

**Histone deacetylases inhibitors:
a new strategy for Radiosensitization
in WHO Grade-IV glioma**

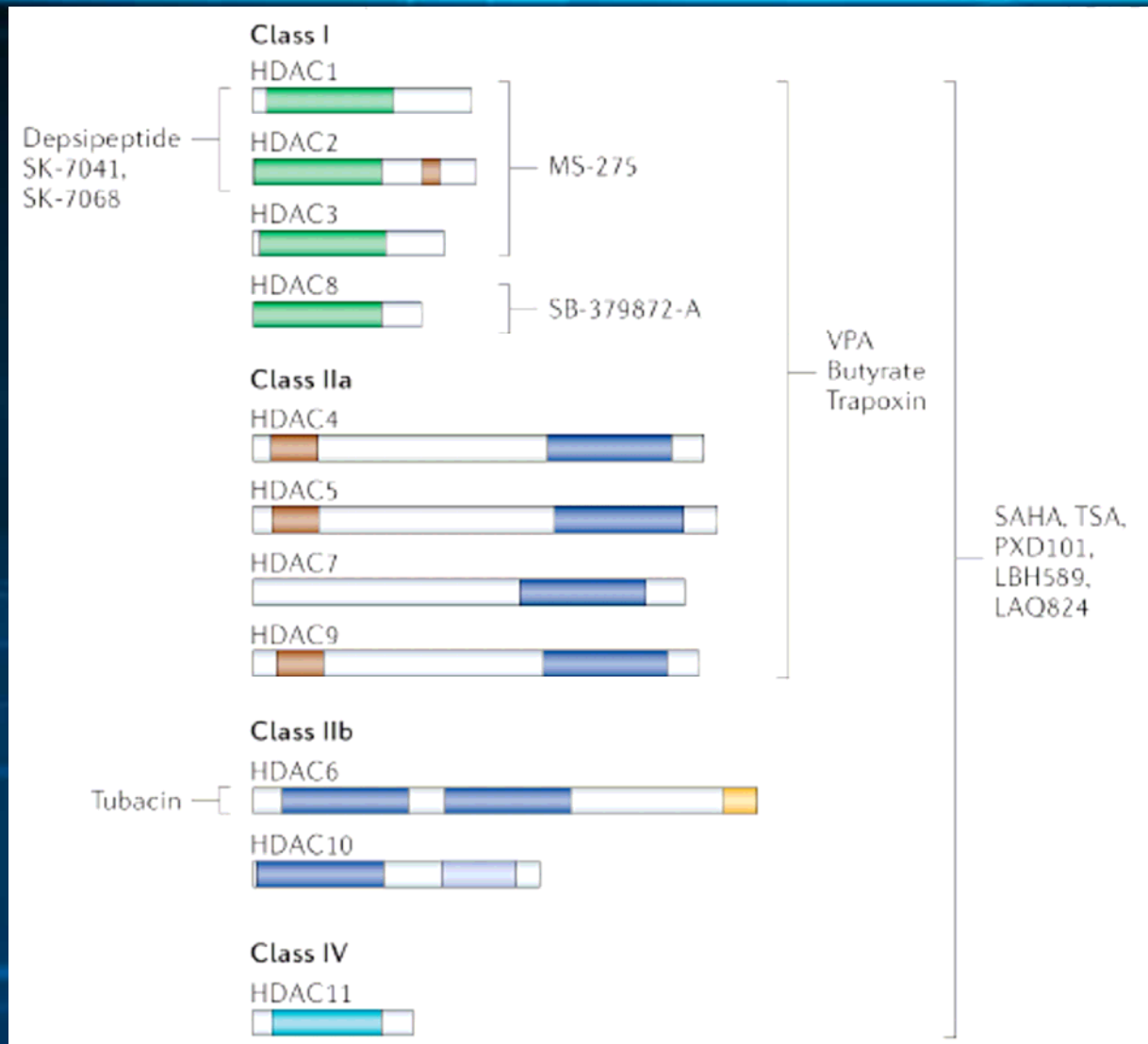
Giovanni Luca Gravina M.D.

*Department of Oncology
Division of Radiation Oncology
University of L’Aquila
Prof. Vincenzo Tombolini*



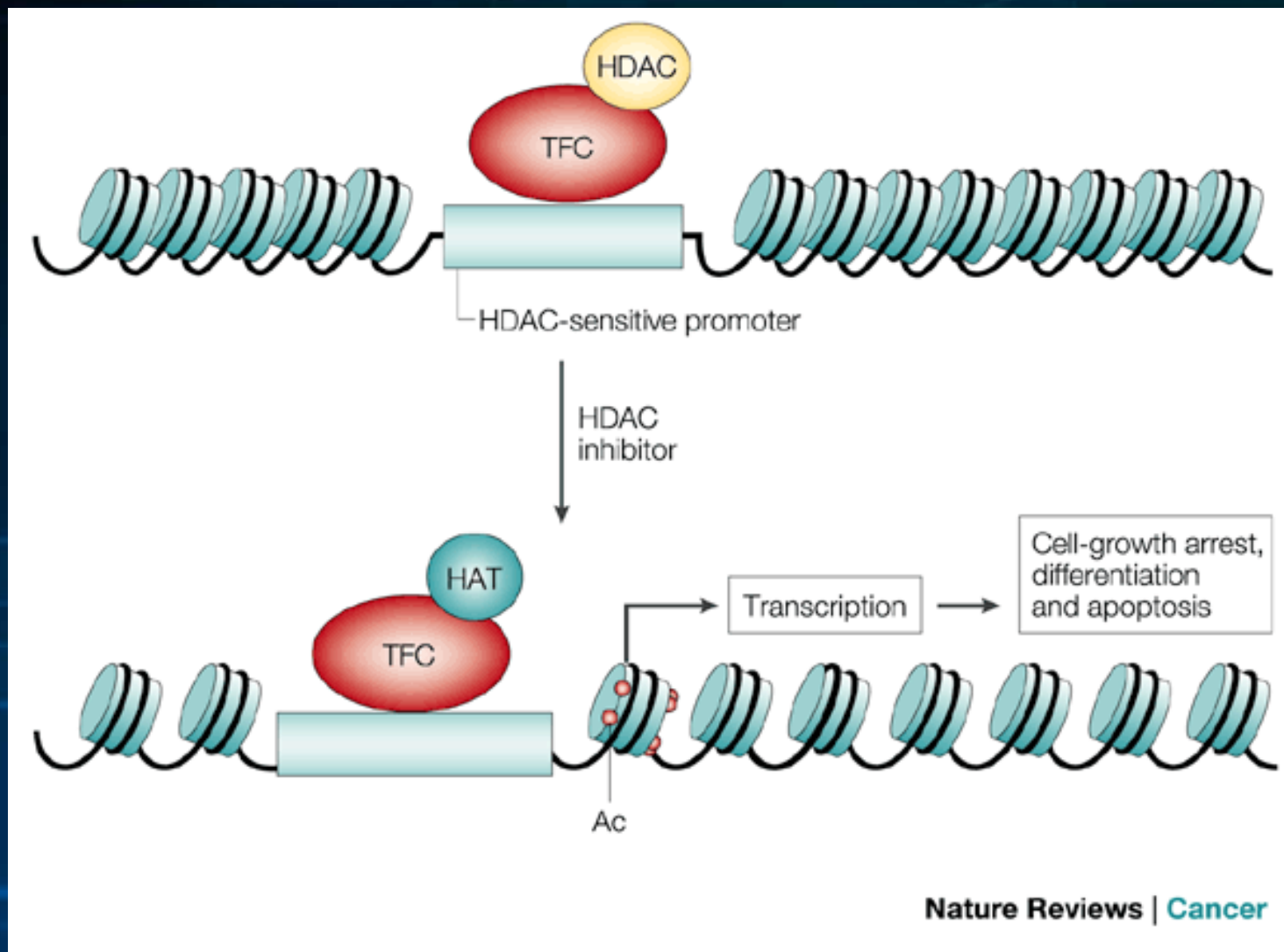
Epigenetic Cancer Therapy Makes Headway

2



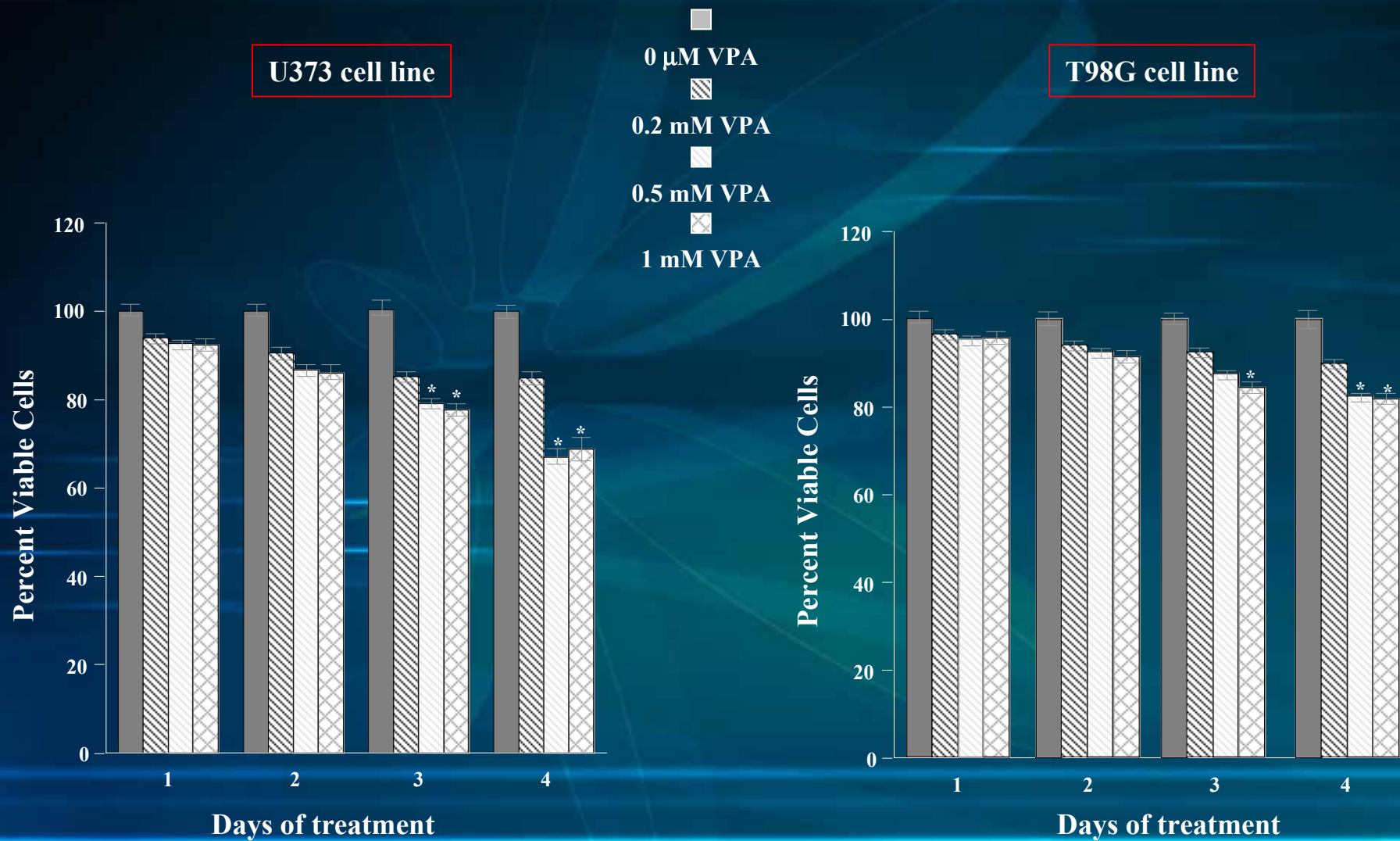
Histone deacetylase inhibitors: How they do work?

3



Experimental data





Meeting in radiobiology – AIRB L'Aquila 2008

6

U373 cell line

VPA acute treatment (day 4)

	Control	VPA (0.5 mM)	P value*
Apoptosis	5+/- 2.1%	25+/- 7.2%	0.010

*Unpaired t -student test

U373 cell line

VPA acute treatment (day 4)

	Control	VPA (0.5 mM)	P value*
G1/G0	50+/- 6.7%	40+/-5.2%	0.11
S	21+/- 3.9%	10+/-2.9%	0.017
G2/M	29+/- 2.8%	50+/- 6.1%	0.006

*Unpaired t -student test

T98G cell line

VPA acute treatment (day 4)

	Control	VPA (0.5 mM)	P value*
Apoptosis	3+/- 1.8%	10.0+/-5.2%	0.092

*Unpaired t -student test

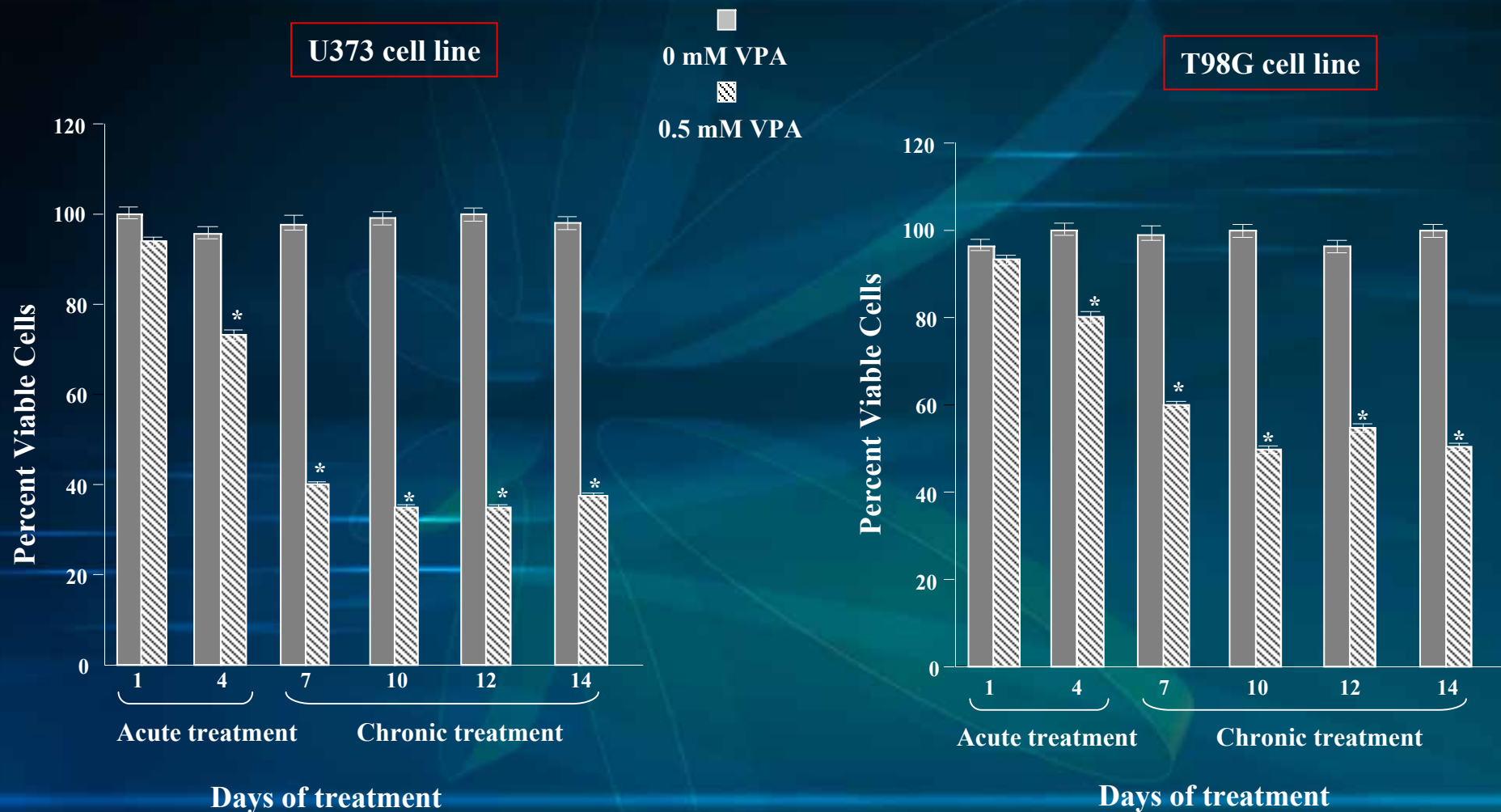
T98G cell line

VPA acute treatment (day 4)

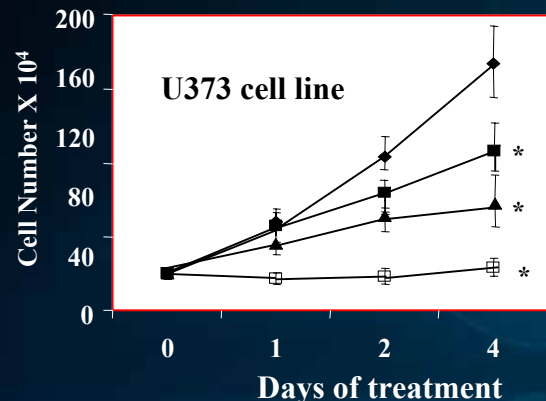
	Control	VPA (0.5 mM)	P value*
G1/G0	60+/- 10.1%	46+/- 11.6%	0.18
S	19+/- 4.1%	11+/-2.9%	0.051
G2/M	21+/-4.9%	40+/-8.5%	0.028

*Unpaired t -student test





◇ Basal } Cells without chronic
 □ TMZ } VPA treatment
 △ Basal } Chronic treatment
 ▣ TMZ } with VPA



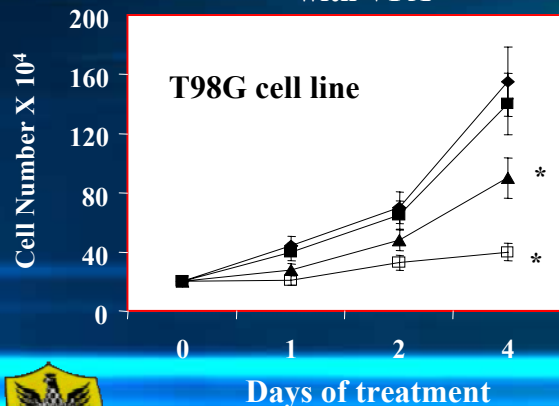
U373 cell line

VPA chronic treatment (day 10)

	Control	TMZ 50 μM	TMZ 50 μM	P value*
<u>Apoptosis</u>	4+/- 2.1%	39.7+/-5.1%	59.5+/-9.1%	<0.0001

*One-Way ANOVA test

◇ Basal } Cells without chronic
 □ TMZ } VPA treatment
 △ Basal } Chronic treatment
 ▣ TMZ } with VPA



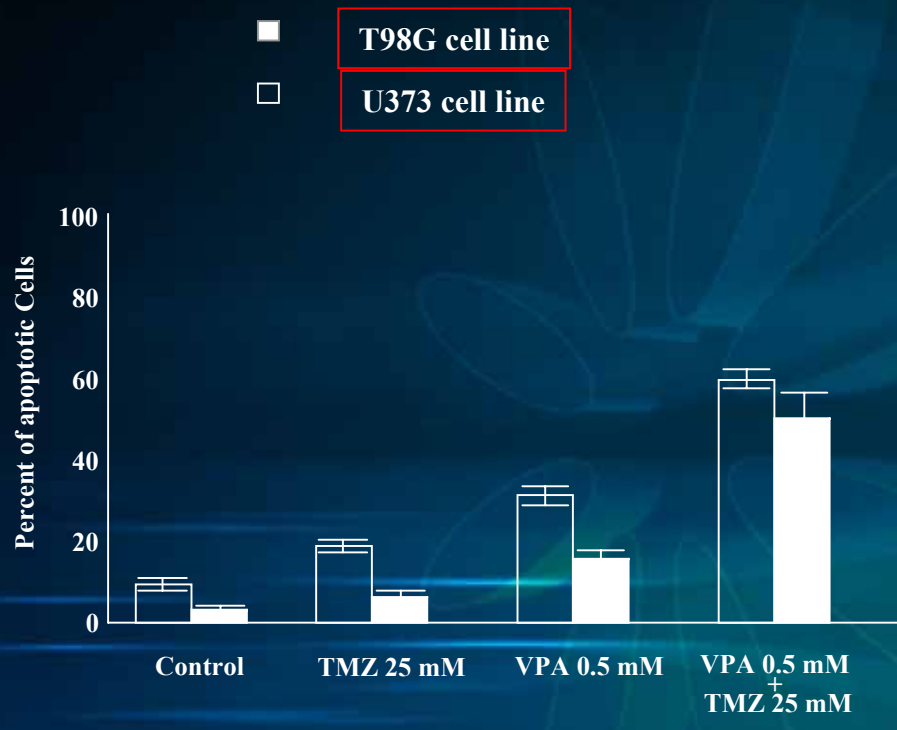
T98G cell line

VPA chronic treatment (day 10)

	Control	TMZ 50 μM	TMZ 50 μM	P value*
<u>Apoptosis</u>	3+/- 2.2%	18.0+/-7.4%	38.2+/-6.6%	<0.0001

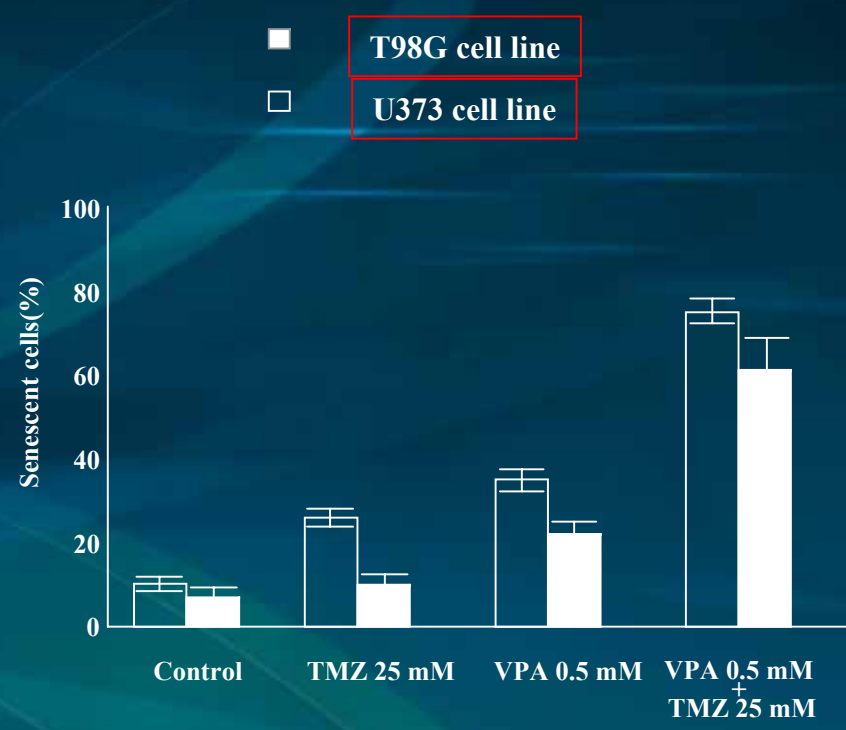
*One-Way ANOVA test





RT (2 Gy)

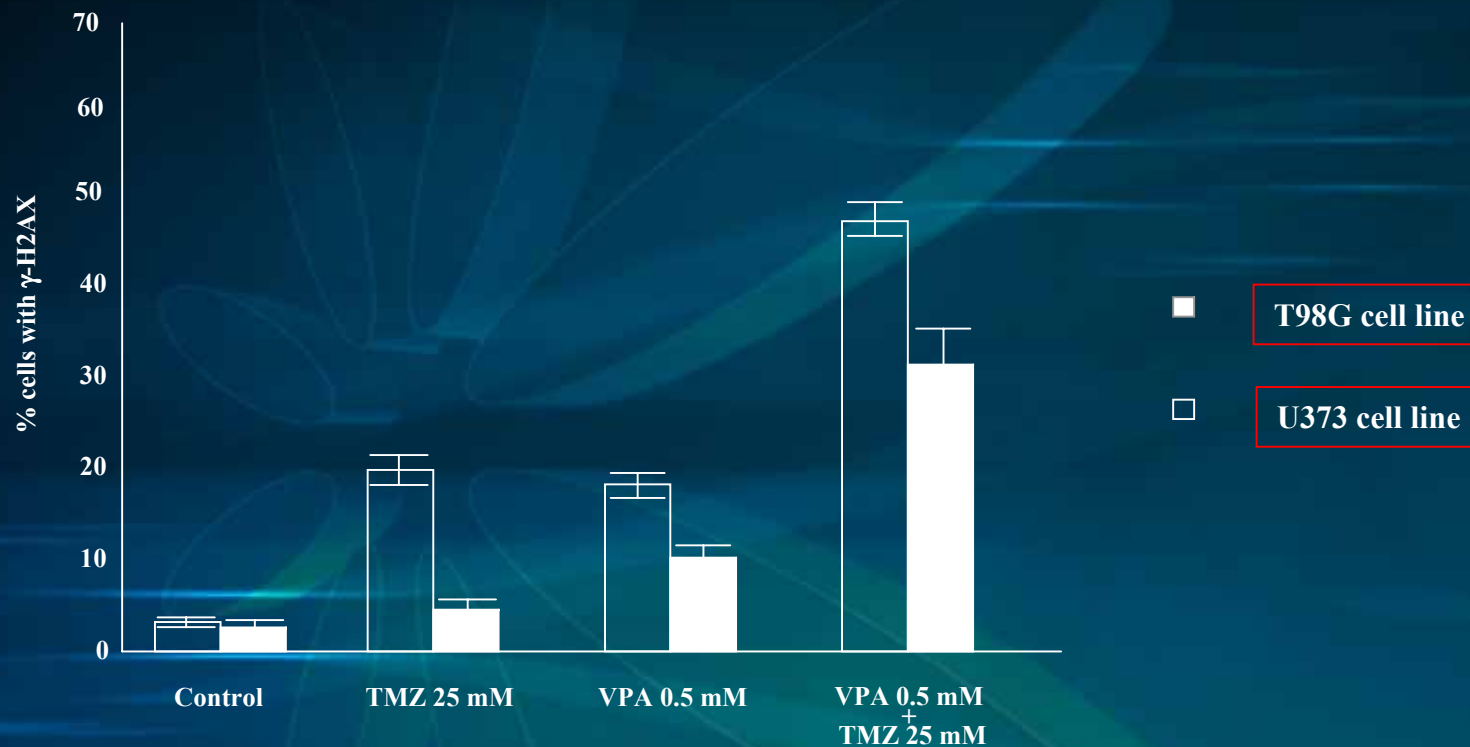
Apoptosis



RT (2 Gy)

Senescence





RT (2 Gy)

DNA double strand breaks



Conclusions

11

- **Acute treatment** with VPA results in a **modest** antitumor effects
- **Chronic administration** of VPA causes a more **pronounced** modulation of cell proliferation and apoptosis
- VPA **sensitizes chemotherapy resistant** tumor cells to **temozolomide** antitumor effects
- VPA **enhances** the **radiosensitivity** of tumor cells by suppressing the cellular DNA repair capacity
- Our results indicate that the **combination** of valproic acid with temozolomide could be a promising strategy for the **controls** of **glioblastomas** regardless of whether the cells are **sensitive** or **resistant** to DNA damaging anticancer drugs





Università Degli Studi Dell'Aquila
Facoltà di Medicina e Chirurgia

Dipartimento di Medicina Sperimentale

U.O. di Radioterapia

Presidio Ospedaliero – S. Salvatore – L'Aquila

Prof. Vincenzo Tombolini

Dr. Pierluigi Bonfili

Dr. Mario Di Staso

Dr. Pietro Franzese

Dr. Sergio Bonopane

Dr. Milena Di Genesisio Pagliuca

Dr. Emilia Varrassi

Dr. Caterina Fardella

Dr. Leda Di Nicola

Dr. Adele Piscopo

Dr. MariaPaola Petrella

Dipartimento di Medicina Sperimentale

Prof. Vincenza Dolo

Dr. Claudio Festuccia

Dr. Danilo Millimaggi

Dr. Sandra D'Ascenzo



Thank you for the attention

