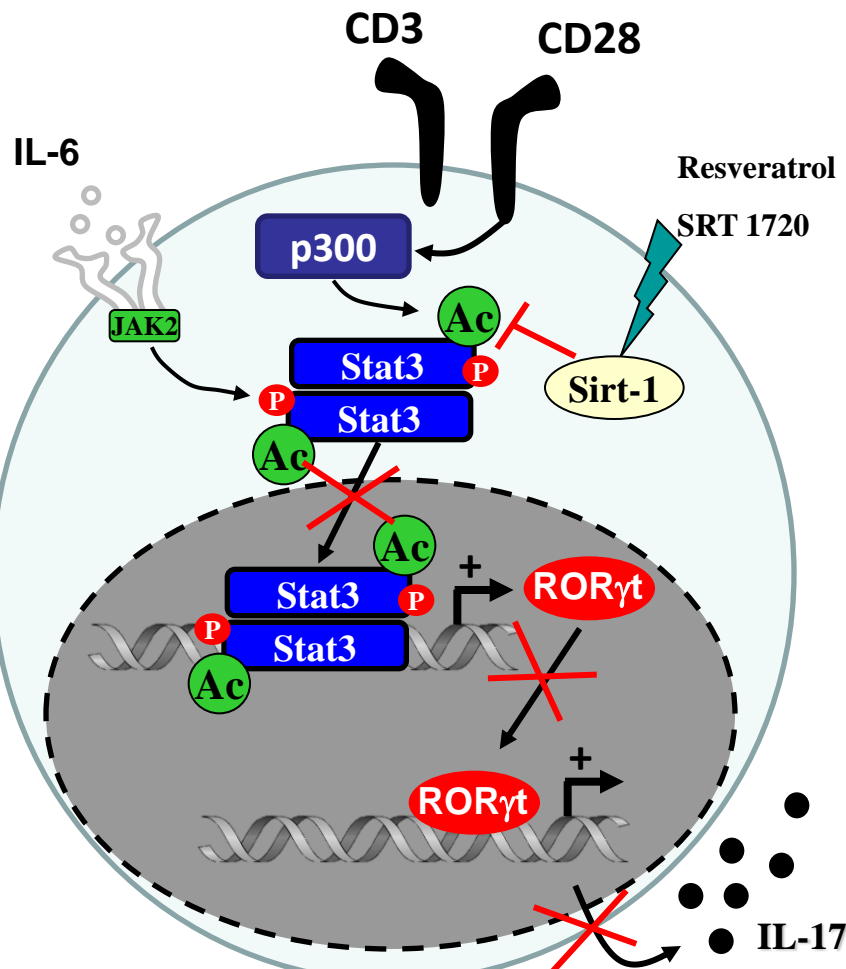


(Limagne et al. Cell Reports, 2017)

Resveratrol, a safe molecule with health benefits

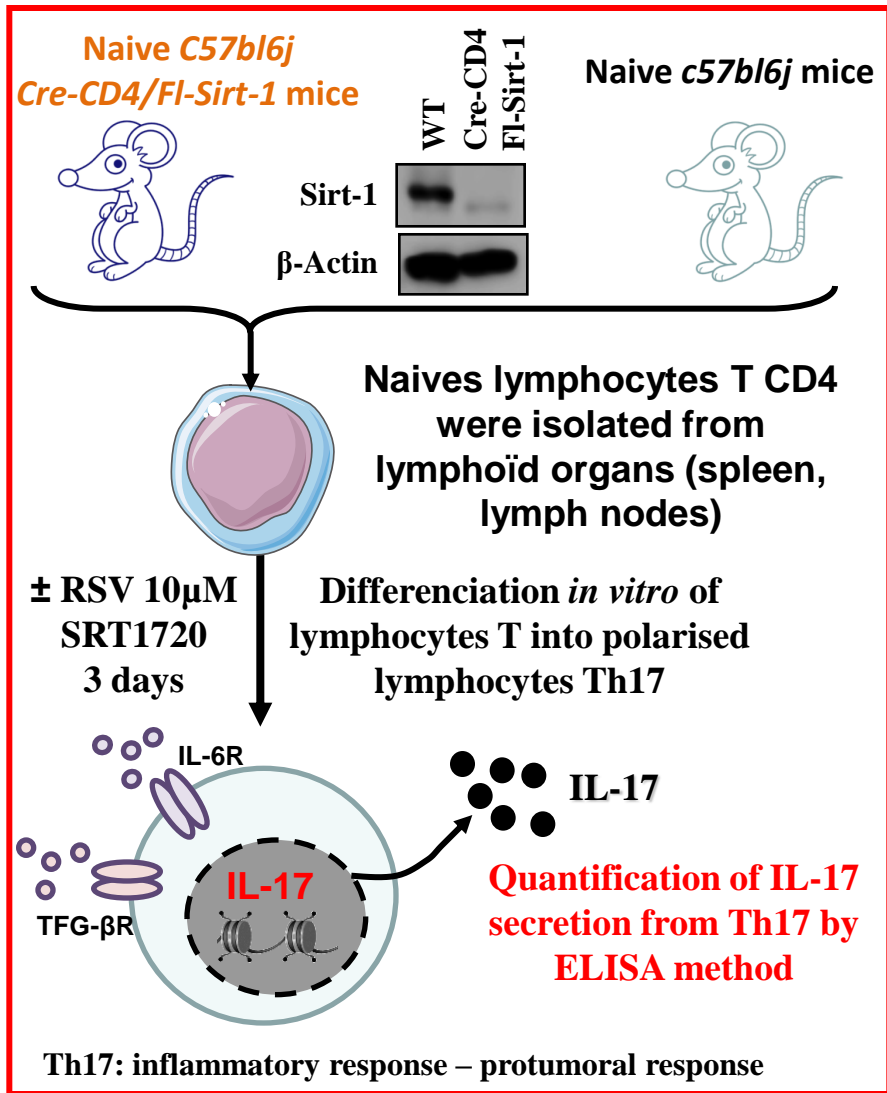
11- Resveratrol: a modulator of the immune system

- RSV prevents STAT3 binding on putative binding site 3 (B.S.3) on *Rorc* promoter

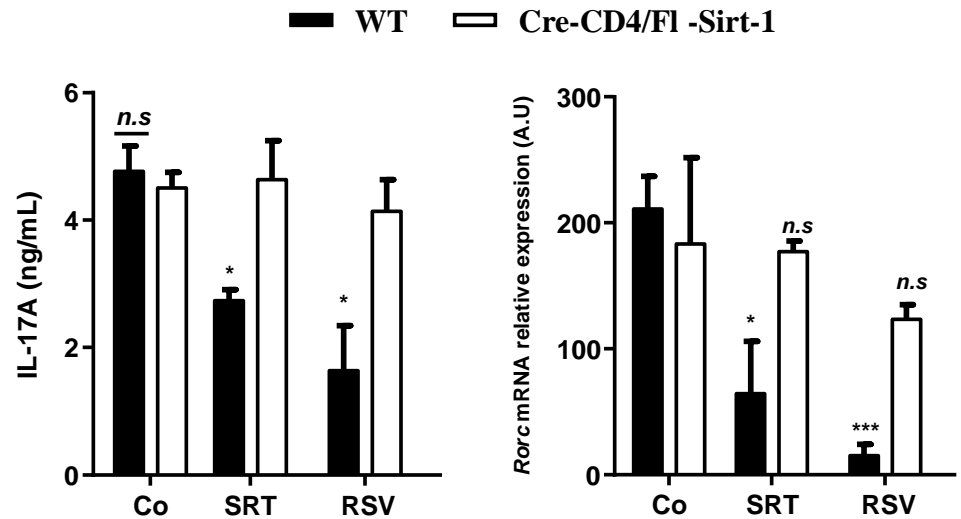


Resveratrol, a safe molecule with health benefits

11- Resveratrol: a modulator of the immune system

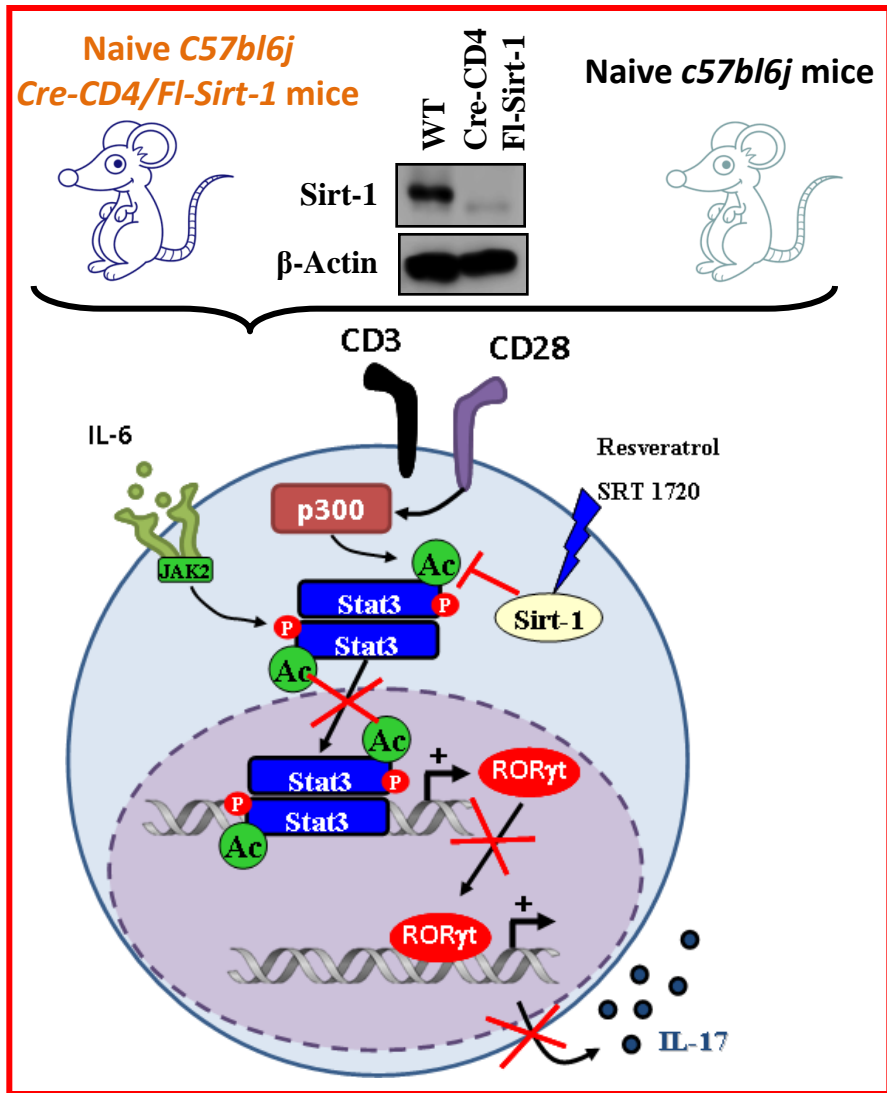


- Invalidation of Sirt-1 in T CD4⁺ prevents the decreases of IL-17A protein and ROR mRNA induced by RSV

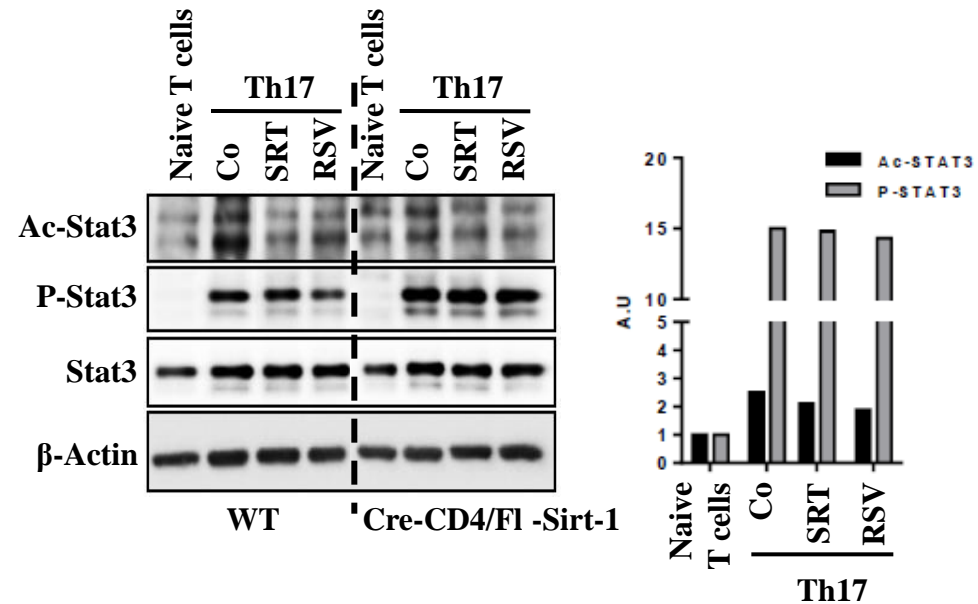


Resveratrol, a safe molecule with health benefits

11- Resveratrol: a modulator of the immune system

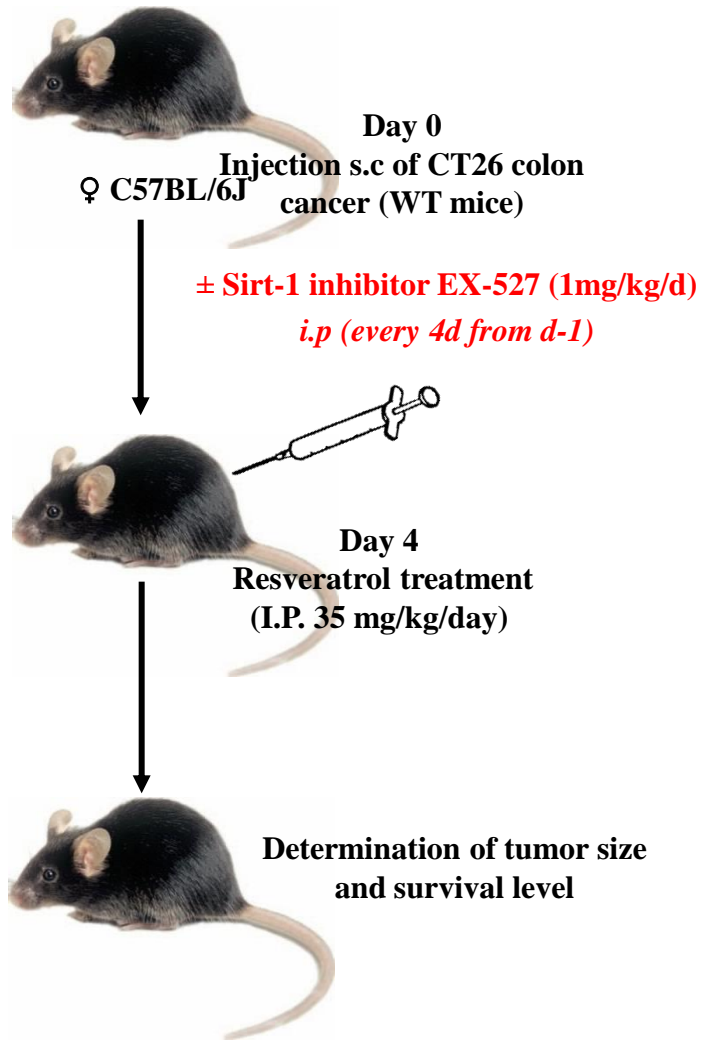


- Invalidation of Sirt-1 in T CD4⁺ prevents the decreases of Stat3 acetylation

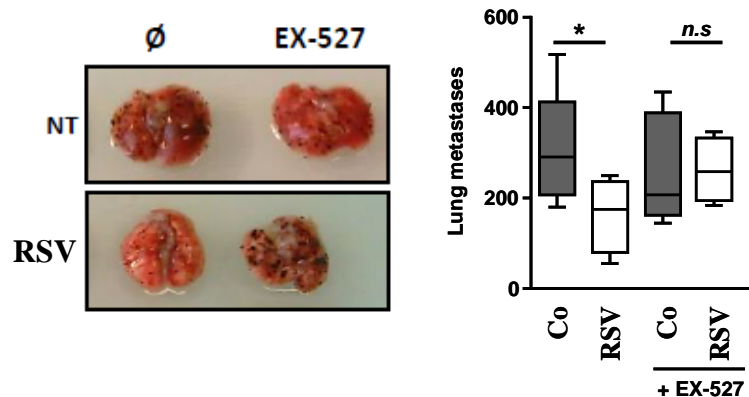
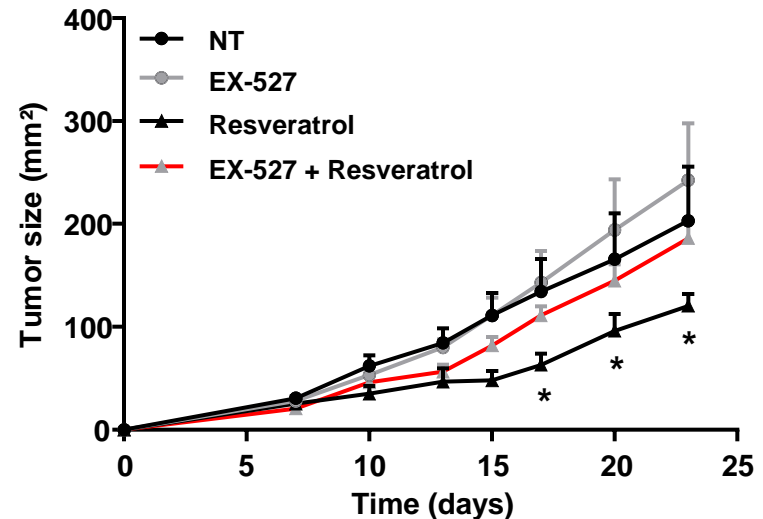


Resveratrol, a safe molecule with health benefits

11- Resveratrol: a modulator of the immune system



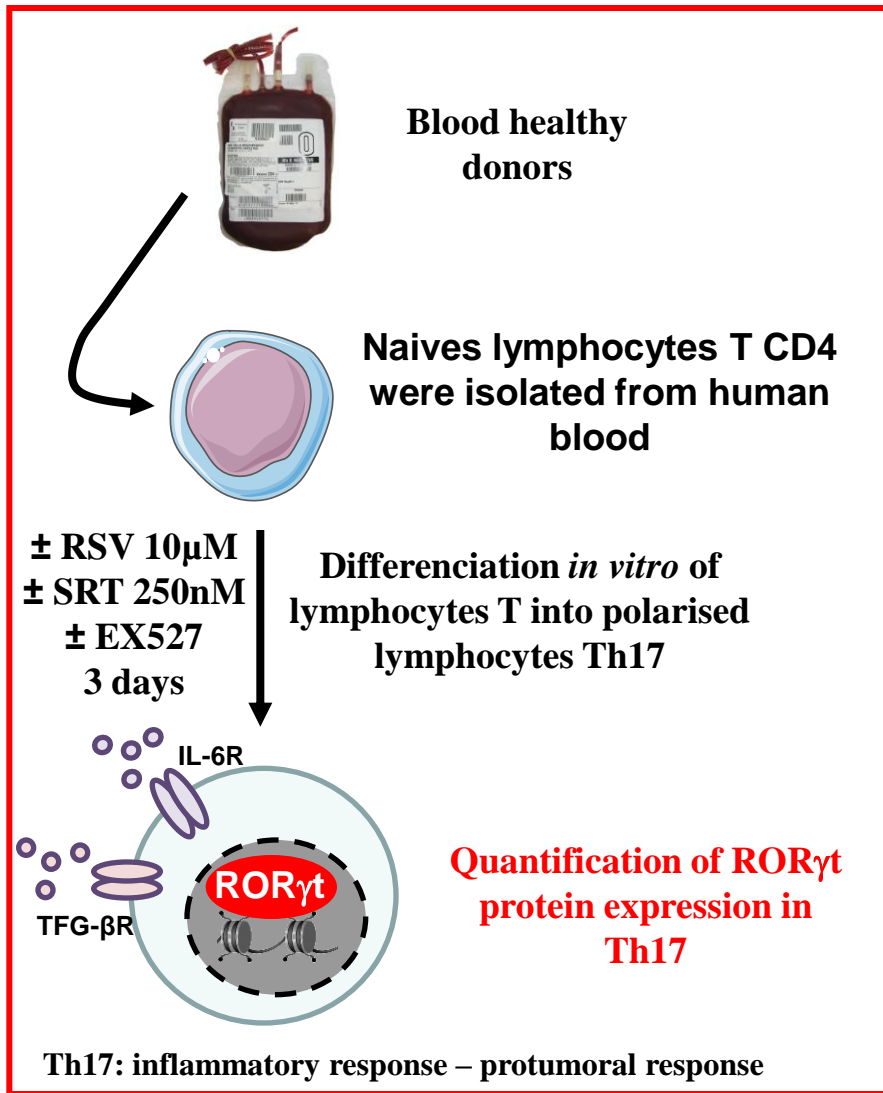
■ Sirt-1 inhibitor EX527 prevents RSV antitumoral effects *in vivo*



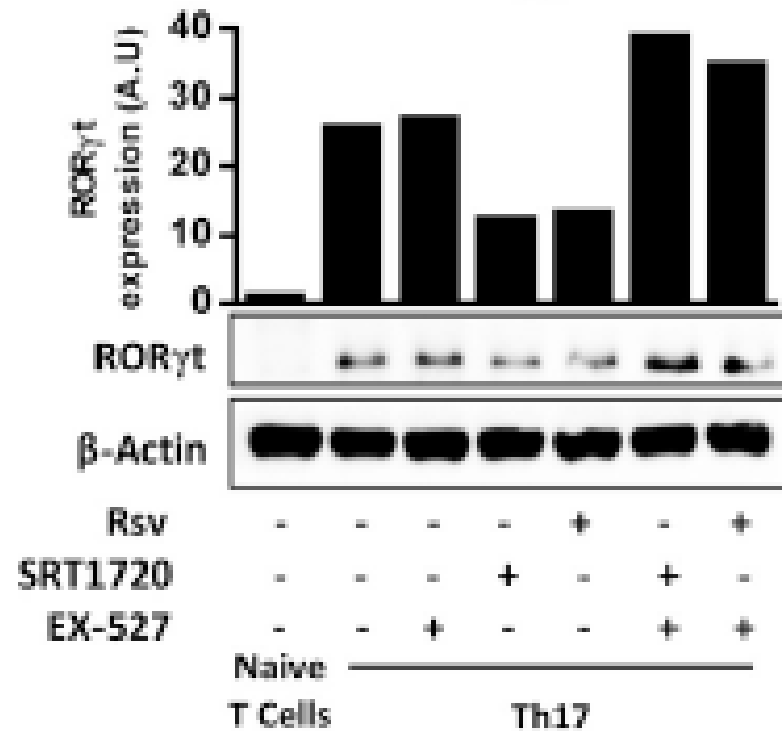
(Limagne et al. Cell Reports, 2017)

Resveratrol, a safe molecule with health benefits

11- Resveratrol: a modulator of the immune system

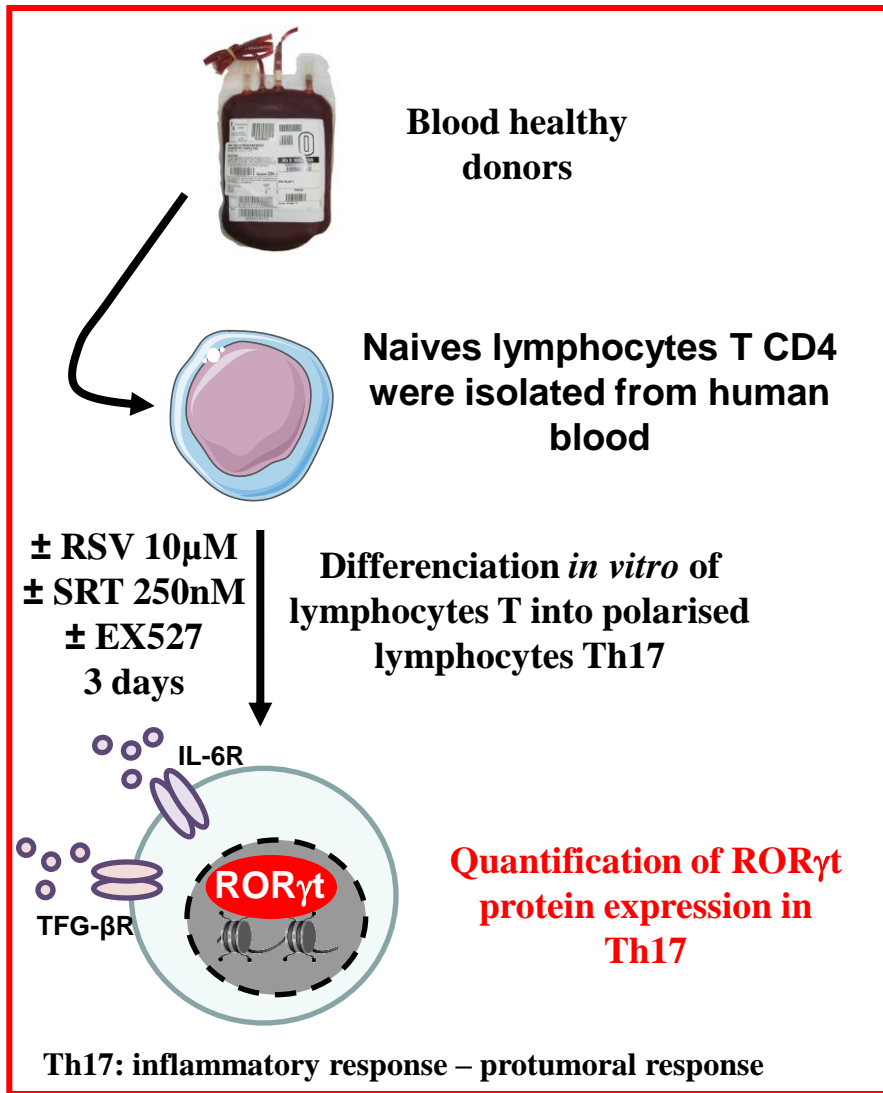


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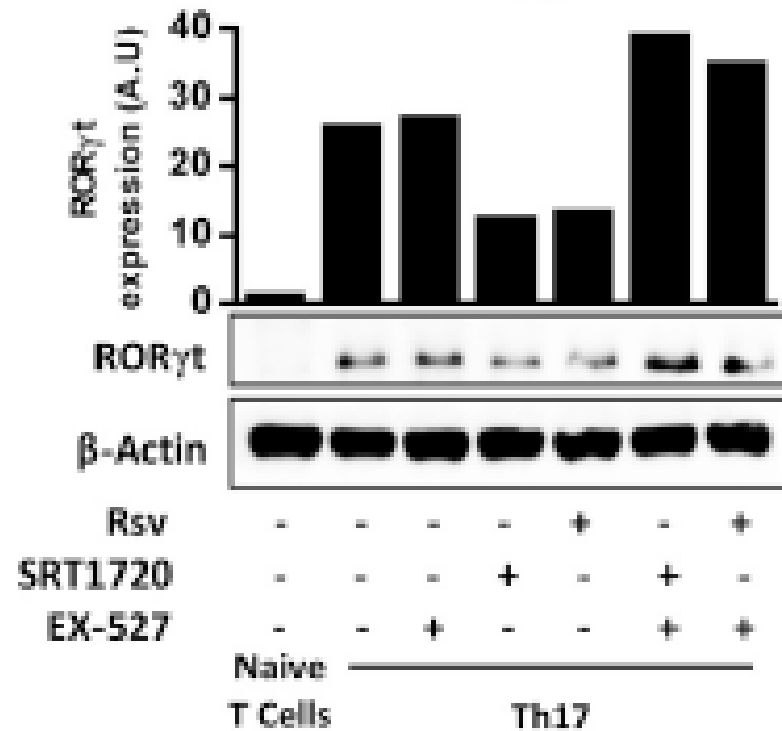


Resveratrol, a safe molecule with health benefits

11- Resveratrol: a modulator of the immune system



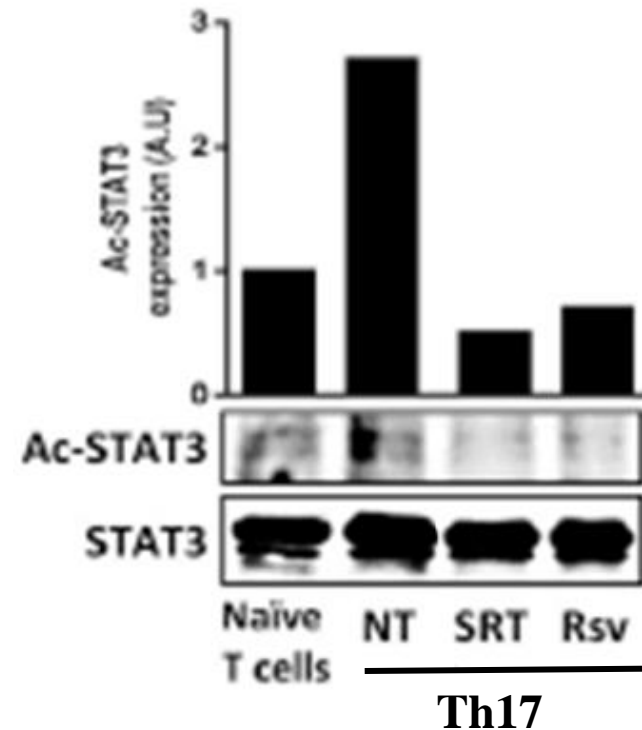
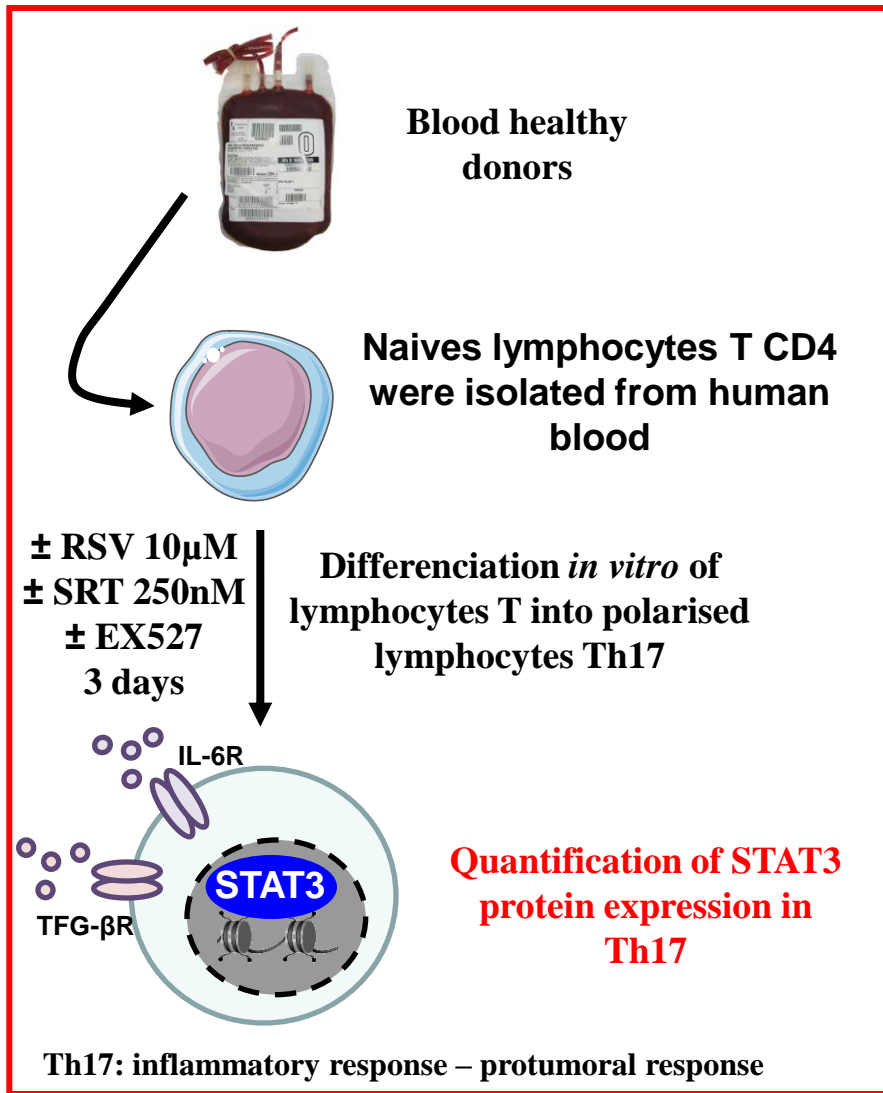
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11- Resveratrol: a modulator of the immune system

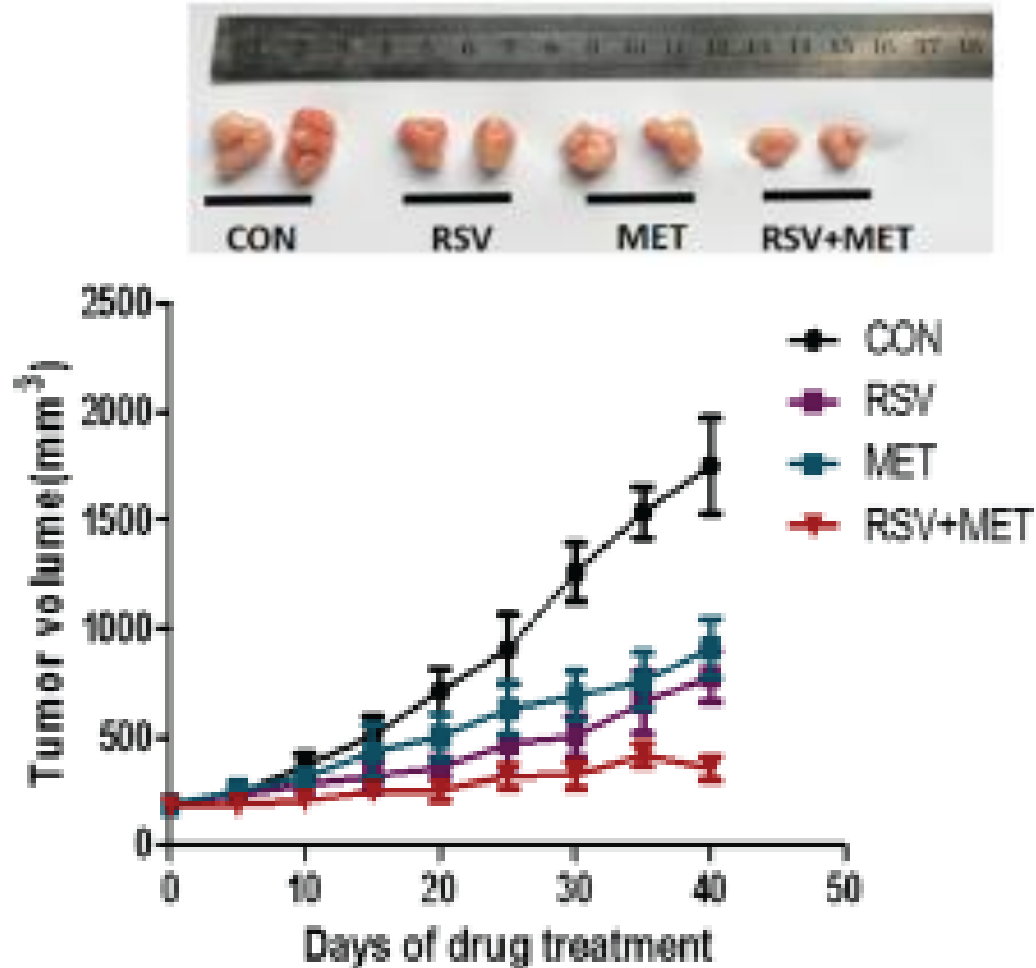
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Resveratrol, a safe molecule with health benefits

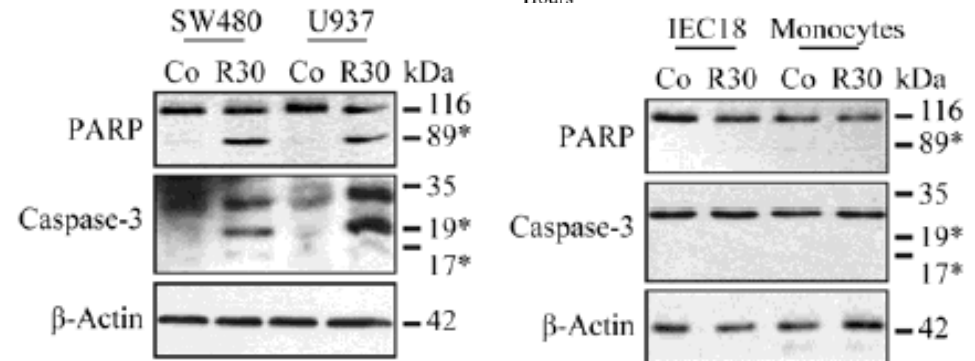
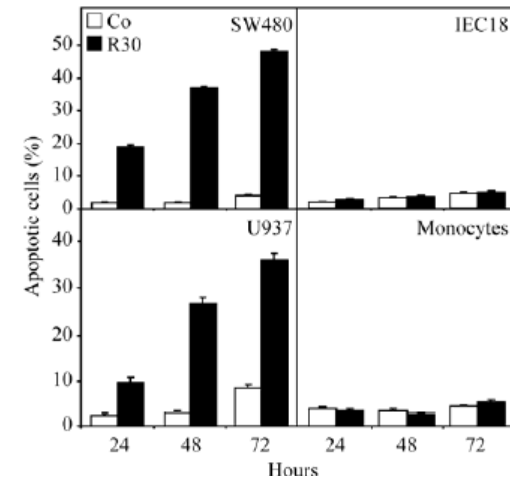
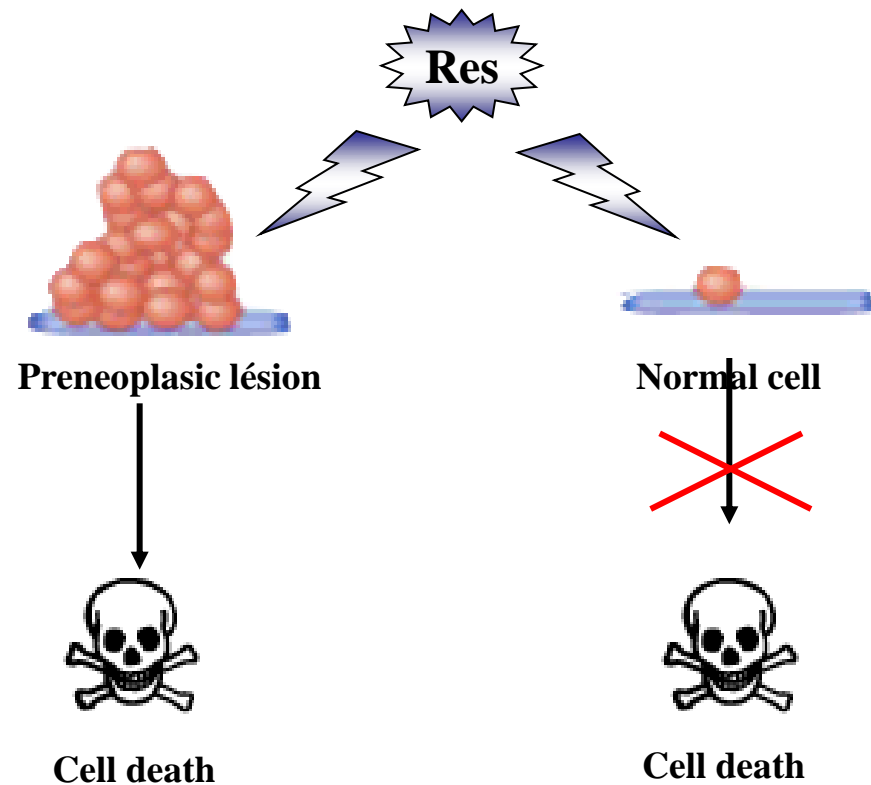
11- Resveratrol: a modulator of the immune system



Resveratrol, a safe molecule with health benefits

12- Resveratrol: a safe molecule

- Resveratrol induces only cell death in tumoral cells and not in normal cells



Conclusion & Perspectives

- **Resveratrol presents a strong potential as chemopreventive agent in many cancer models and particularly in colorectal cancers ;**
- **Despite a low bioavailability, resveratrol metabolites accumulates into tissues approaching the concentrations reported to have pharmacological activity *in vitro* ;**
- **Resveratrol as therapeutic adjuvant is a promising approach to sensitize resistant cancer cells to death induced by classical anticancer agents.**

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