

# **Estrés del reticle endoplasmàtic com estratègia terapèutica contra els tumors cerebrals**



**Clínica  
Universidad  
de Navarra**

**Departamento  
de Oncología**

**Enric Xipell Badals**

1 de juny de 2016

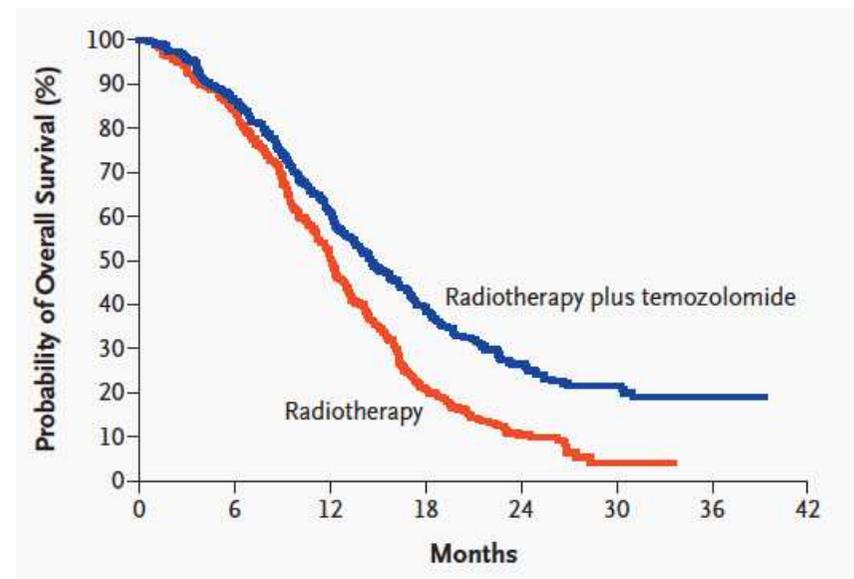
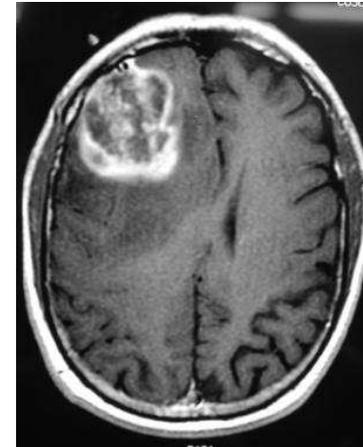
60% of the brain tumors in adults.

High proliferation rate and invasiveness.

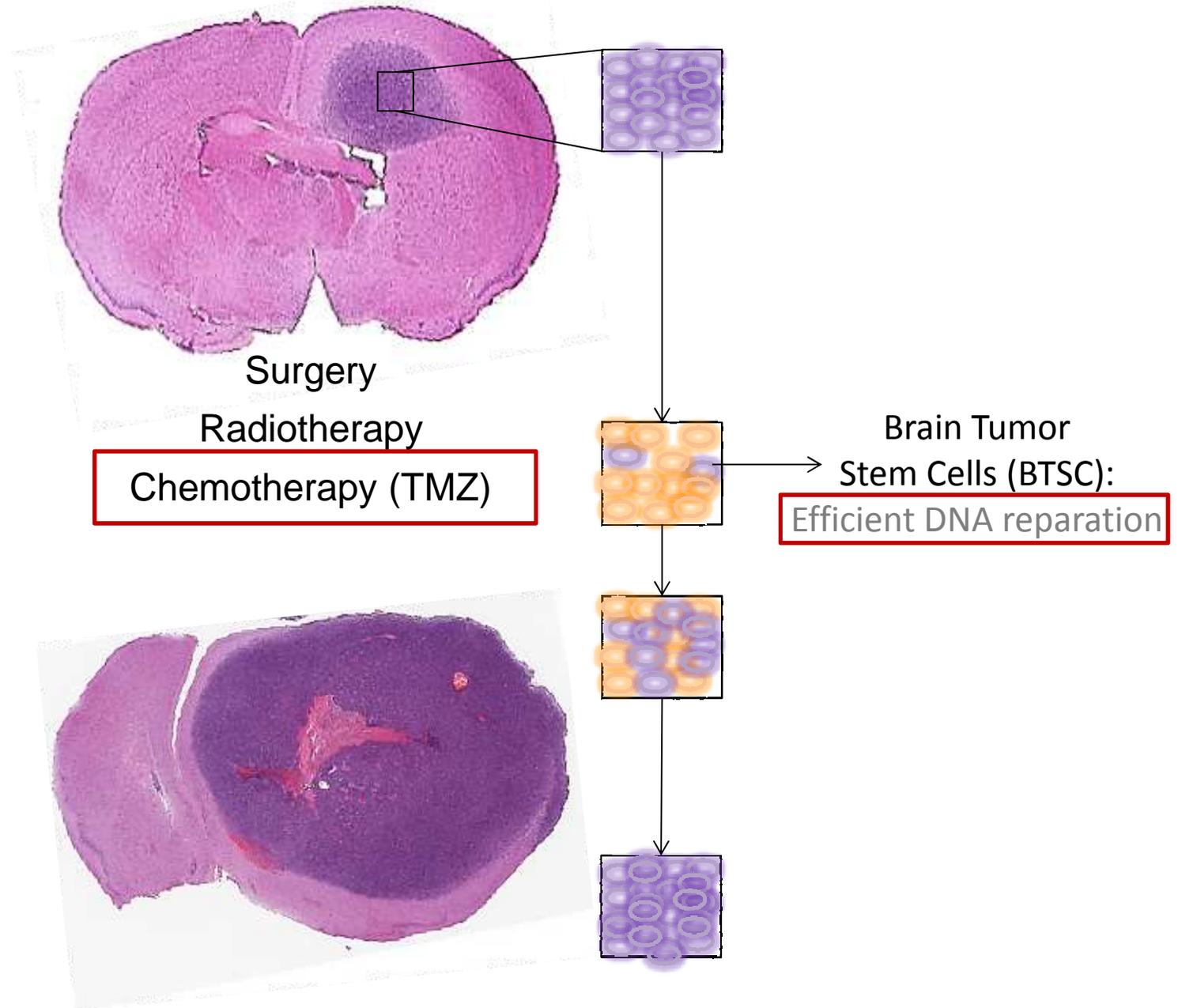
Standard Treatment: **surgery, radiotherapy and chemotherapy.**

Despite maximum therapeutic efforts, the prognostic is dismal.

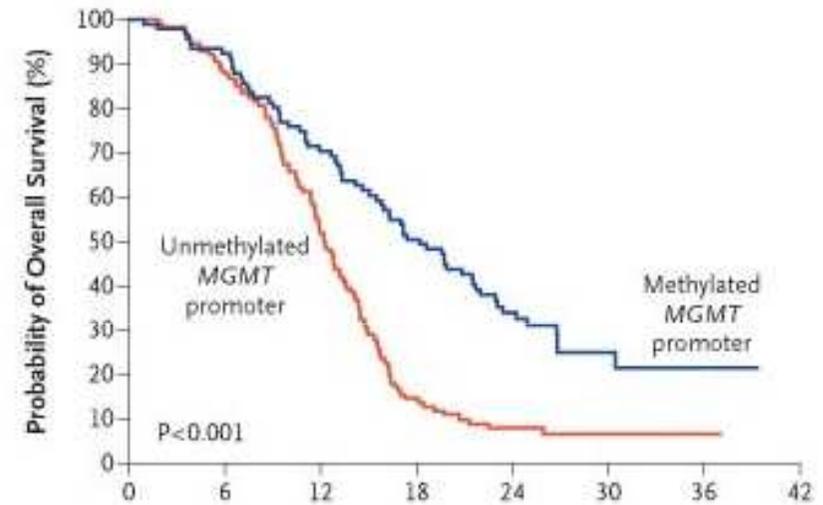
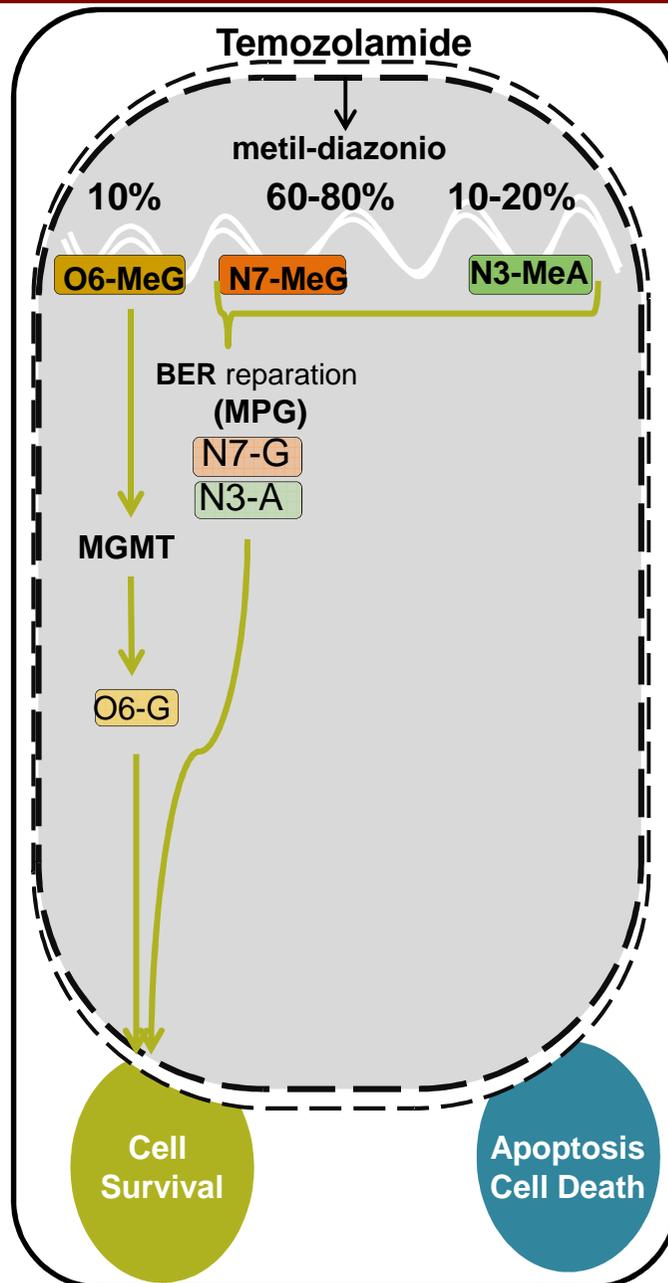
High mortality rate and relapse.



# Temozolamide (TMZ)



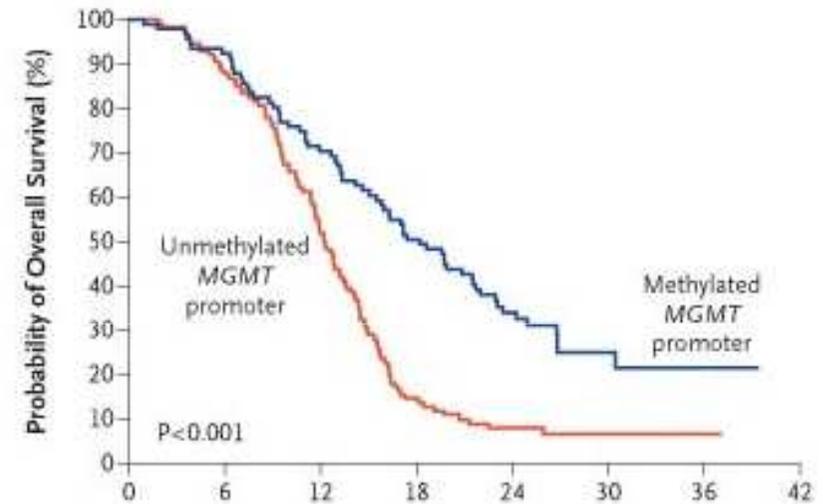
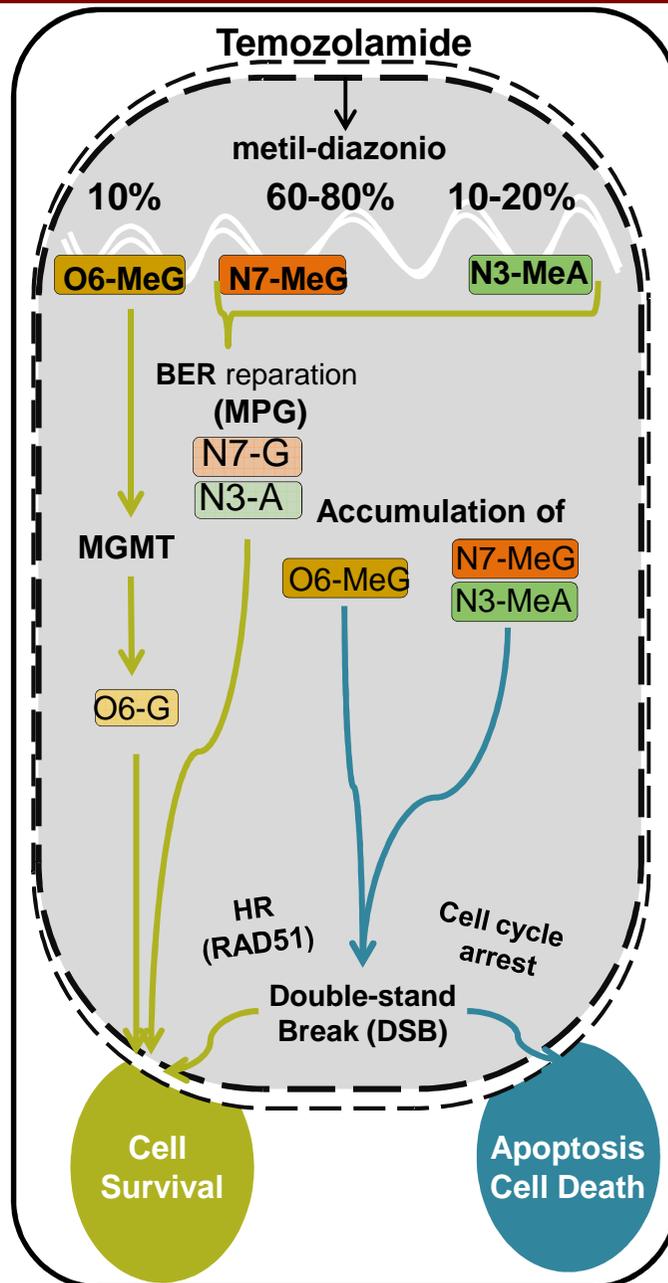
# Temozolamide (TMZ)



Adapted from Hegi et al. 2005

Adapted from Xipell et al., 2016

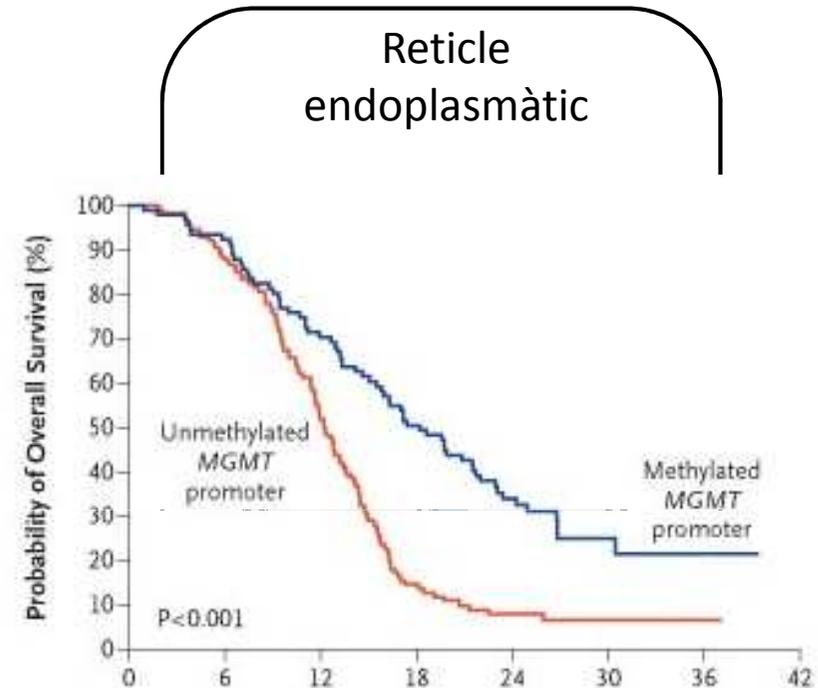
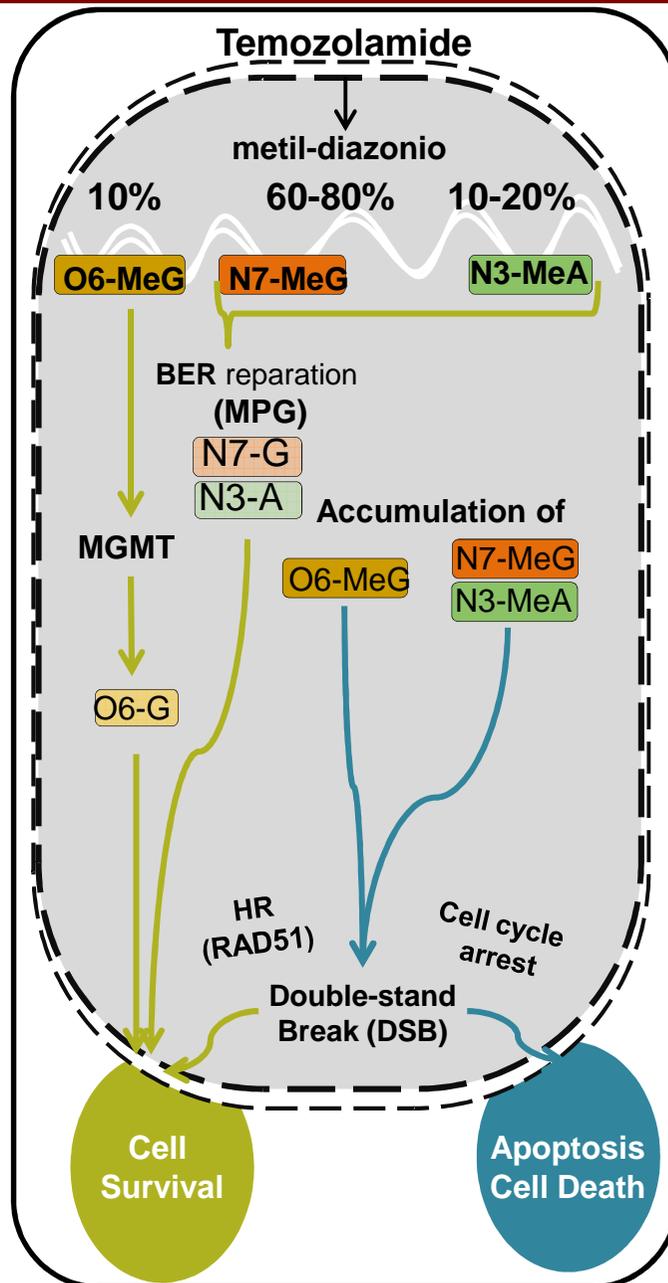
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# Hypothesis

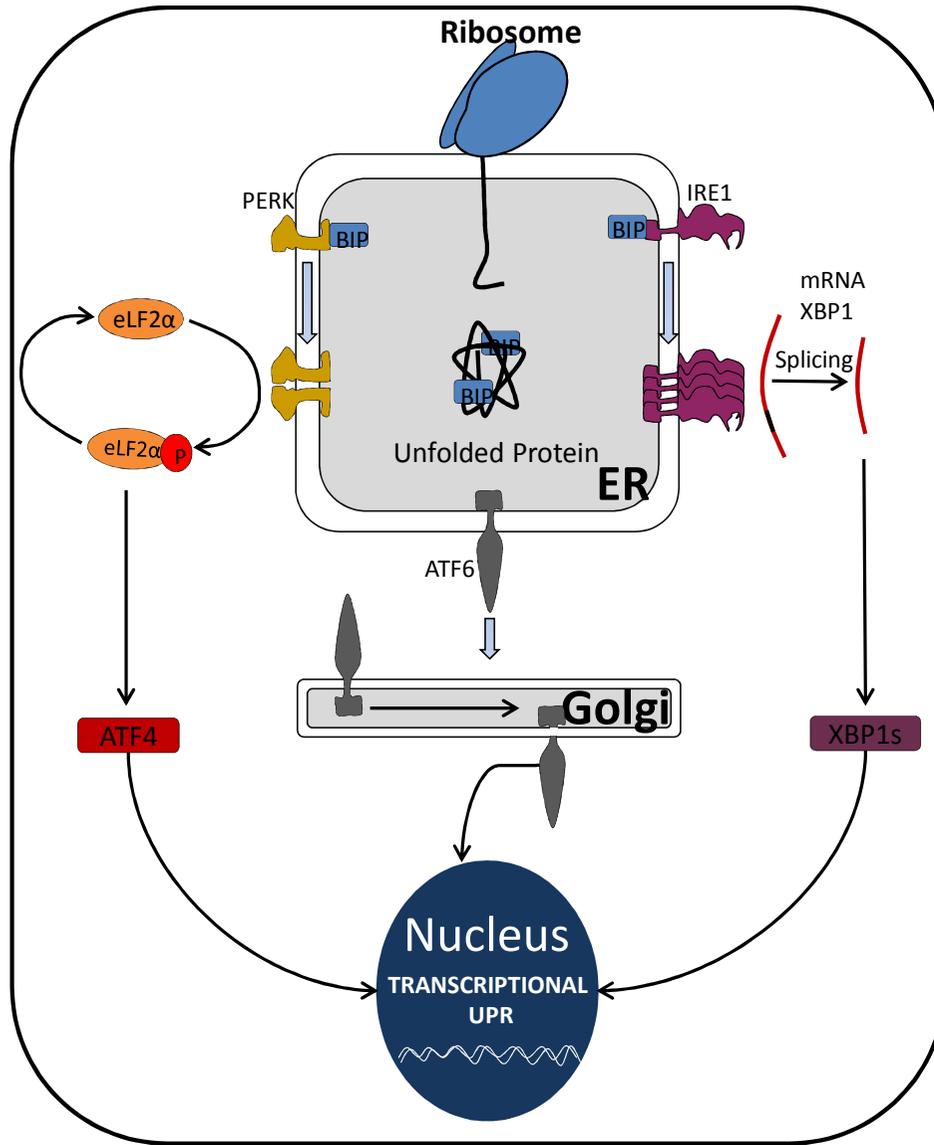


Adapted from Hegi et al., 2005

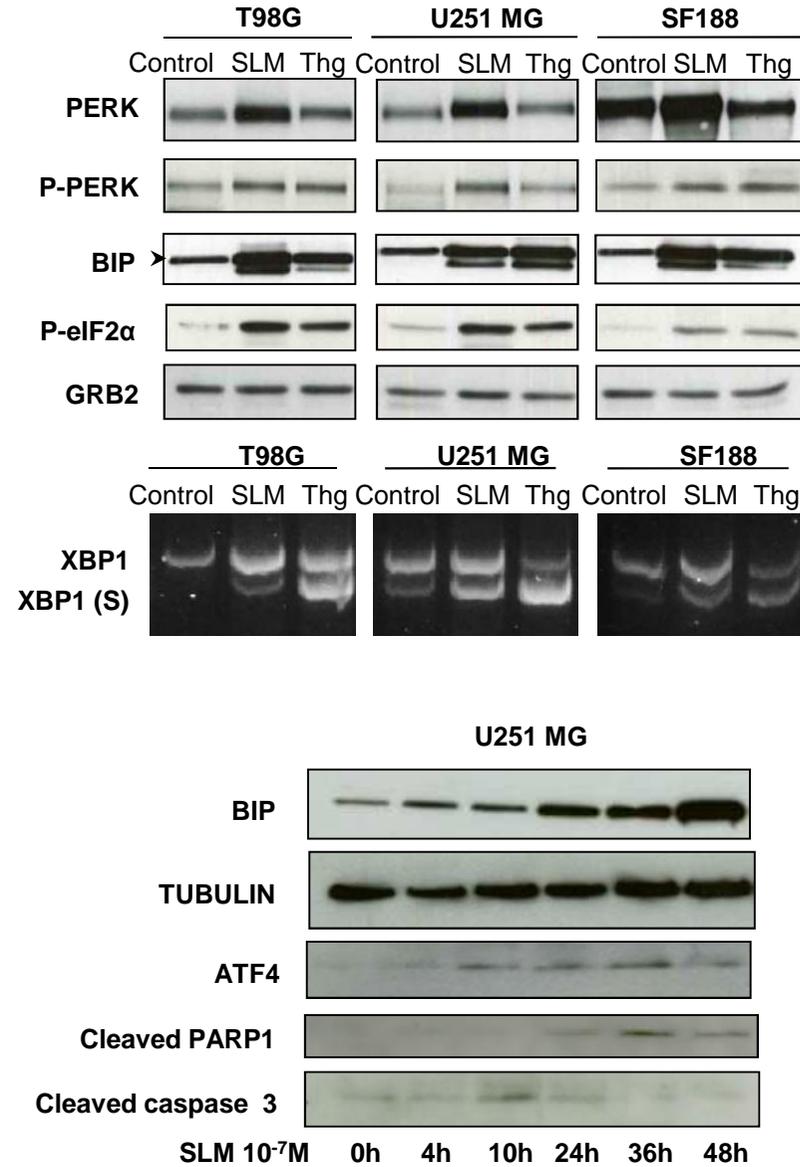
Adapted from Clarke et al., 2009

Adapted from Xipell et al., 2016

# SLM induces a maintained and potent ER stress/UPR

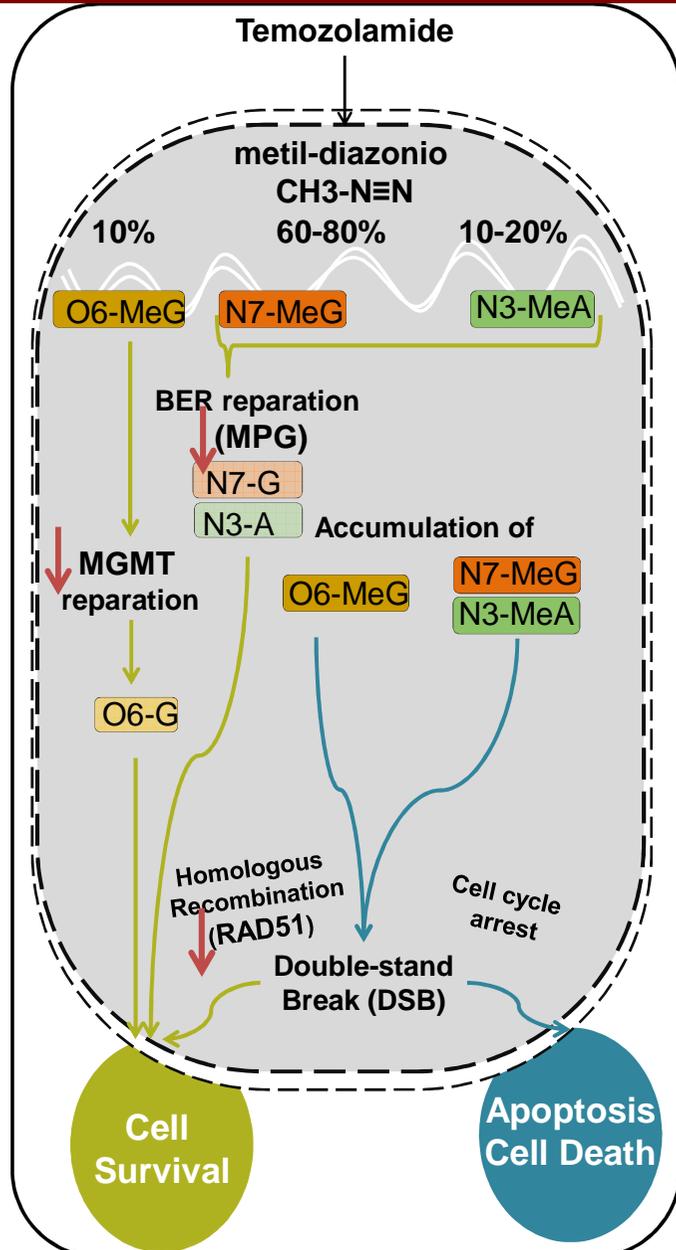


Adapted from Clarke et. al., 2009

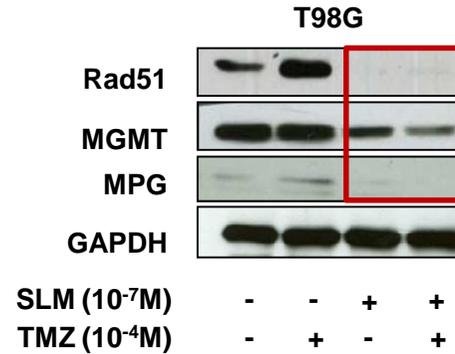




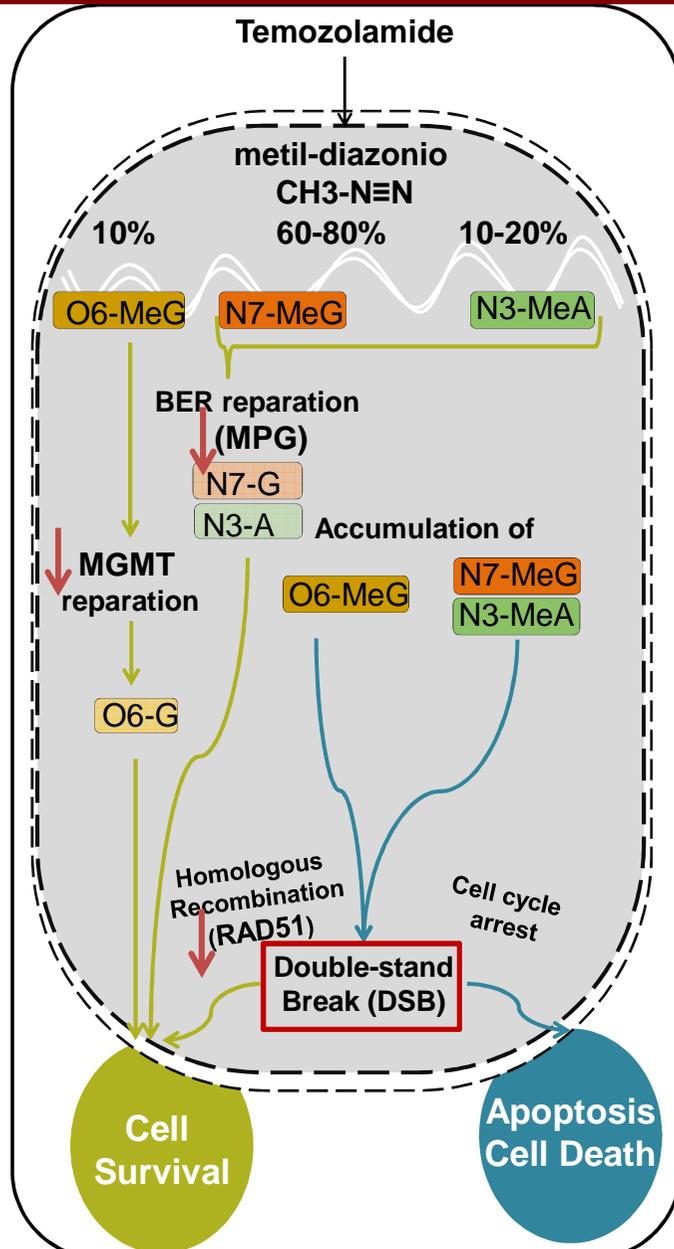
# Combination of SLM/TMZ results in low levels of proteins involved in TMZ response



Adapted from Yoshimoto et al., 2012

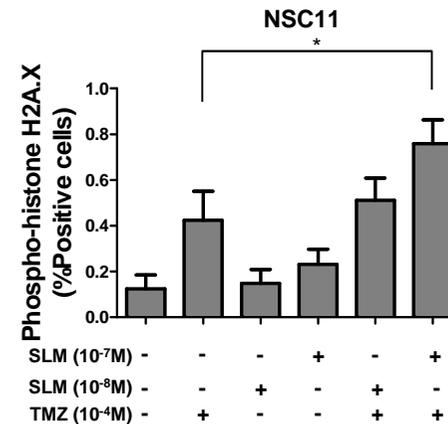
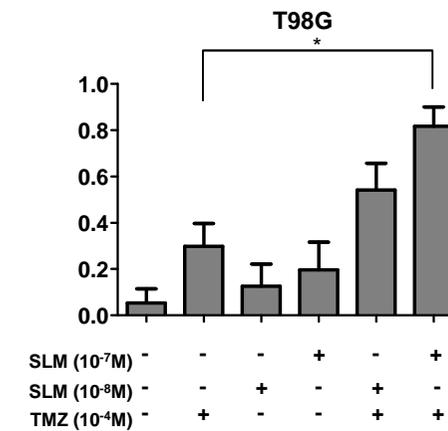
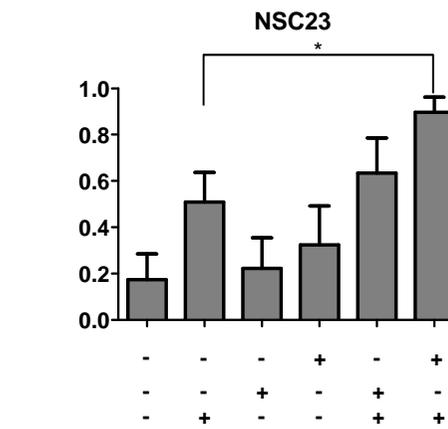
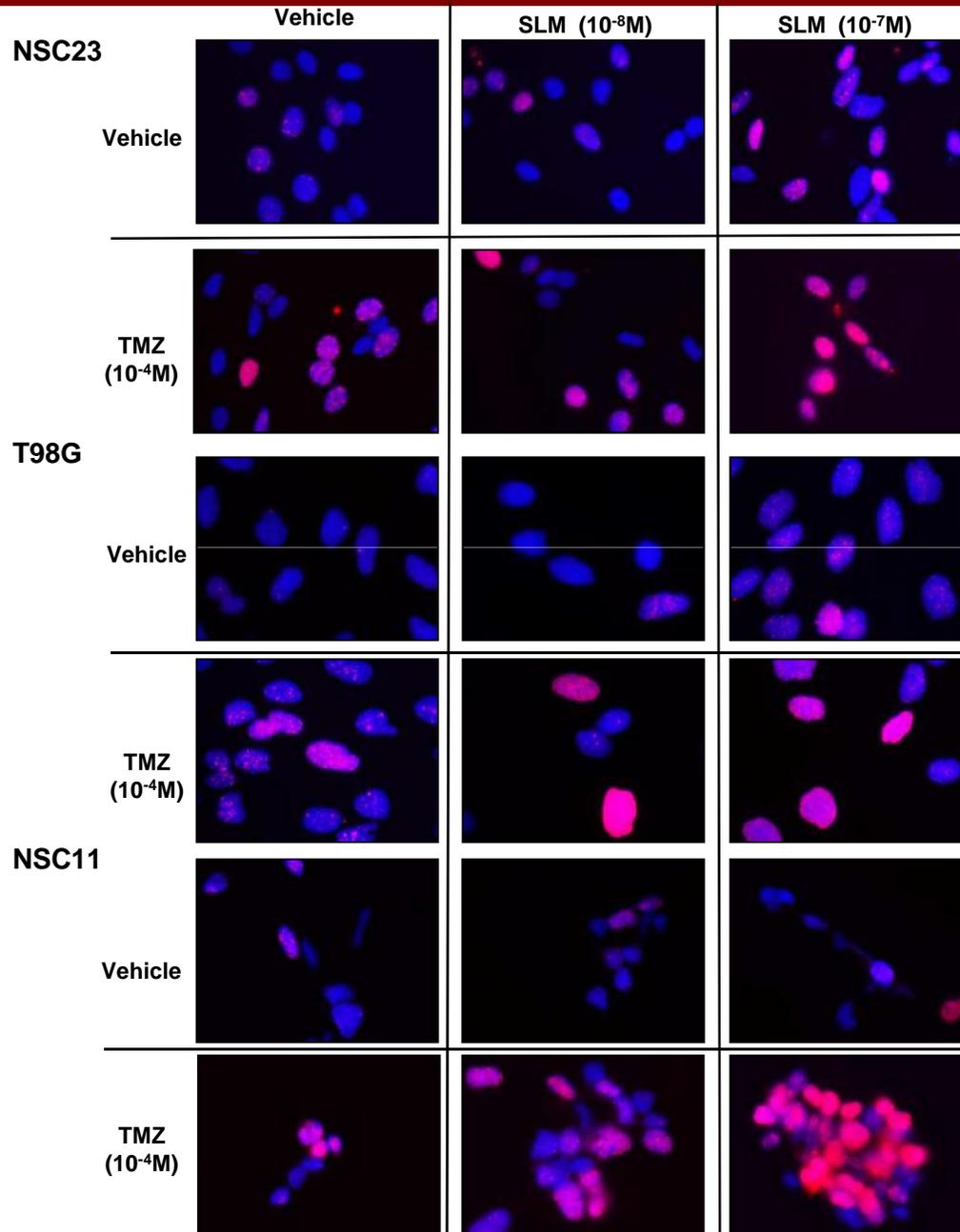


# SLM plus TMZ increments DSB

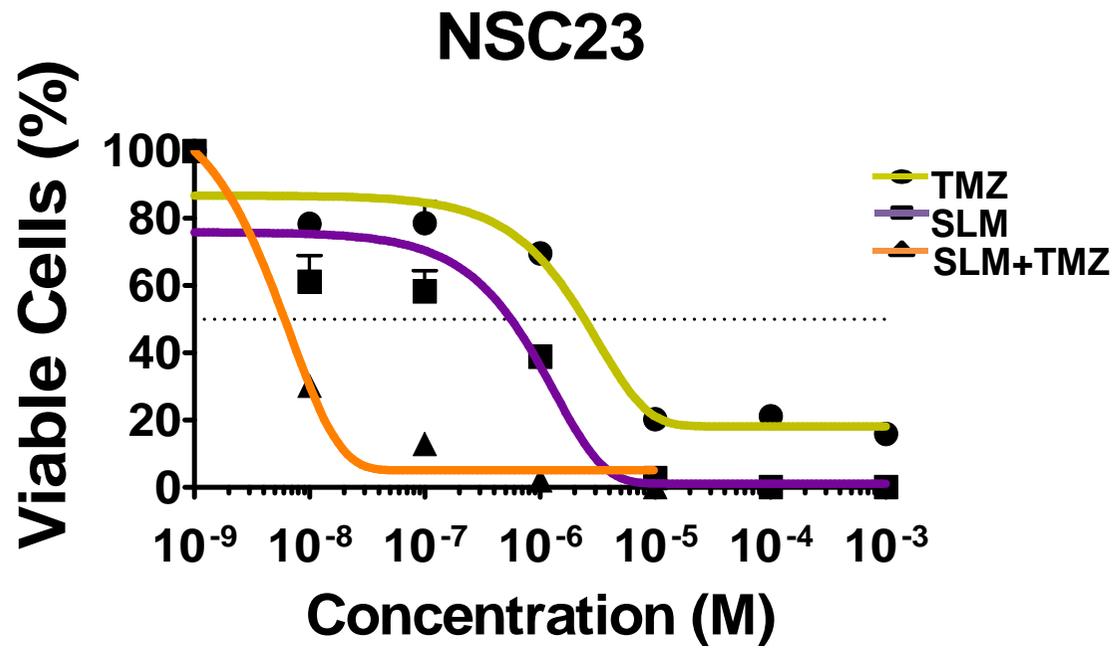


Adapted from Yoshimoto et al., 2012

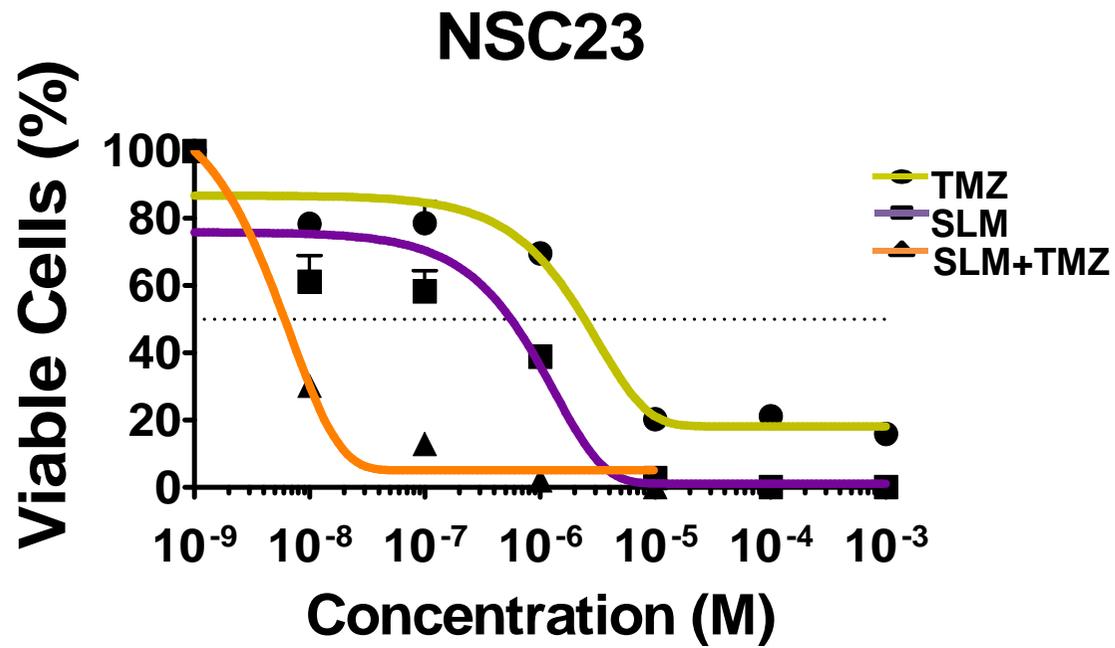
# Combination of SLM with TMZ increments DSB



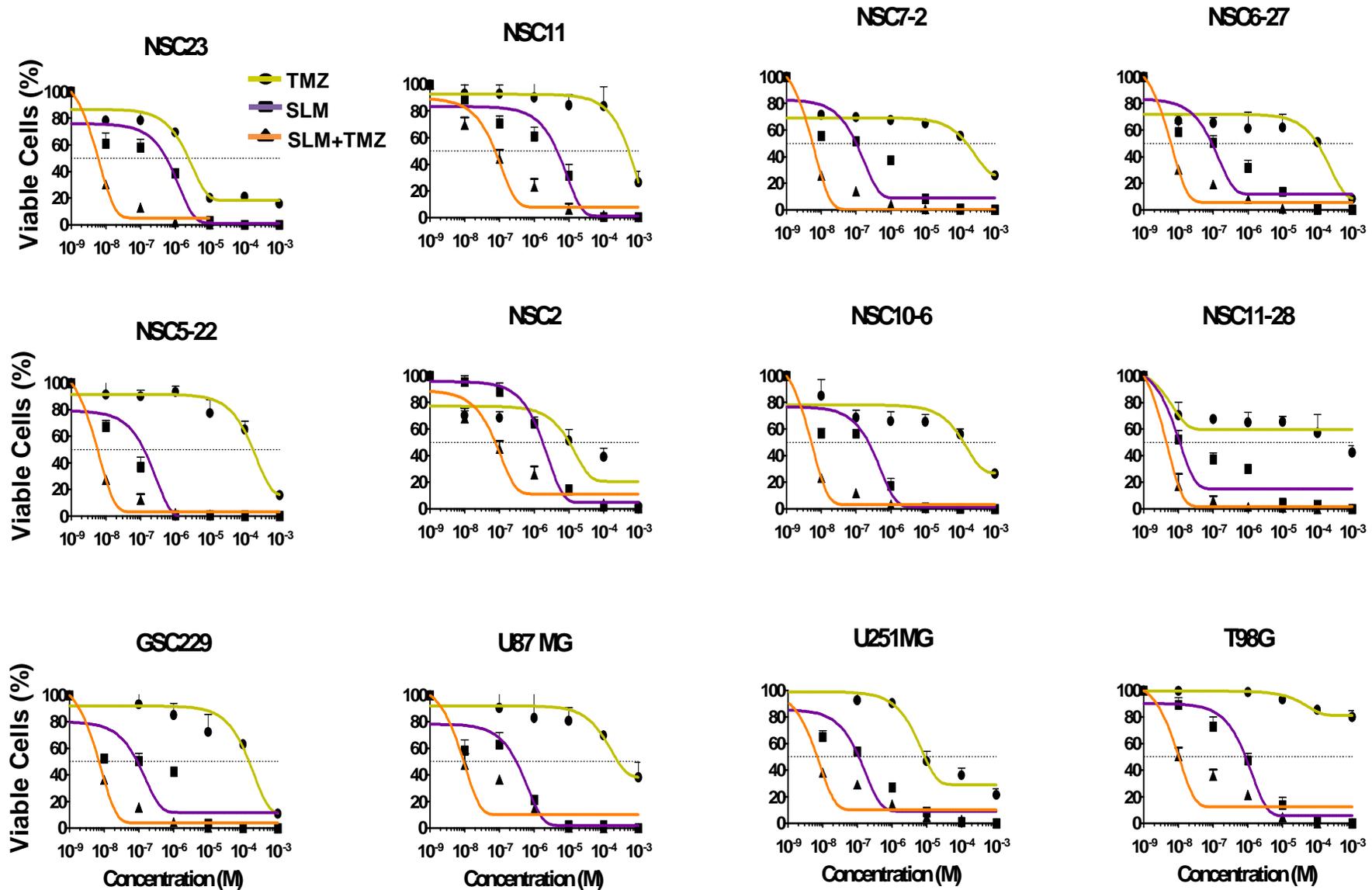
# SLM in combination with TMZ exerts a potent antitumor effect



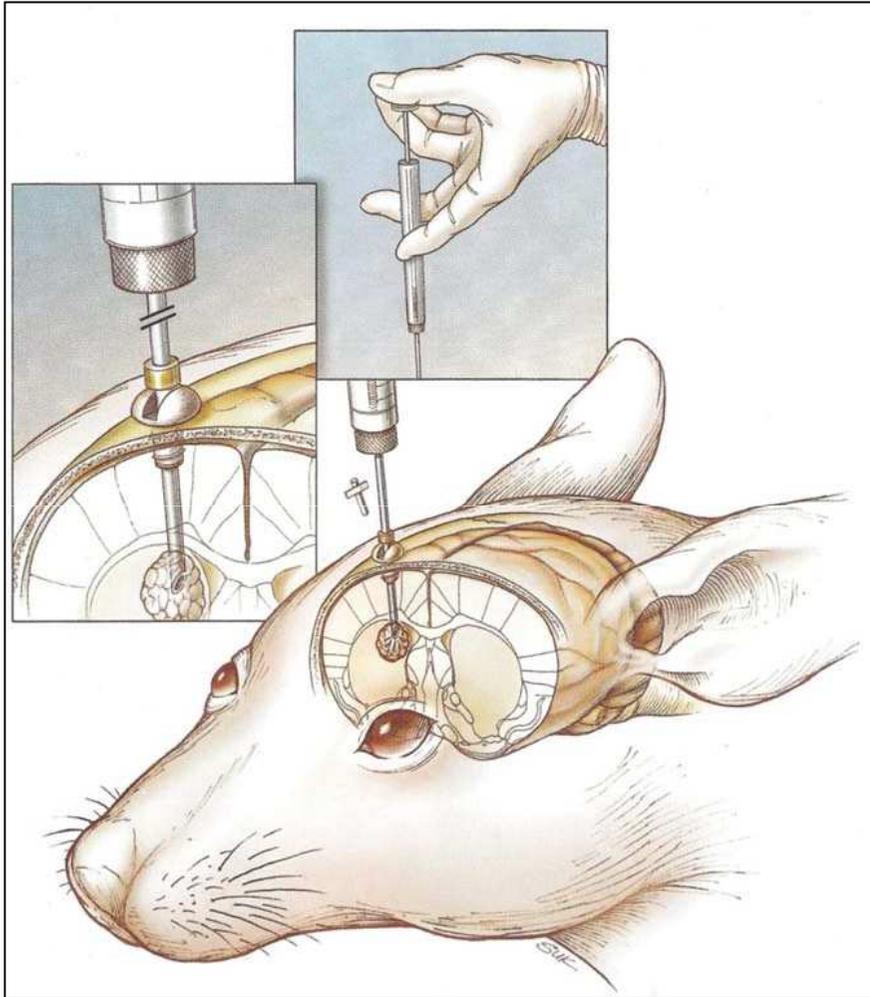
# SLM in combination with TMZ exerts a potent antitumor effect



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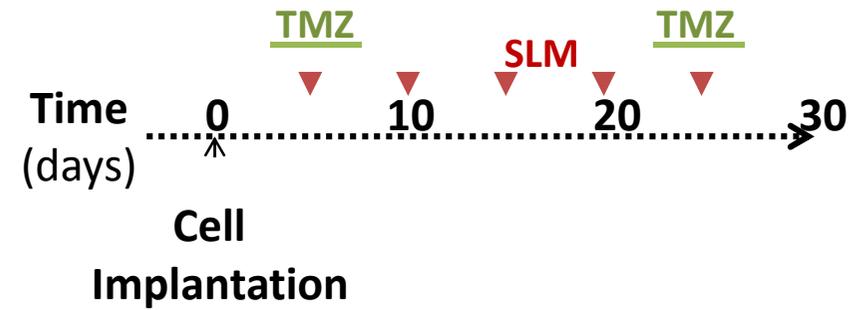


# *in vivo* experiments

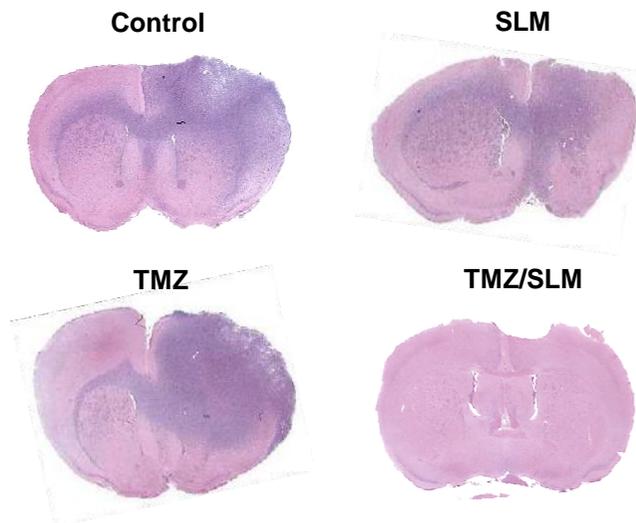
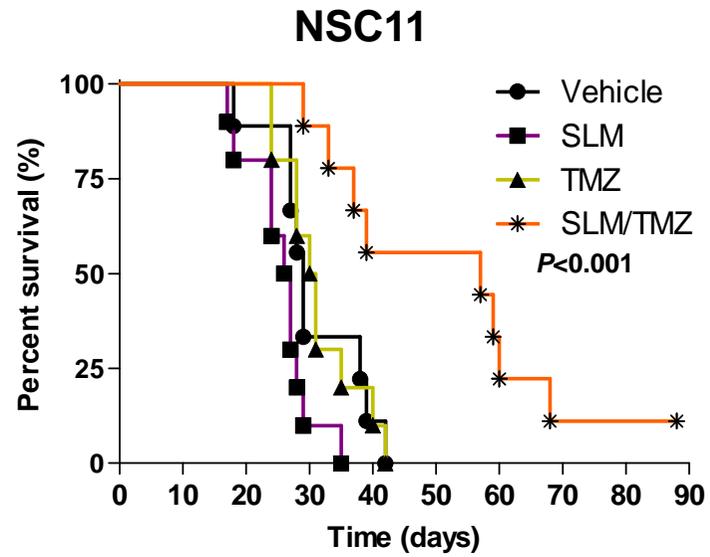


Adapted from Lal et al., 2000

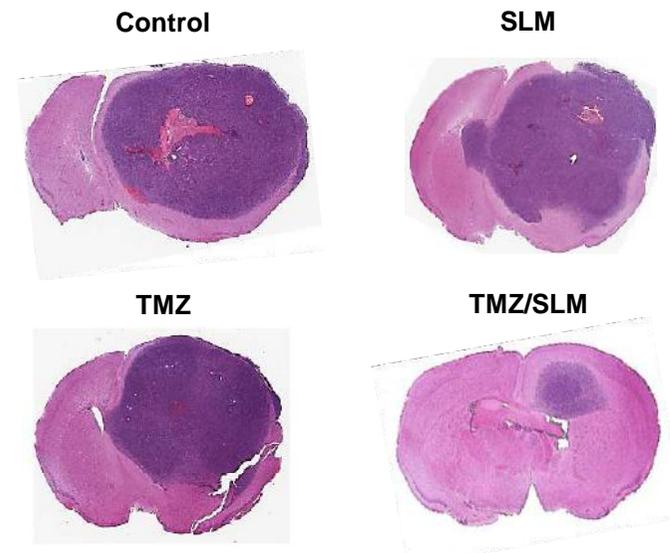
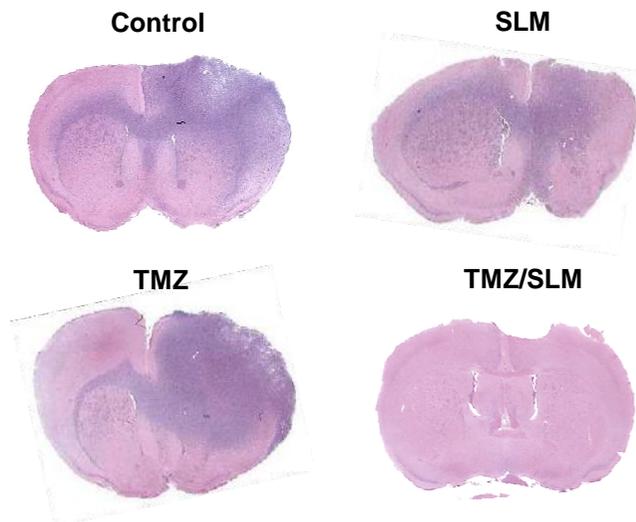
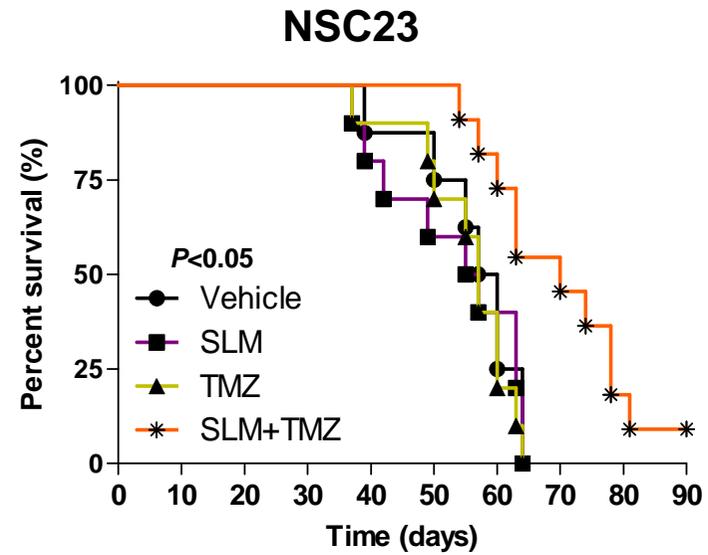
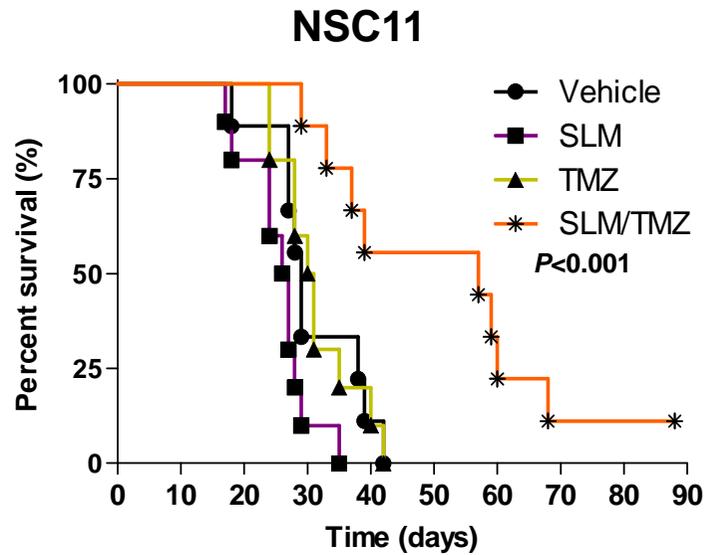
Treatment scheme:



# SLM plus TMZ results in a significant antitumor effect *in vivo*



# SLM plus TMZ results in a significant antitumor effect *in vivo*



# Acknowledgements:

- **Marta M. Alonso Roldán**
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- **Cristian Smerdou**
- **Pepe Quetglas**

- **Juan Fueyo**
- **Candelaria Gómez**
- Hong Jiang
- Yisel Rivera
- Belayat Hossain
- Shifat Rehnuma
- Fan Xuejun
- Farah Mukheef

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- **Antonia García Garzón**



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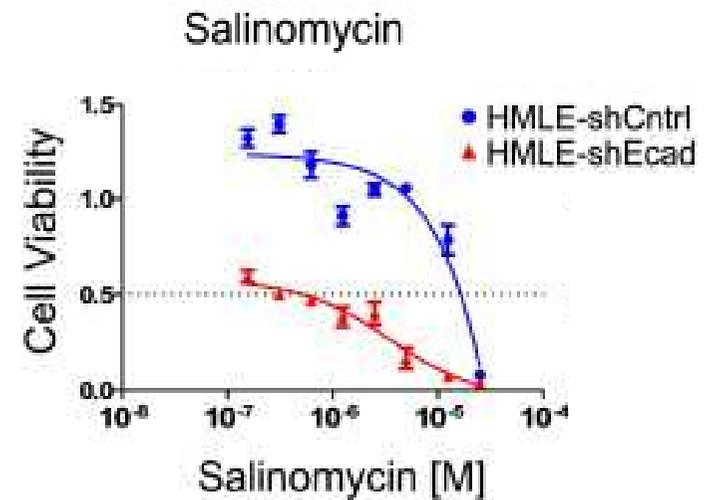
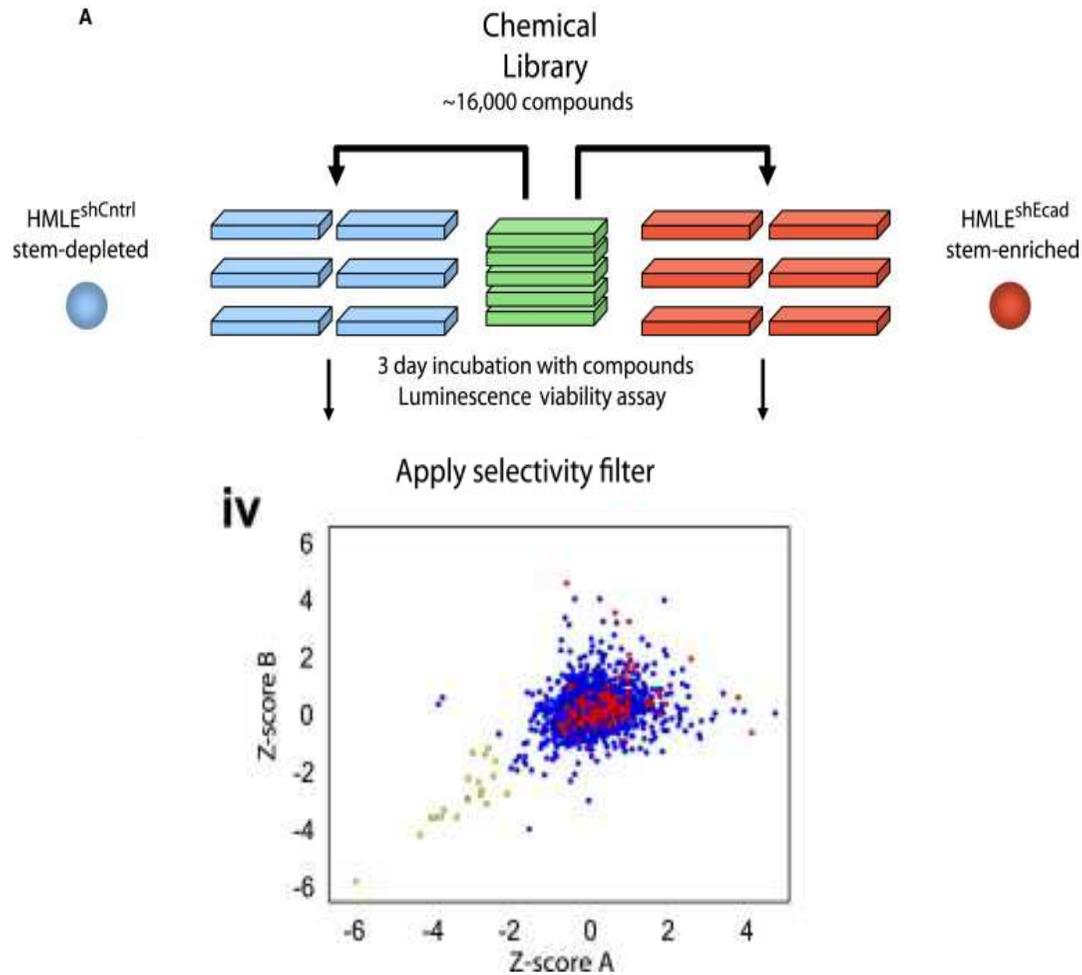
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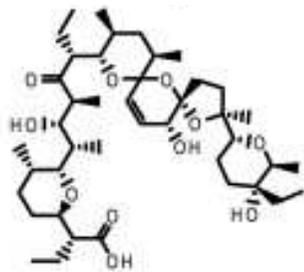
1 de juny de 2016

# High throughput screening on CSC

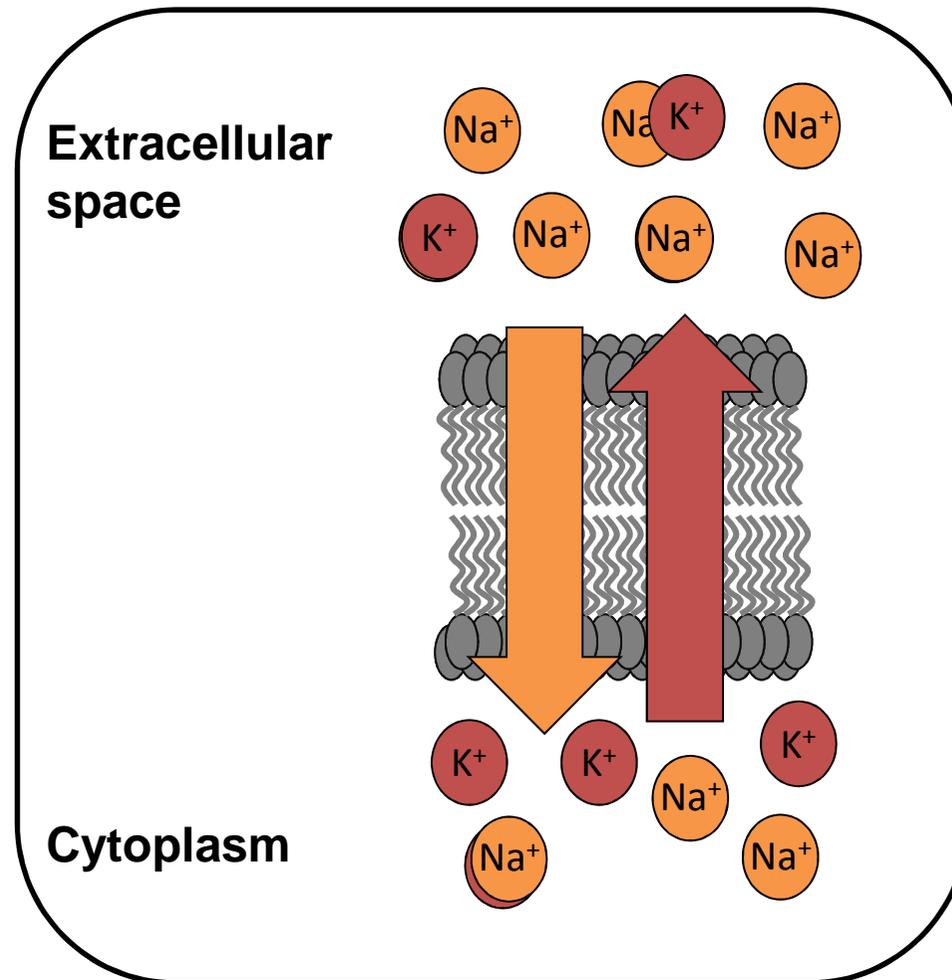


# Molecular mechanism of action of Salinomycin (SLM)

Ionophore for  $K^+$  and  $Na^+$ .



Adapted from  
Gupta et. al., 2009



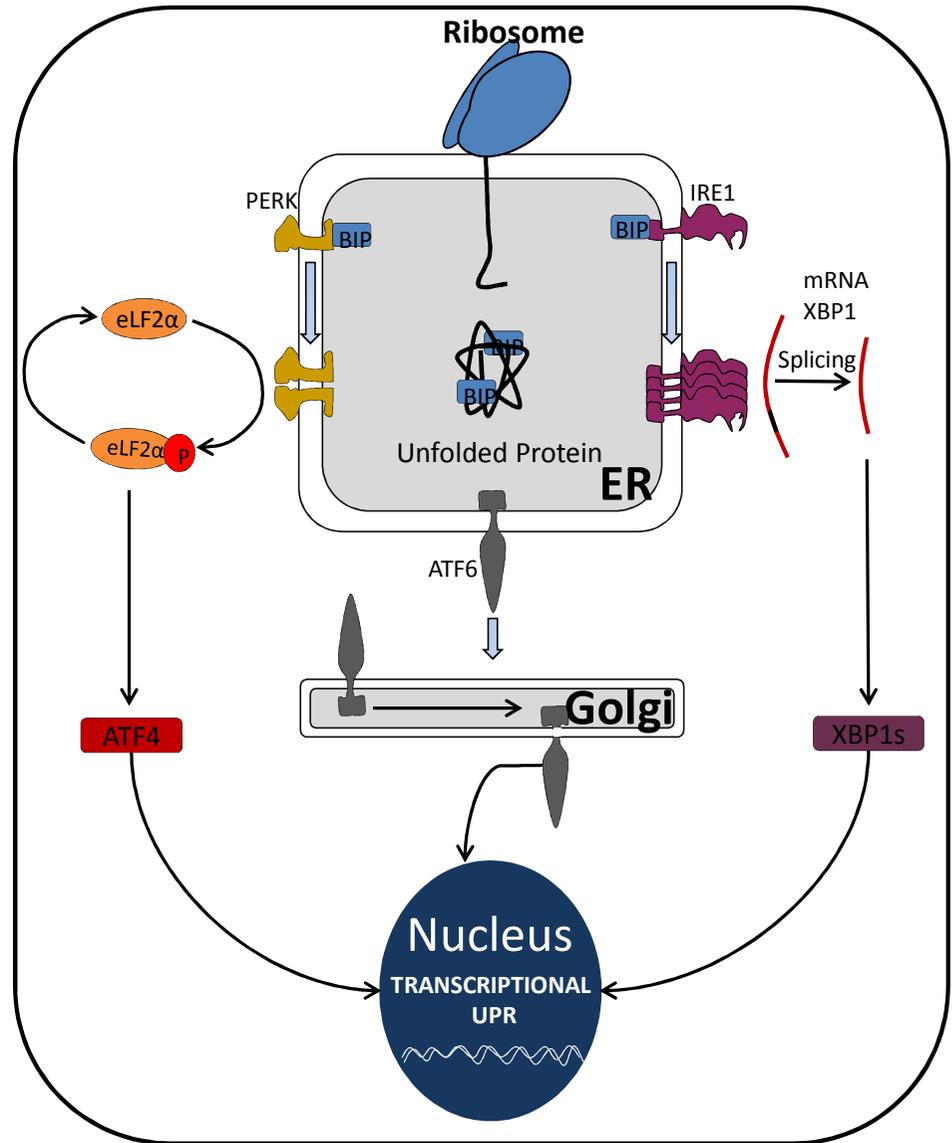
# Salinomycin and UPR

Halting protein translation

Degrading misfolded proteins

Increasing chaperones and/or proteins related to the protein folding

Cell death induction mediated by Apoptosis



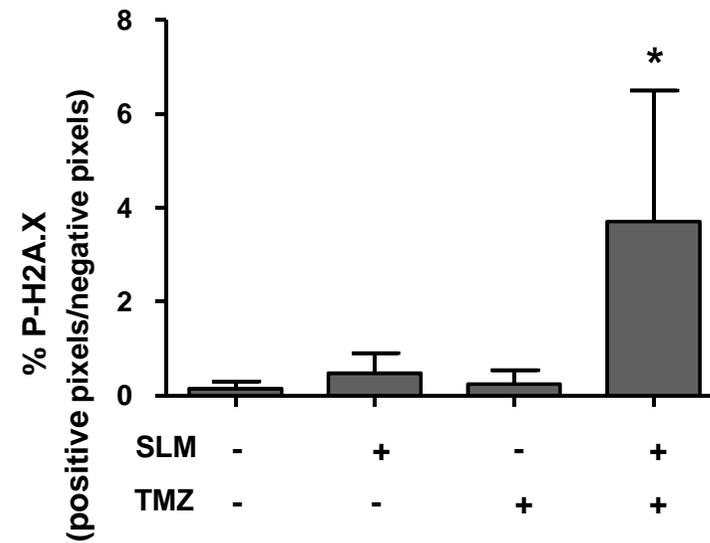
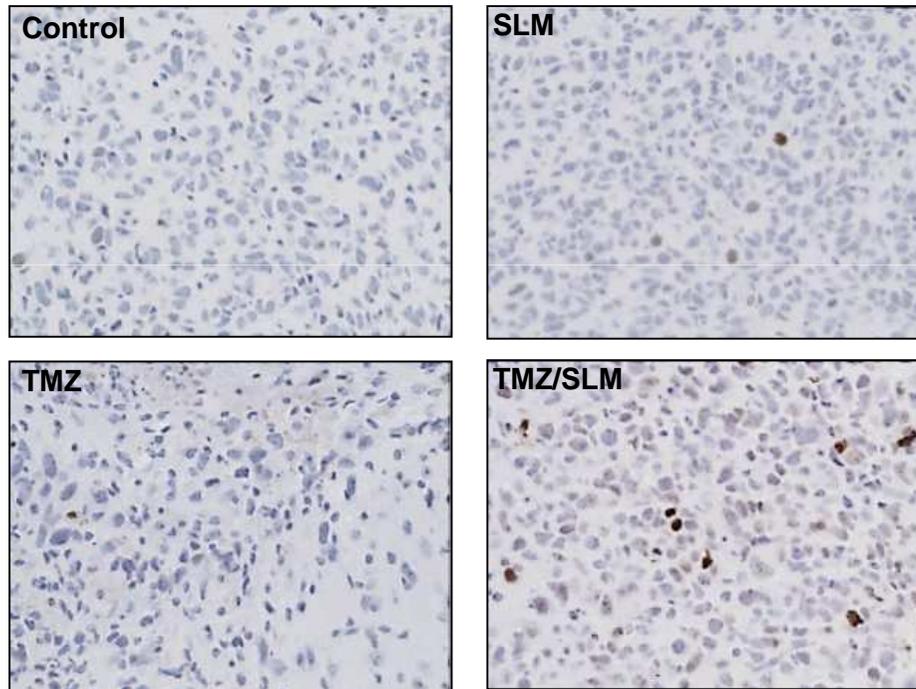
Adapted from Clarke et. al., 2009



## 2. SLM plus TMZ increments DSB *in vivo*

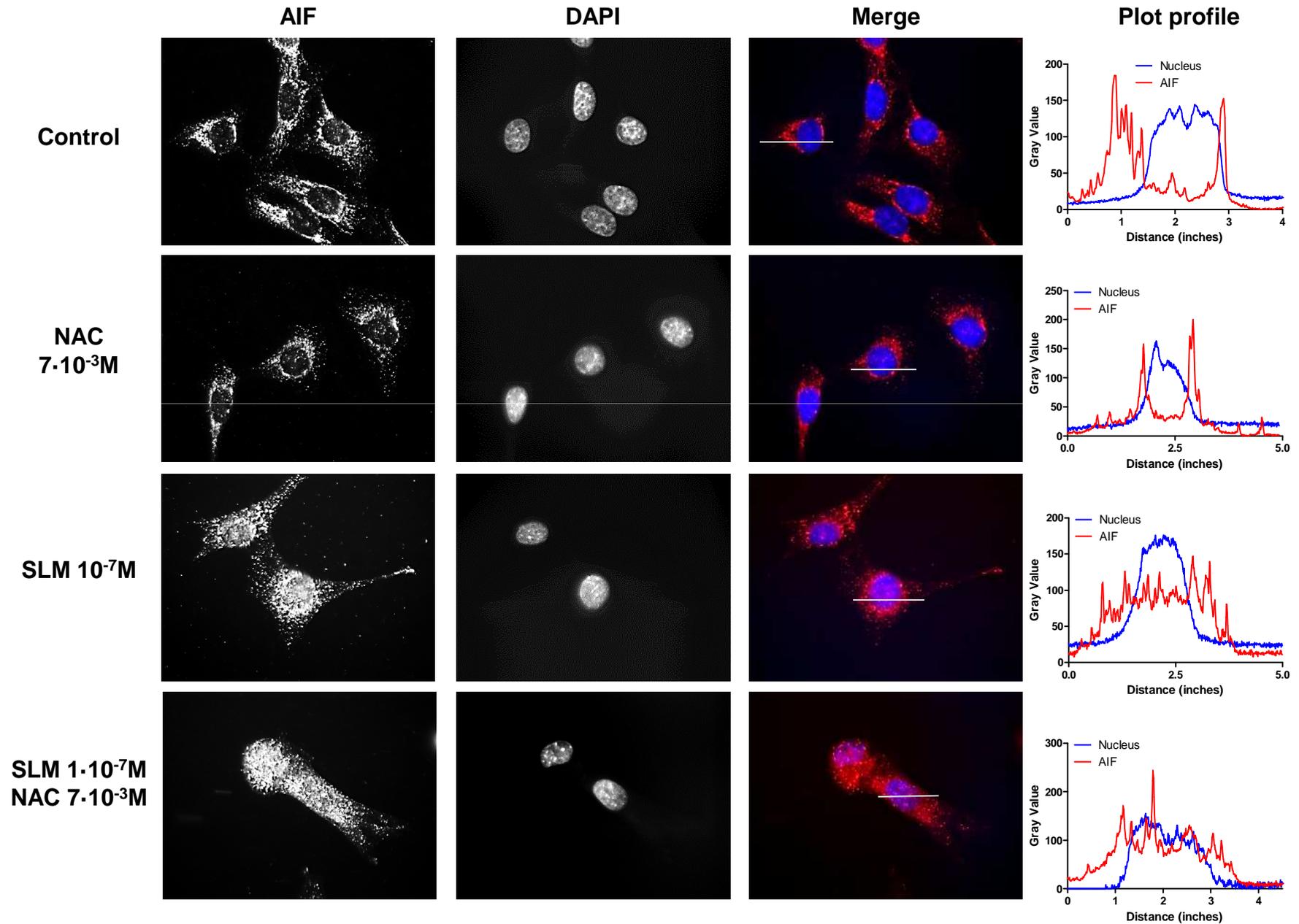
NSC11

P-H2A.X

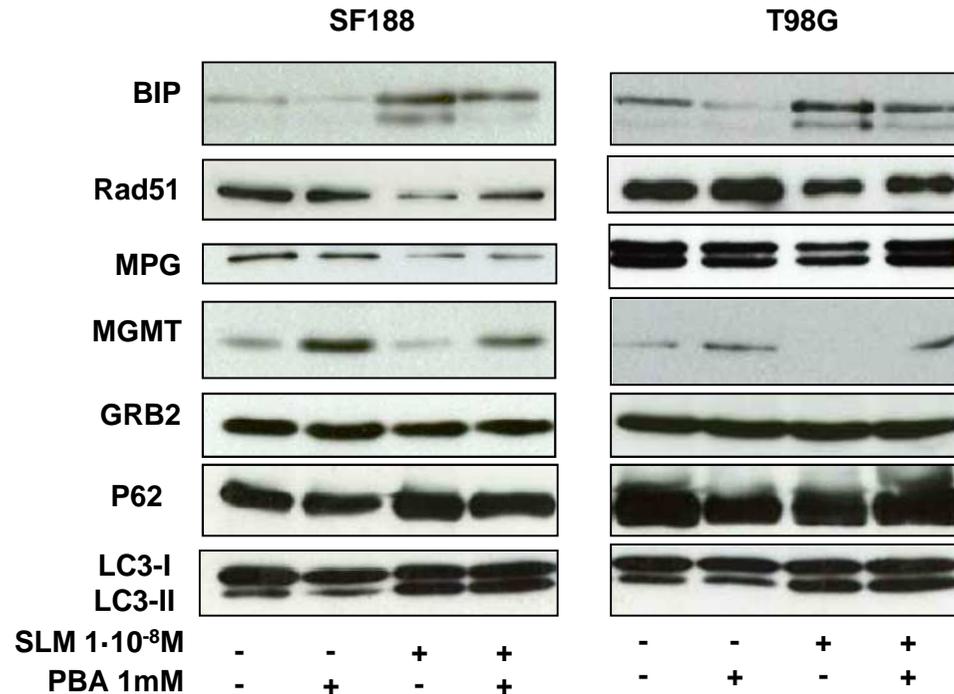
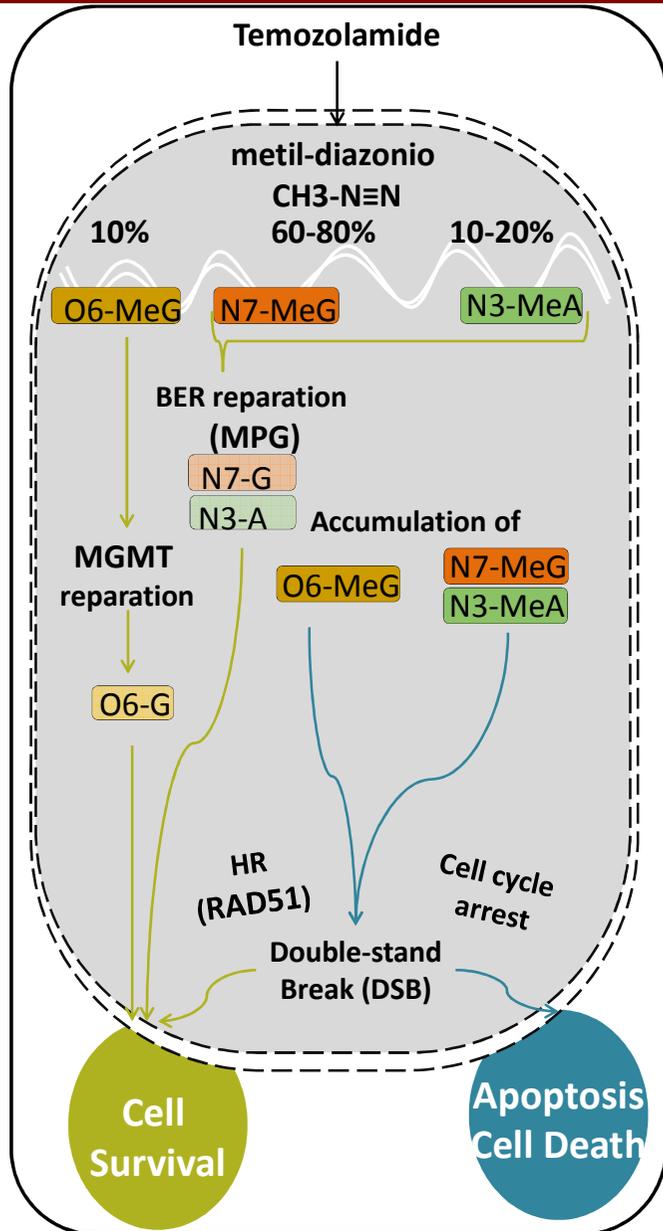




# 1. SLM plus NAC generates autophagy and necrosis



# UPR modulation alters DNA repair protein levels



Adapted from Yoshimoto et al., 2012

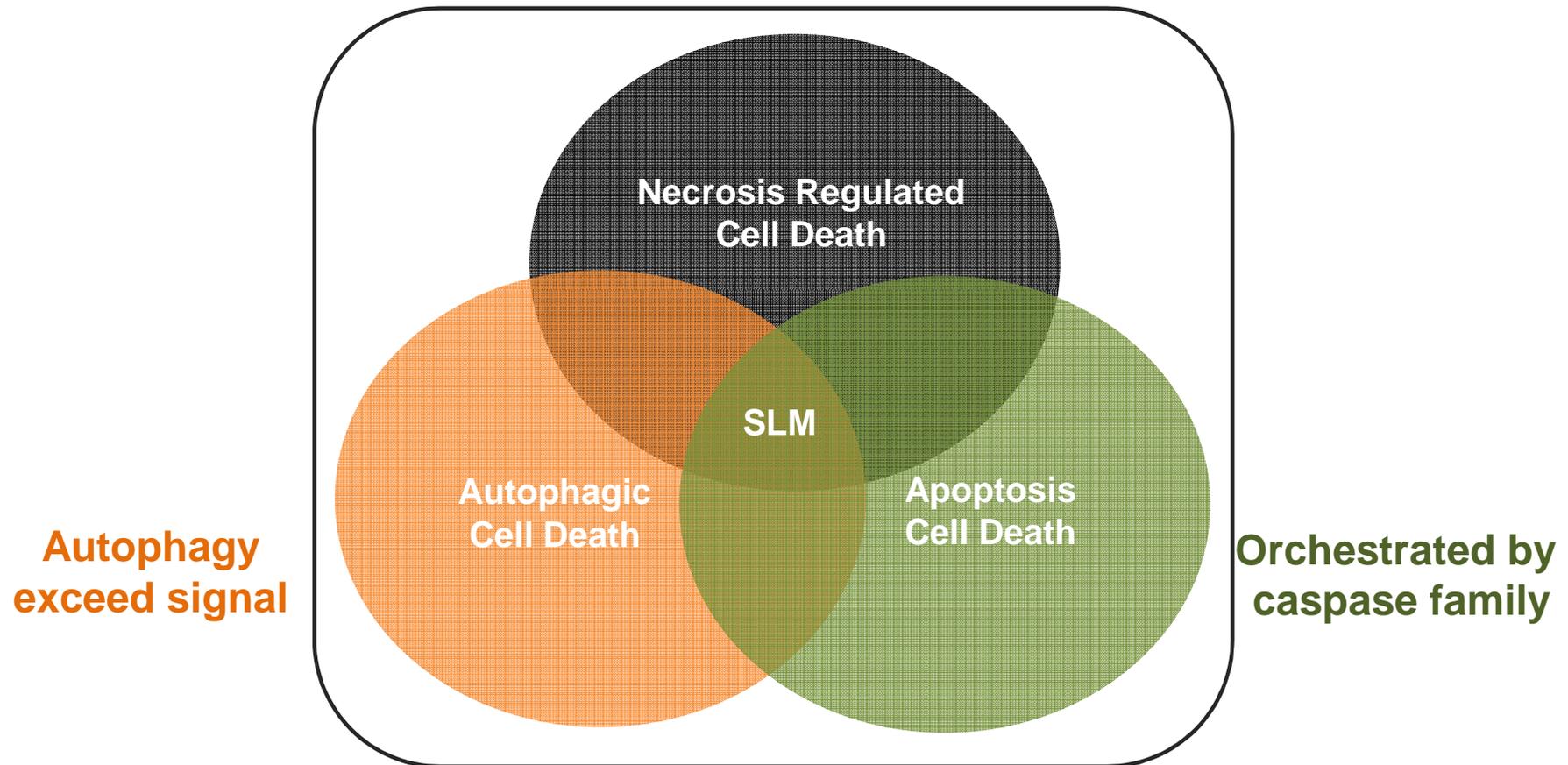
## SLM with TMZ induces a synergistic antiglioma effect

Range of Combination Index	Description	Graded Symbols
<0.1	Very strong synergism	+++++
0.1–0.3	Strong synergism	++++
0.3–0.7	Synergism	+++
0.7–0.85	Moderate synergism	++
0.85–0.90	Slight synergism	+
0.90–1.10	Nearly additive	±
1.10–1.20	Slight antagonism	-
1.20–1.45	Moderate antagonism	--
1.45–3.3	Antagonism	---
3.3–10	Strong antagonism	----
>10	Very strong antagonism	-----

Adapted from **Chou and Talahay ,1984.**

# SLM and regulated cell death

Programmed and different  
cell death from autophagy  
and apoptosis

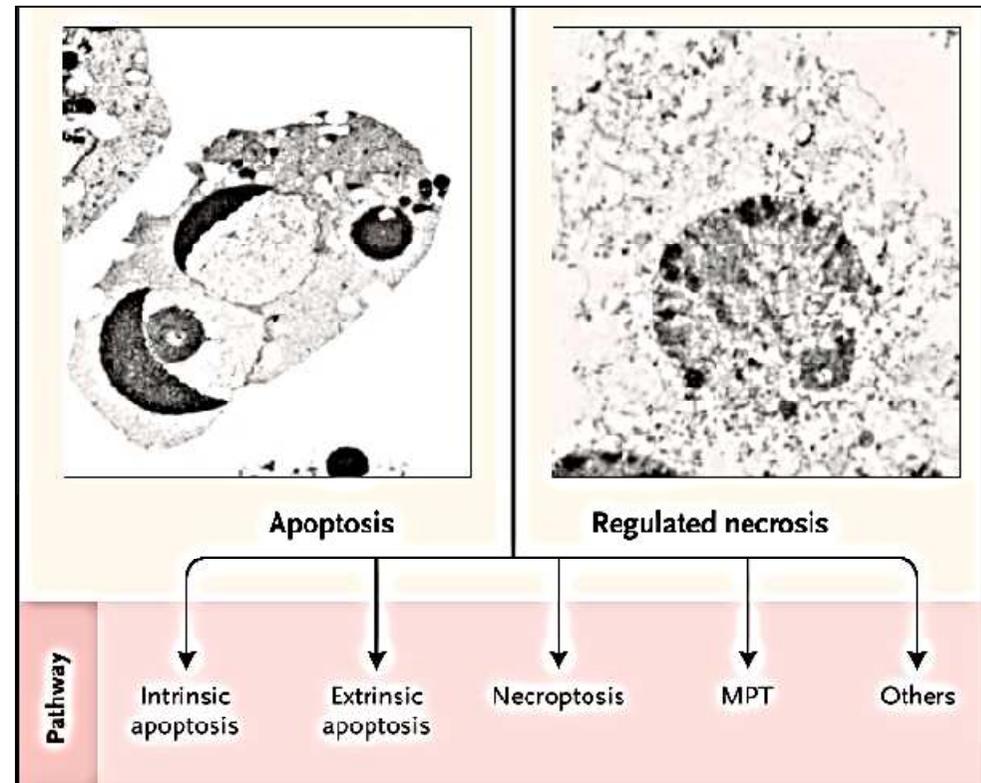


# Necrosis cell death

## Regulated Necrosis:

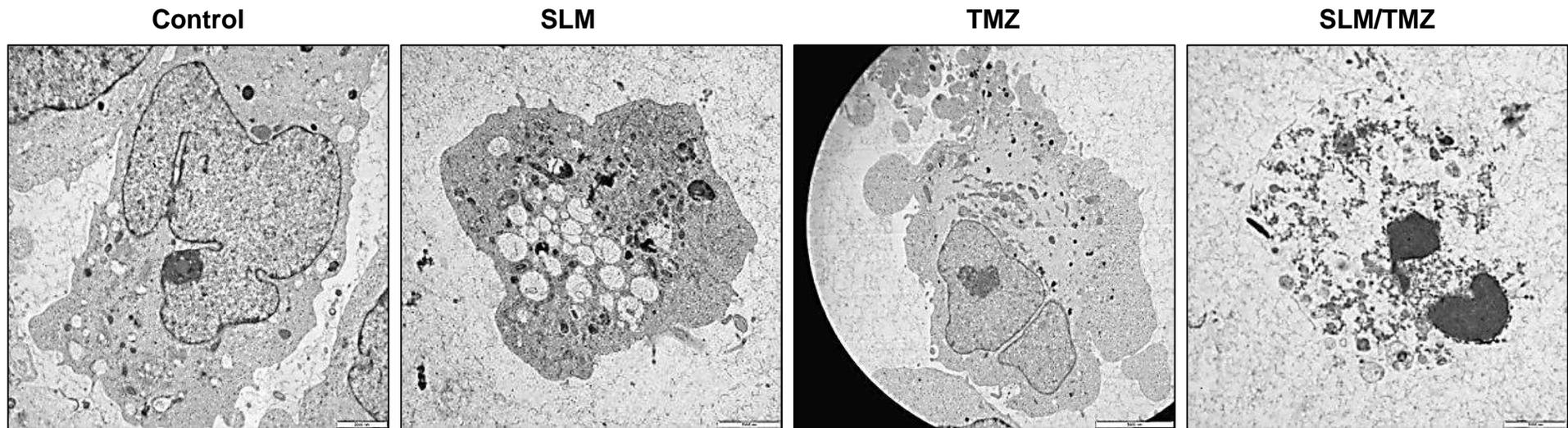
Regulated necrosis cell death is the least characterized cell death.

There are **not determinant markers** for necrosis regulated cell death, however several process have been related with this type of cell death.



Adapted from Linkerman et al., 2014

# TMZ/SLM induces regulated necrosis cell death



SF188

