

Newcastle, Australia



CROSS RESISTANCE OF MELANOMA CELLS TO CHEMOTHERAPY AND TRAIL

Peter HERSEY, Xu Dong
ZHANG, Susan GILLESPIE and Jing
Jing WU

University Of Newcastle

CELL KILLING MECHANISMS USED BY LYMPHOCYTES DEPEND ON INDUCTION OF APOPTOSIS

1. Granzyme – Perforin Mediated Killing

CD8 CTL (CD4 CTL)

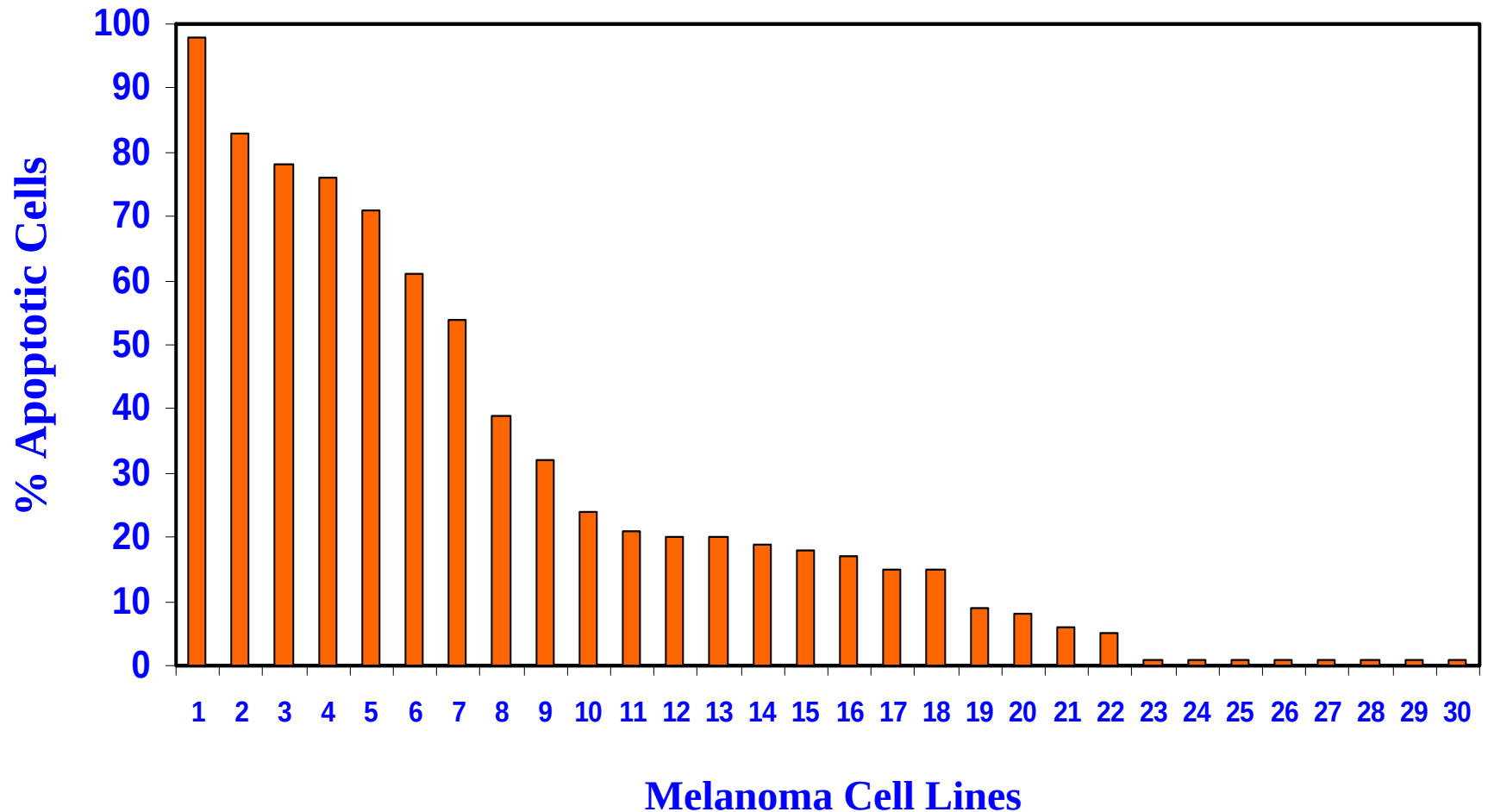
NK Cells and ADCC

2. TRAIL (FasL, TNF- α) Mediated Killing

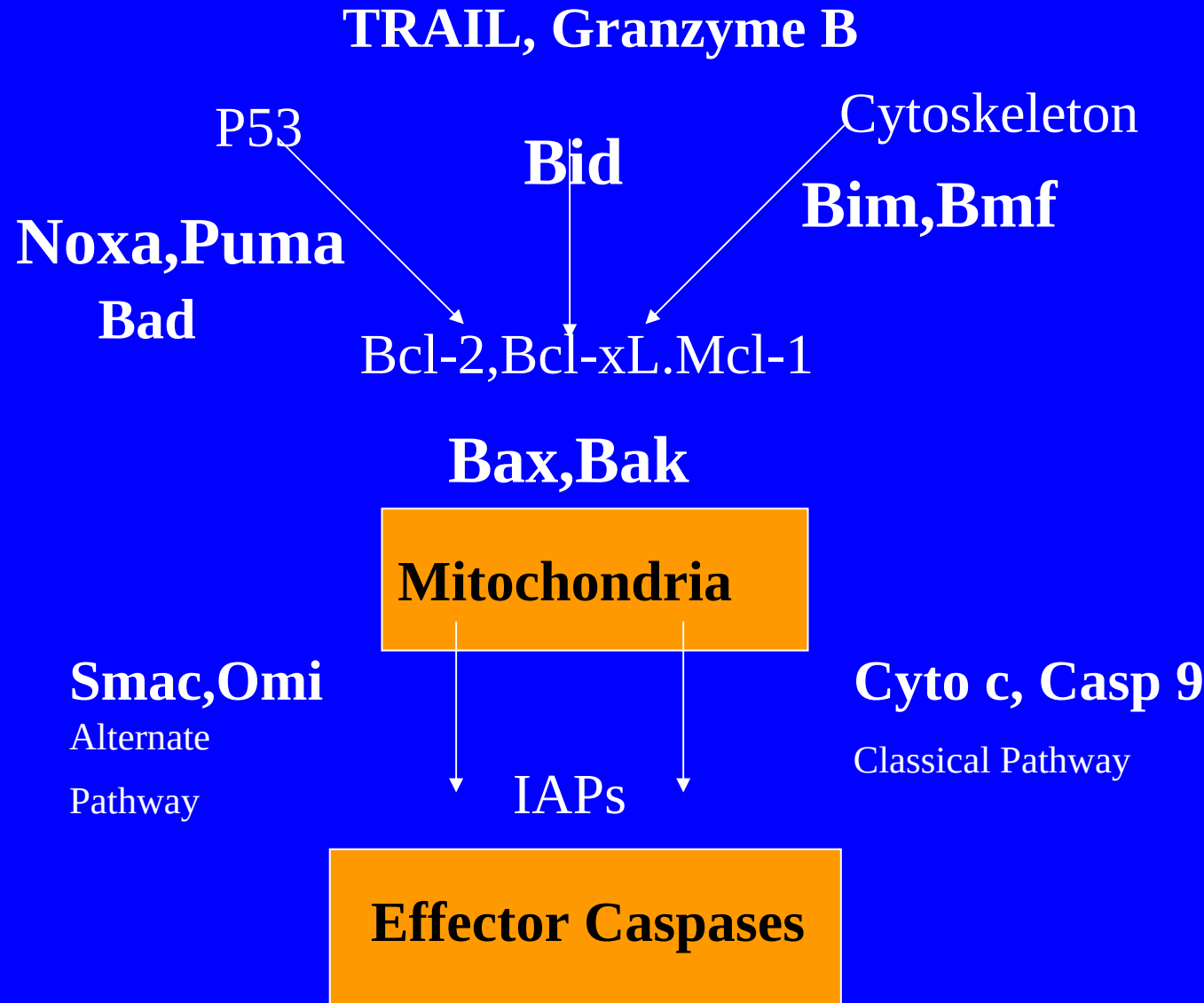
CD4 T Cells

Monocytes, Dendritic Cells

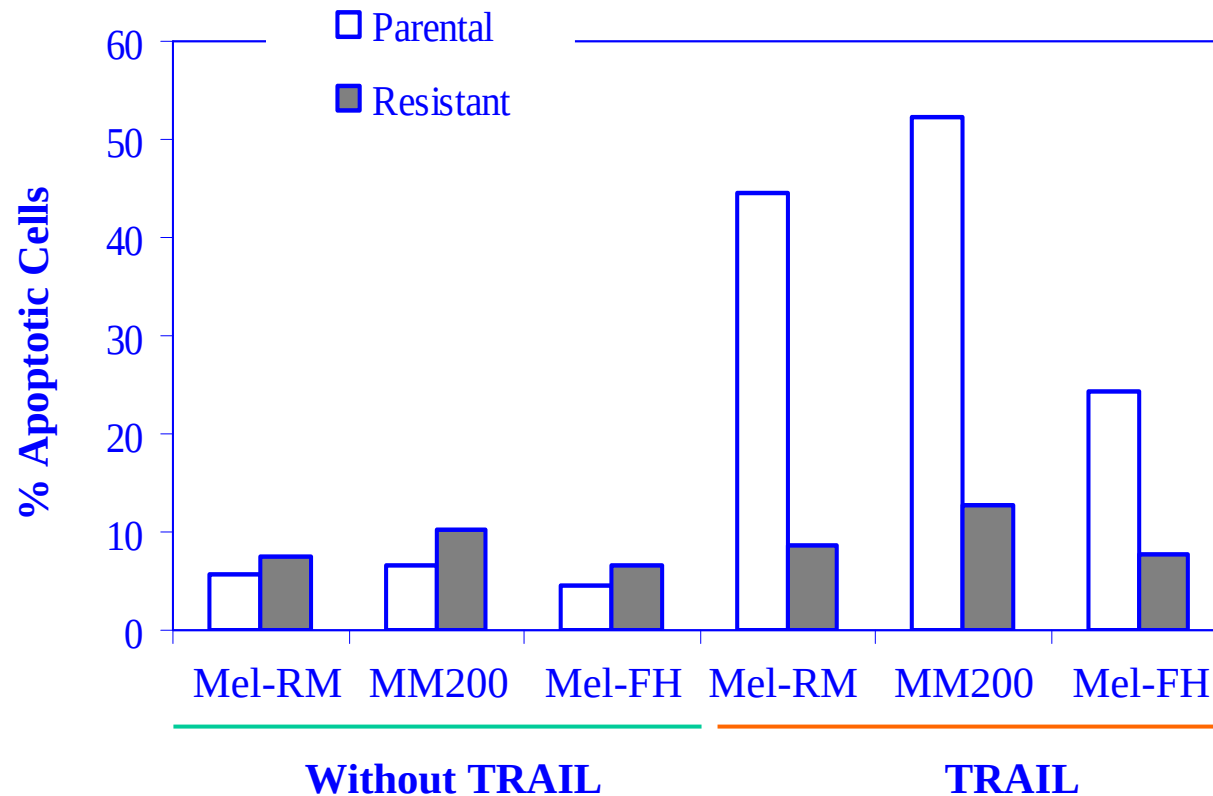
TRAIL Induces Apoptosis in the Majority of Melanoma Cell Lines



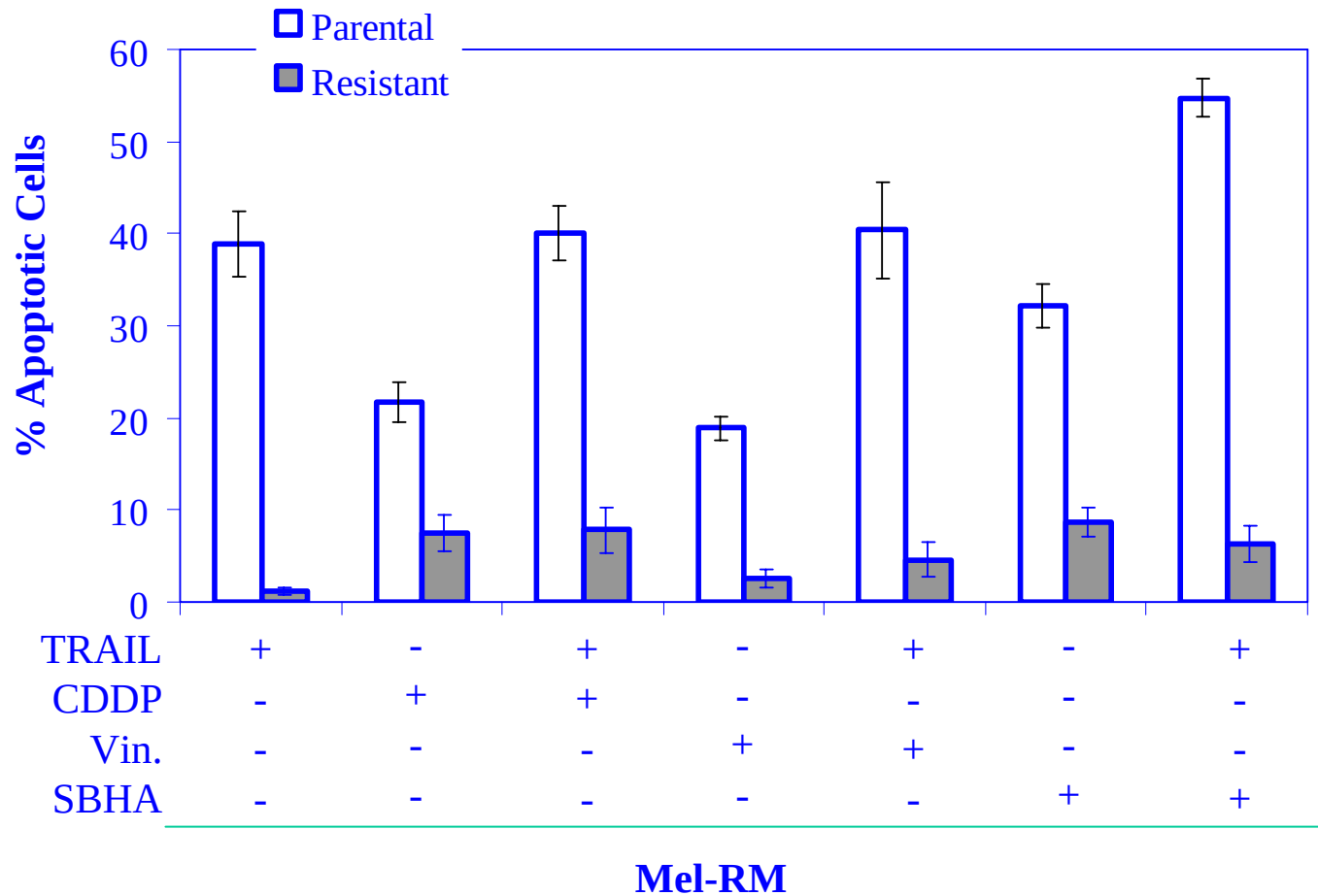
NEW CONCEPTS IN APOPTOSIS



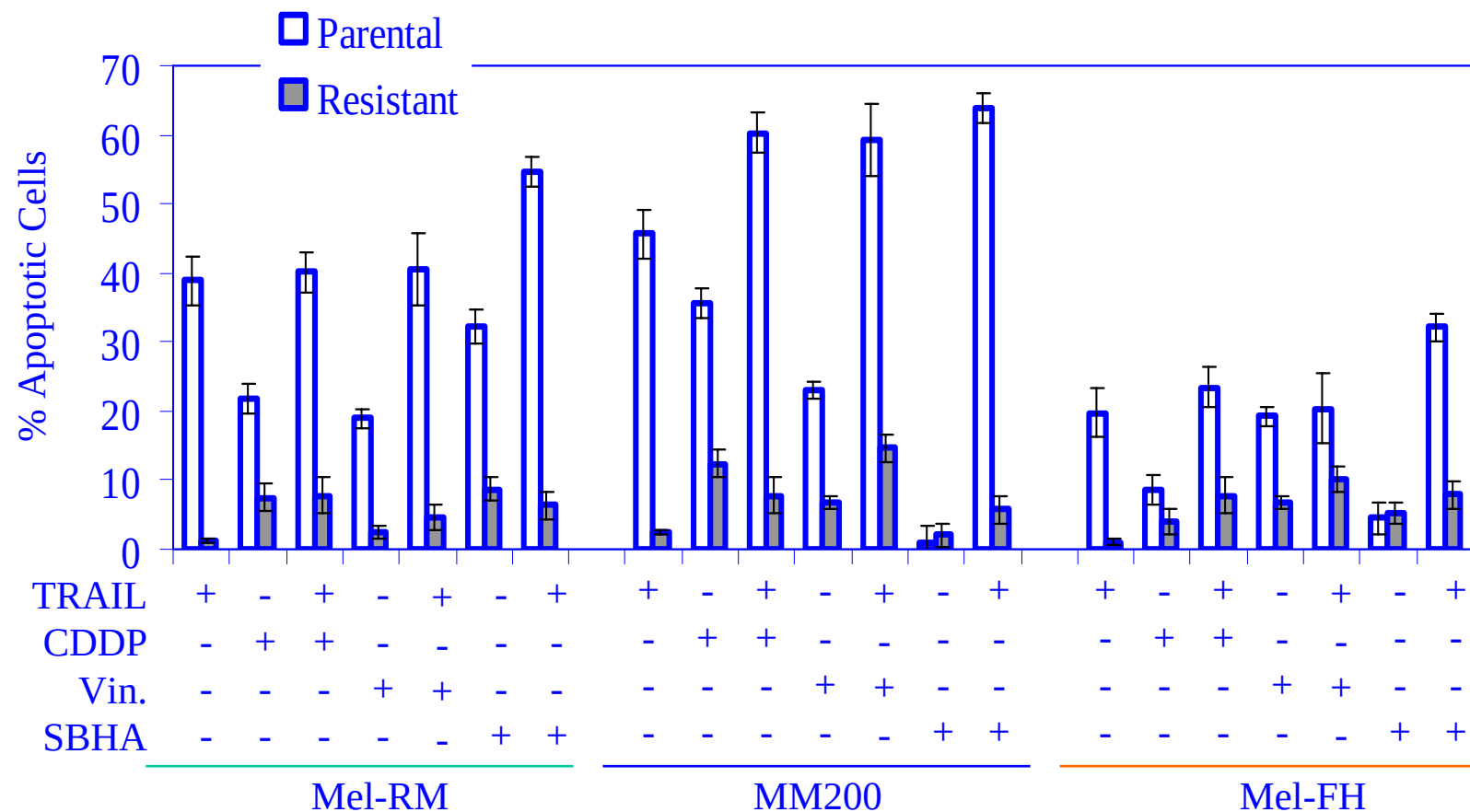
Prolonged exposure of melanoma cells to TRAIL results in TRAIL-resistant sub-lines



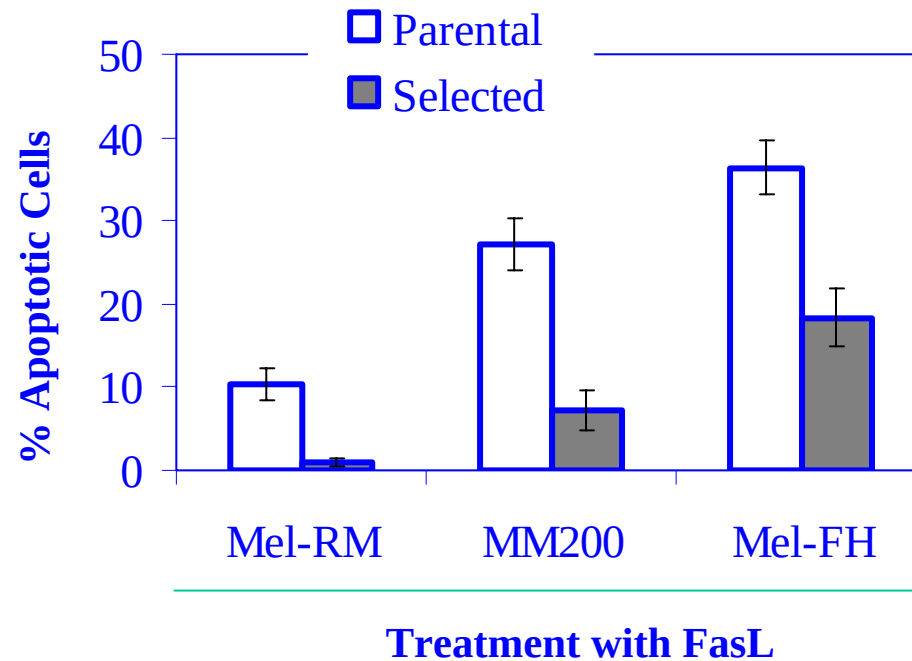
TRAIL-resistant melanoma cells are cross-resistant to various types of chemotherapeutic drugs



TRAIL-resistant melanoma cells are cross-resistant to various types of chemotherapeutic drugs

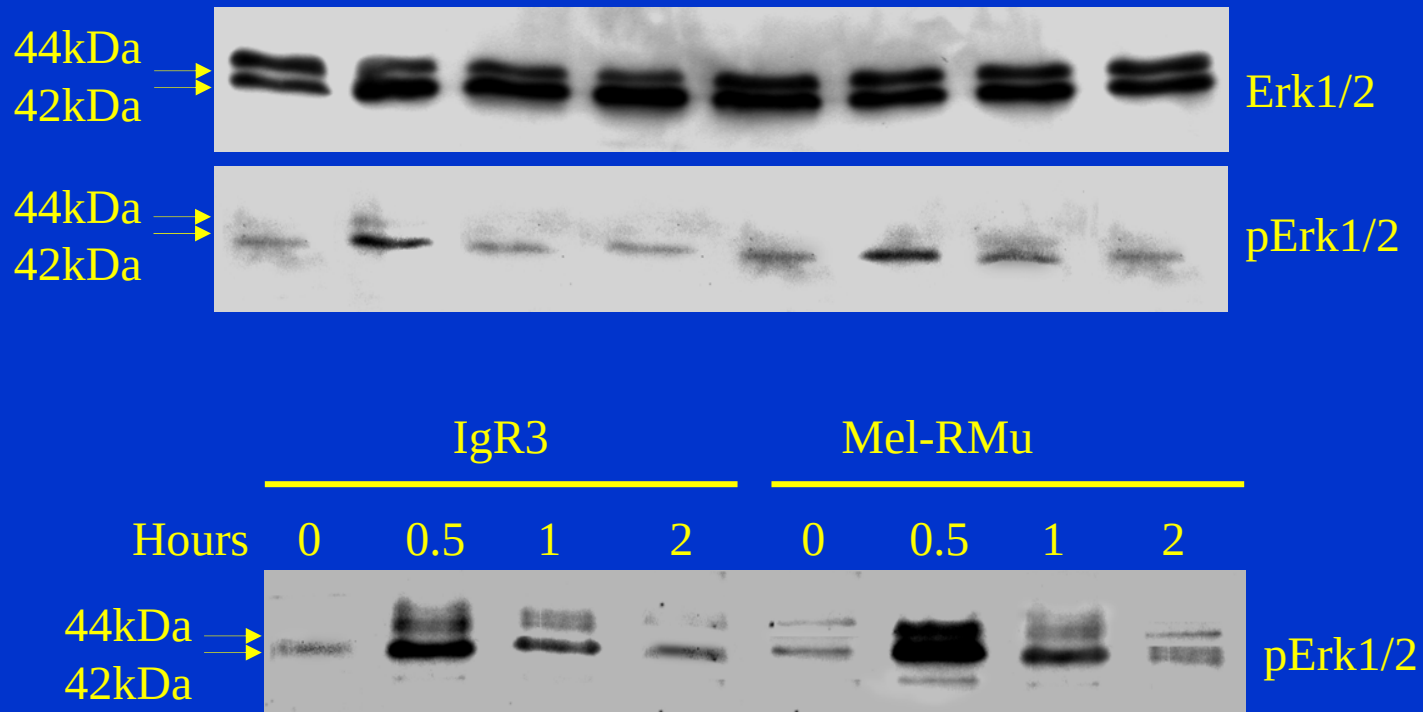


TRAIL-resistant melanoma cells are cross-resistant to FasL-induced apoptosis

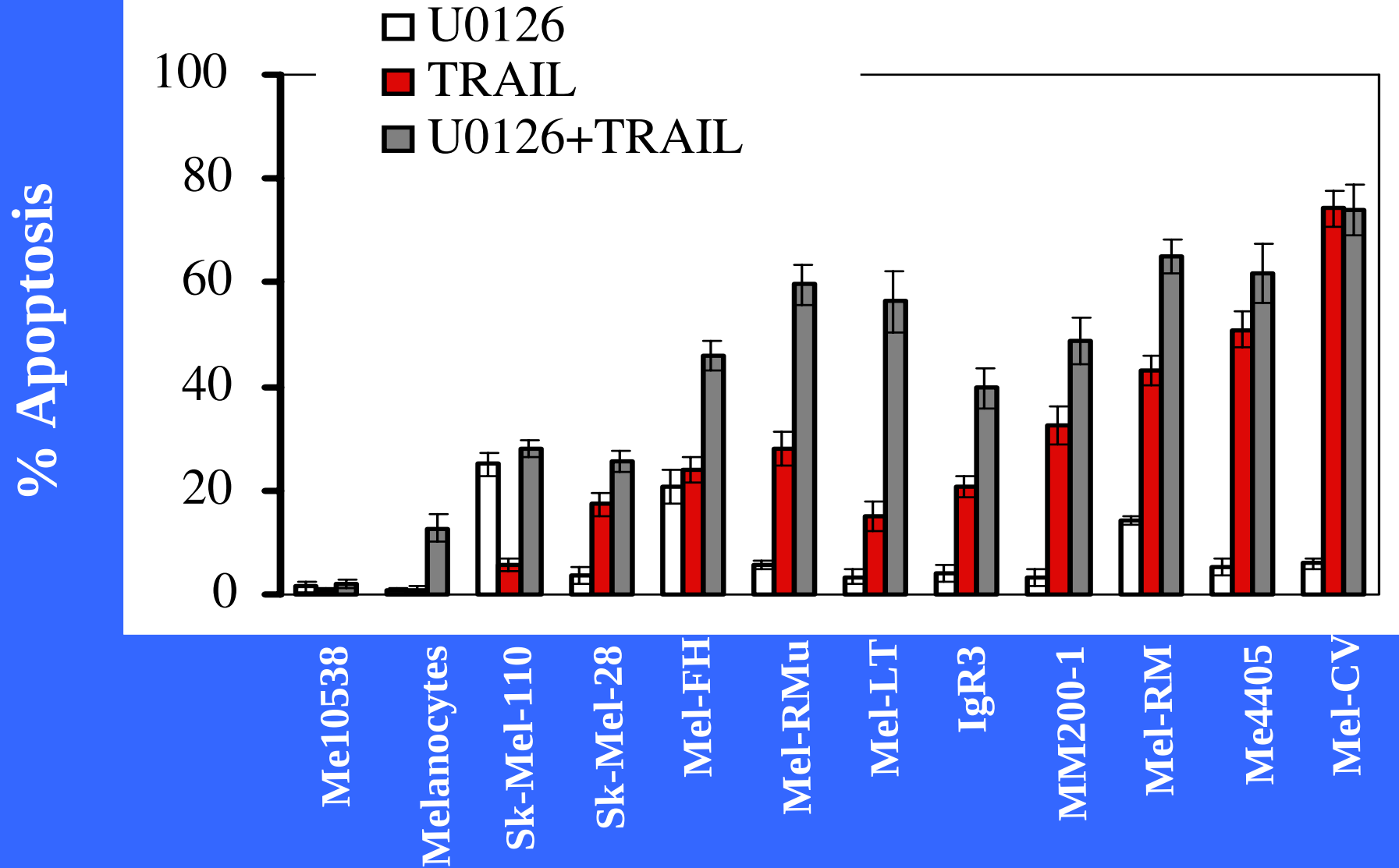


AT LEAST THREE SIGNAL
PATHWAYS INDUCE
RESISTANCE TO TRAIL
INDUCED APOPTOSIS

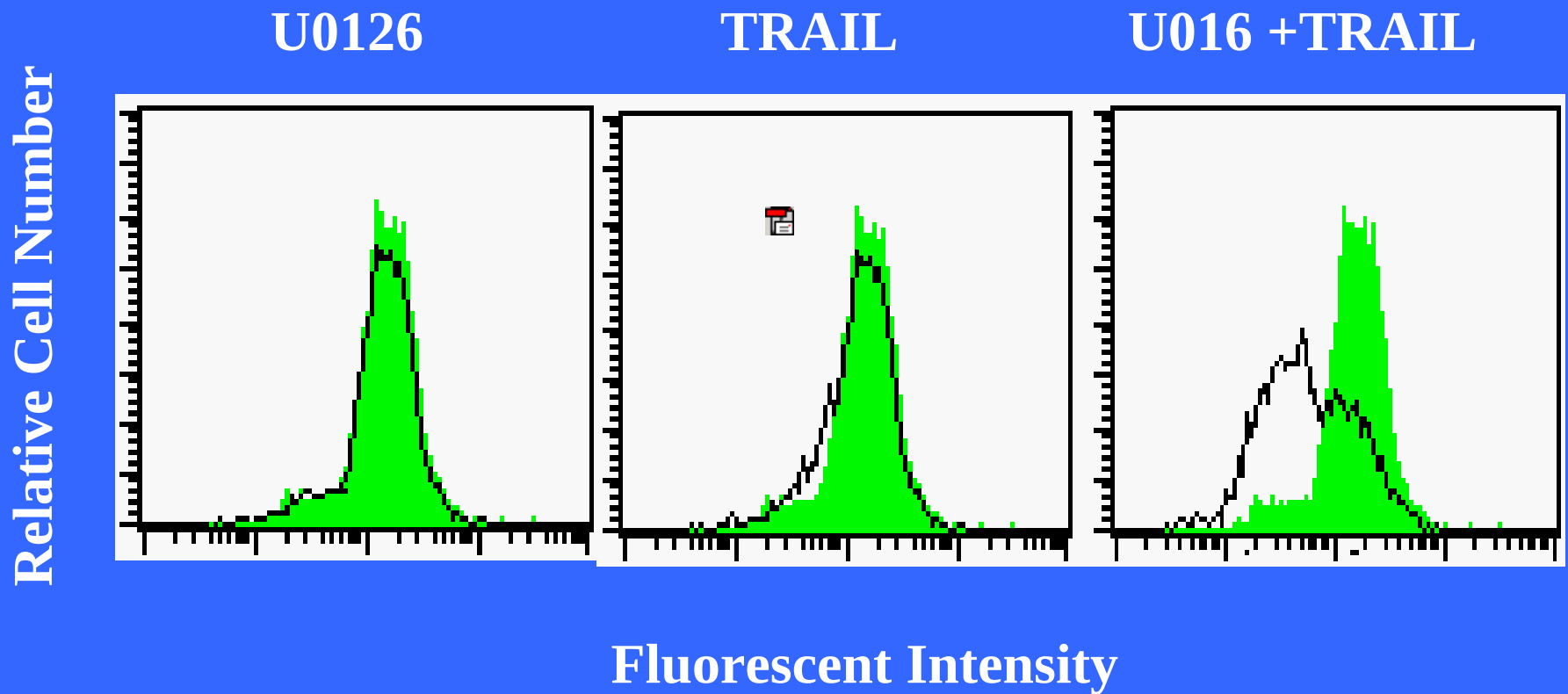
TRAIL Induces Rapid Erk1/2 Activation in Melanoma cells



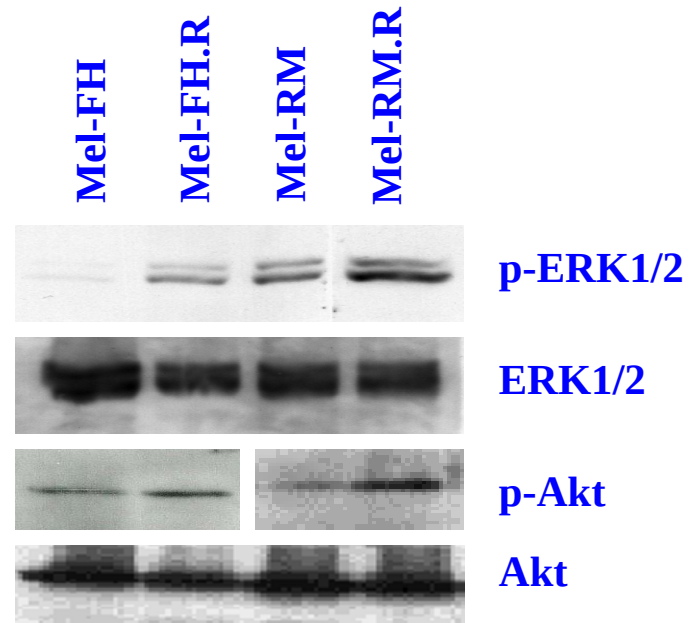
U0126 Sensitises Melanoma to TRAIL-Induced Apoptosis



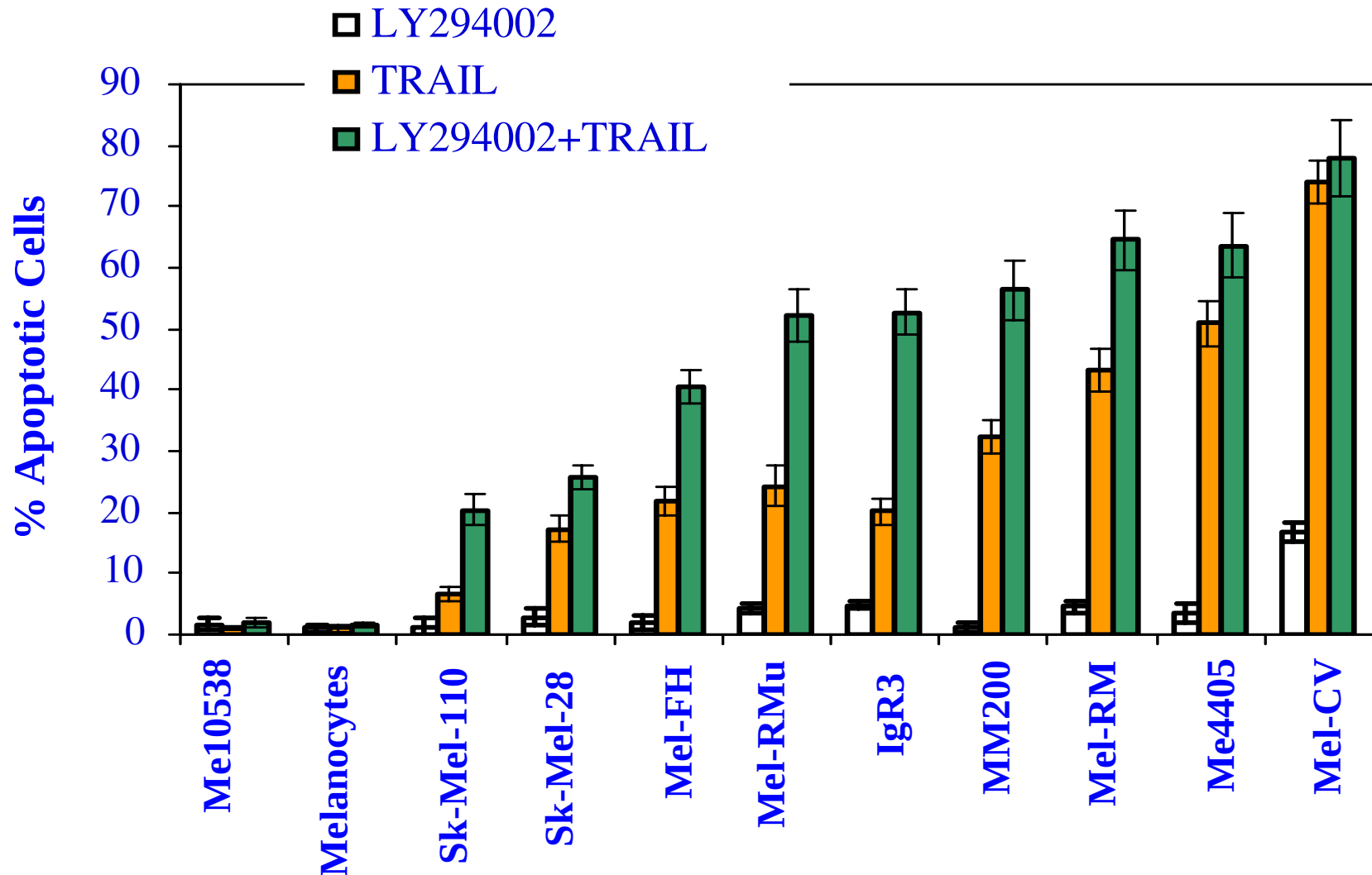
TRAIL Induces a Marked Increase in Reduction of the Mitochondrial Membrane Potential in the Presence of U0126



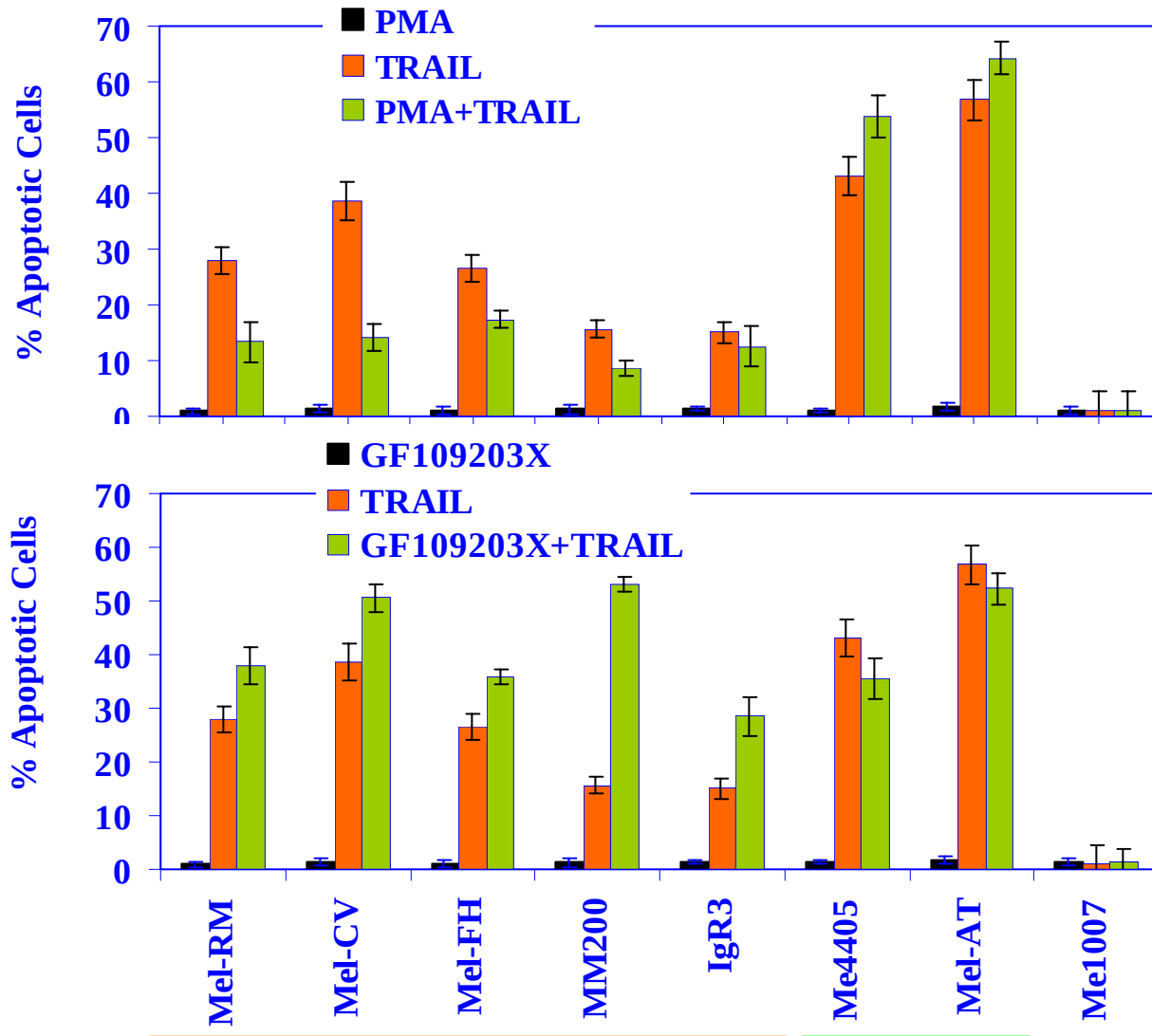
Increased Activation of ERK1/2 and Akt in TRAIL-Selected Resistant Cells



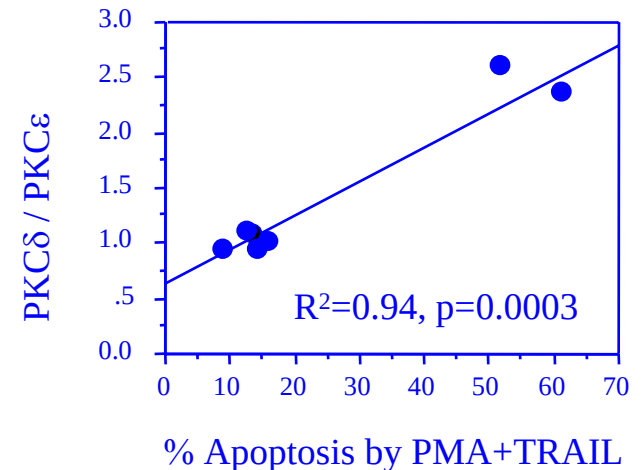
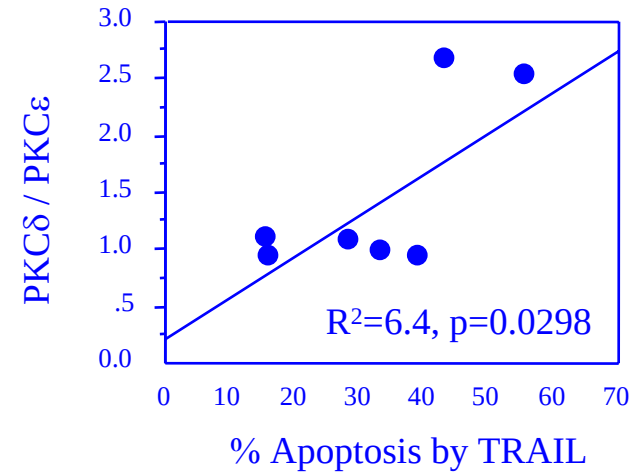
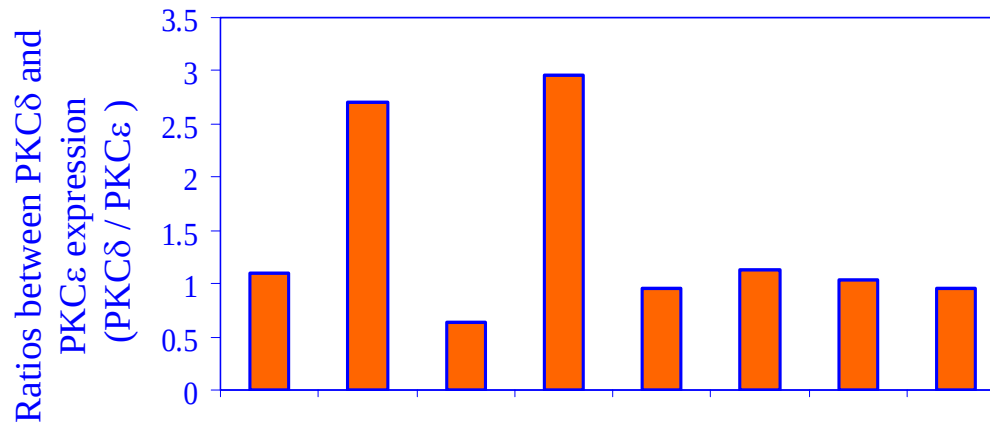
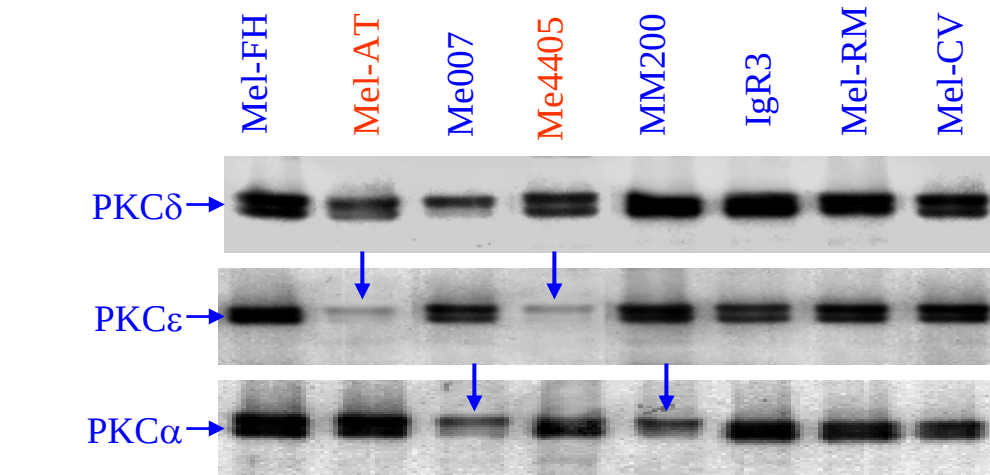
Inhibition of Akt signaling by the PI3-K inhibitor sensitizes melanoma to TRAIL-induced apoptosis



PKC Activation Differentially Regulates Sensitivity of Melanoma to TRAIL-Induced Apoptosis

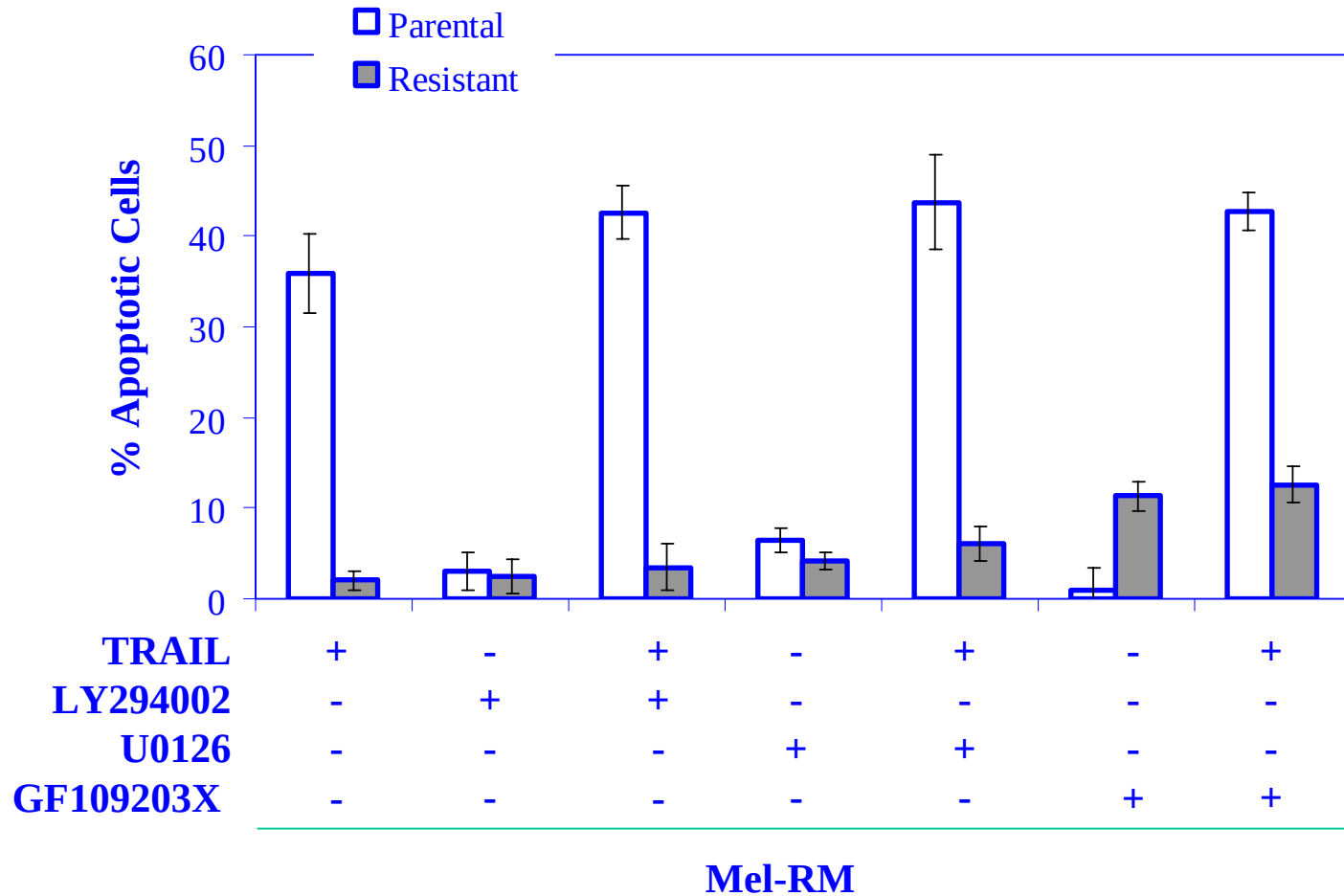


Sensitization of Melanoma Cells to TRAIL by PMA Is Associated with Deficient PKC ϵ Expression

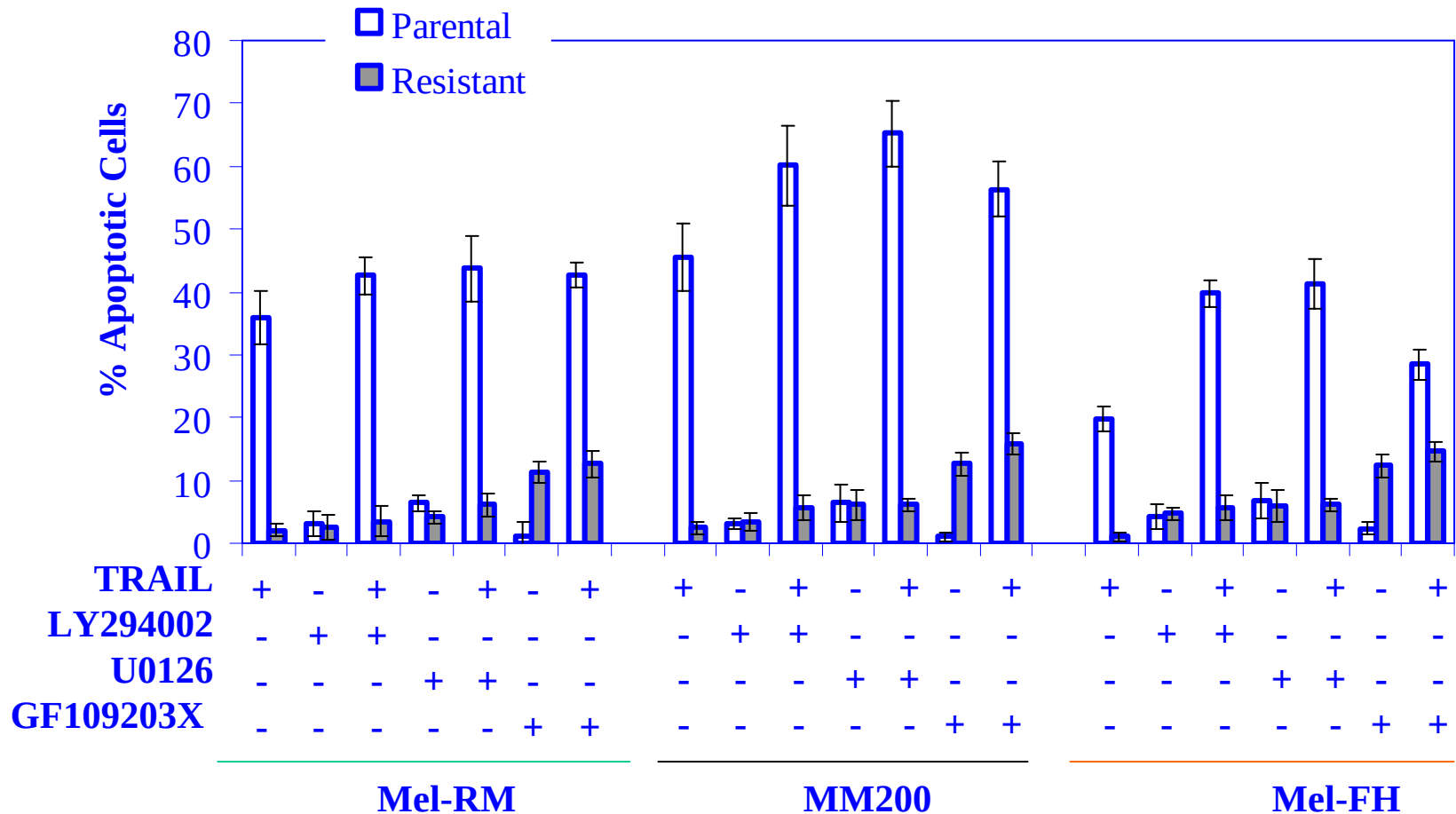


ARE THESE PATHWAYS
INVOLVED IN CROSS
RESISTANCE TO TRAIL AND
CHEMOTHERAPY?

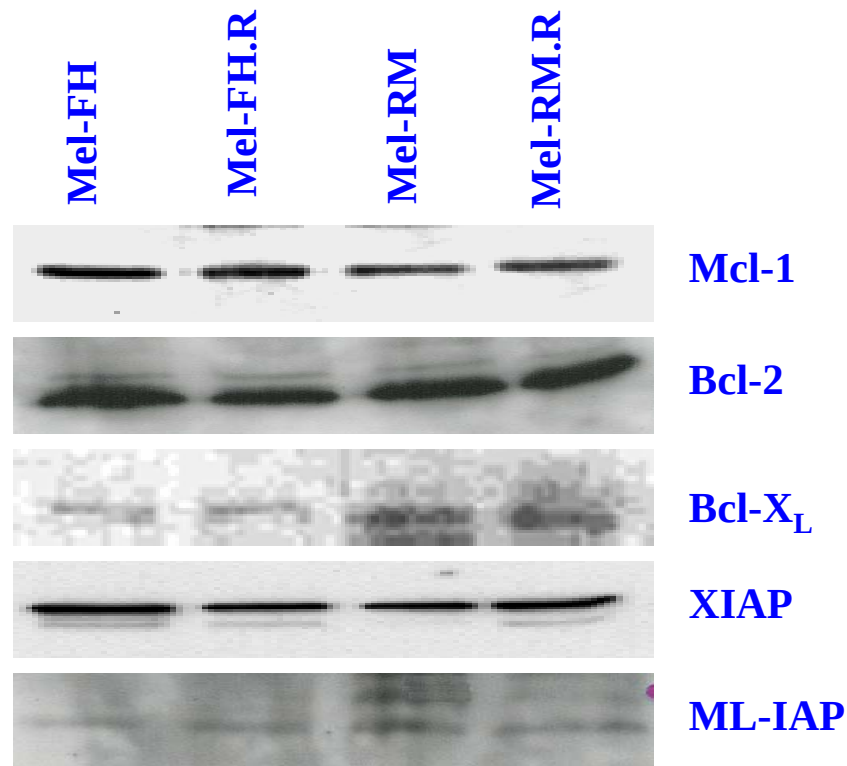
Inhibition of Akt, Erk1/2, or PKC does not sensitize TRAIL-resistant melanoma cells to TRAIL



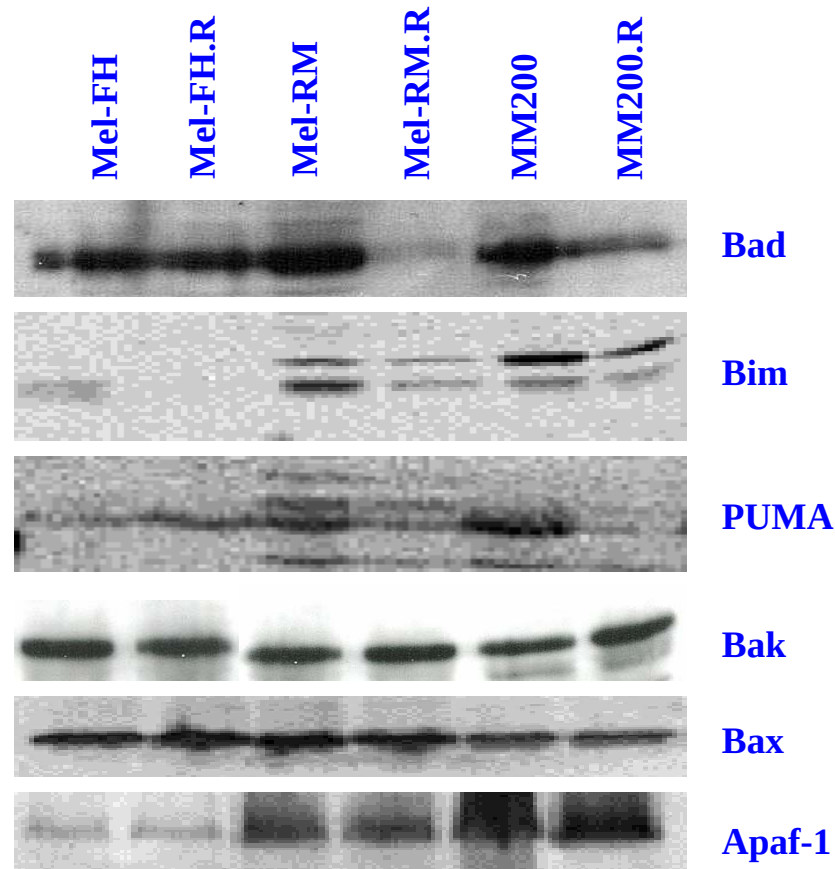
Inhibition of Akt, Erk1/2, or PKC does not sensitize TRAIL-resistant melanoma cells to TRAIL



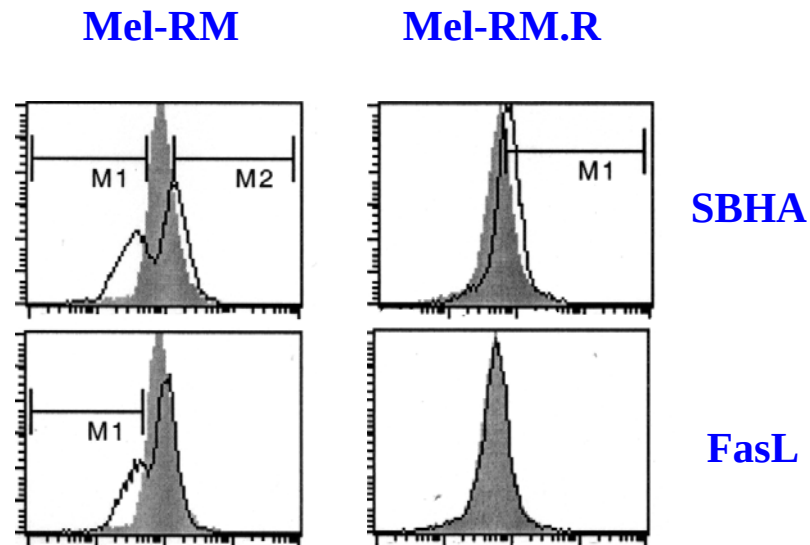
The expression levels of major anti-apoptotic Bcl-2 and IAP family members remain unaltered in TRAIL-resistant melanoma cells



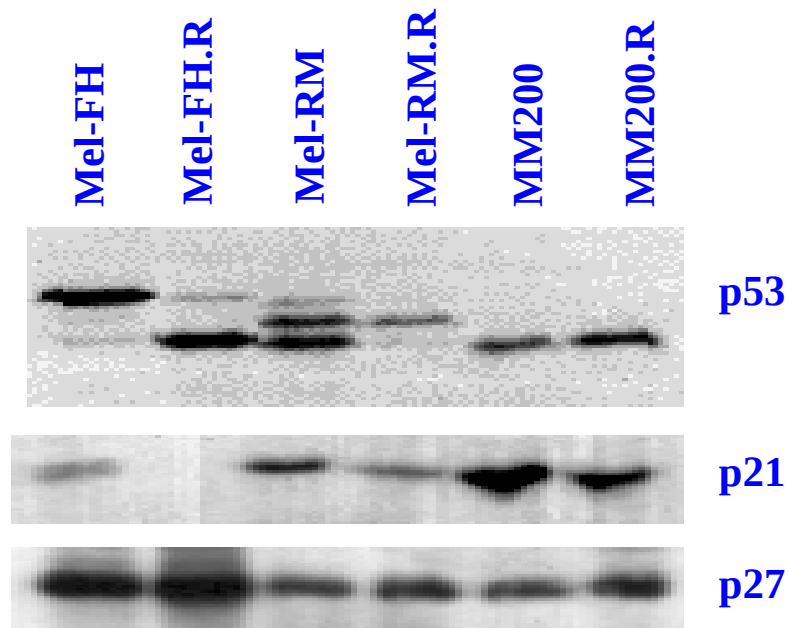
Alterations in the expression levels of proapoptotic Bcl-2 family members in TRAIL-resistant melanoma cell lines



Apoptotic signaling induced by FasL and SBHA
was inhibited upstream of mitochondria in
TRAIL-resistant melanoma cells



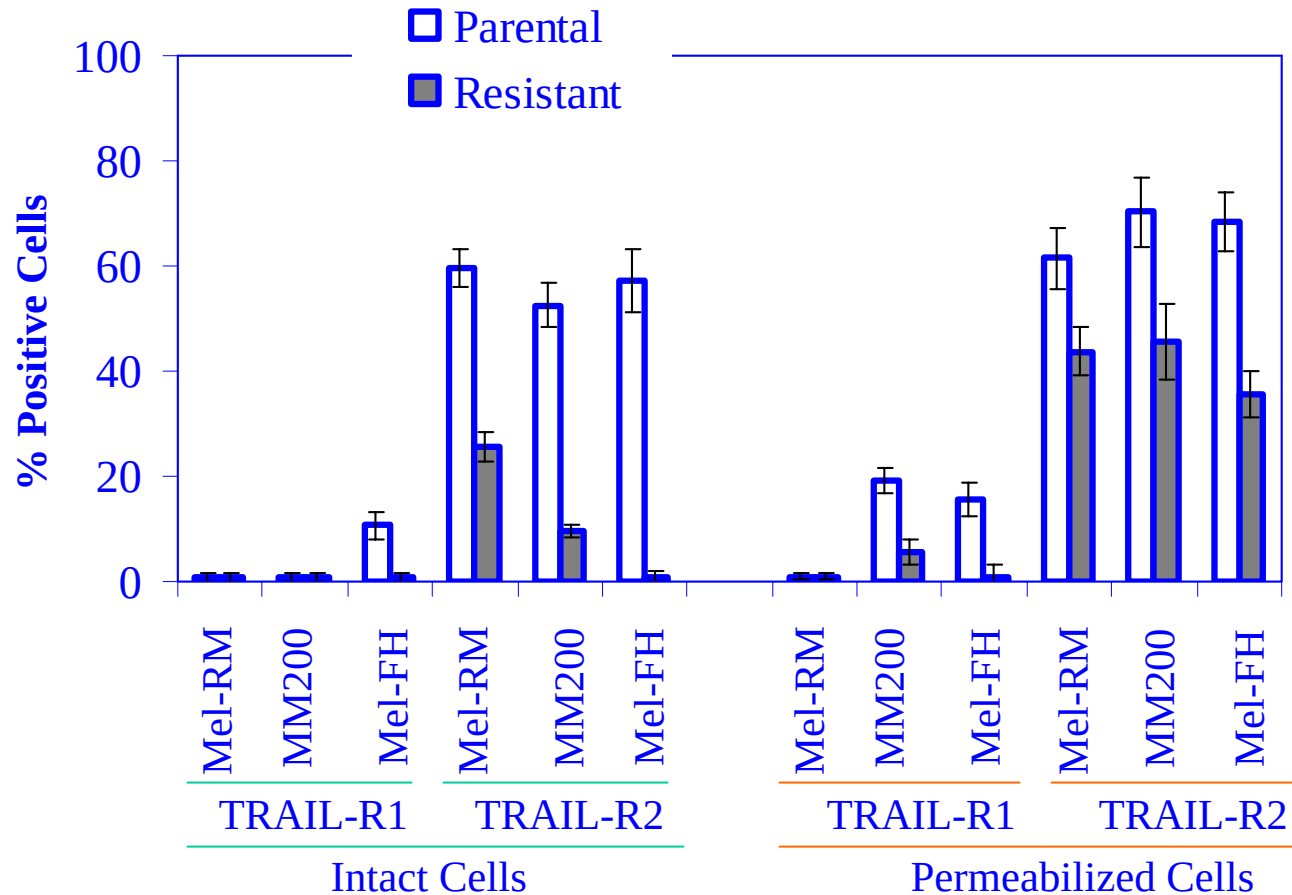
Decreased expression of p53 and p21, but not p27 in TRAIL-resistant cells



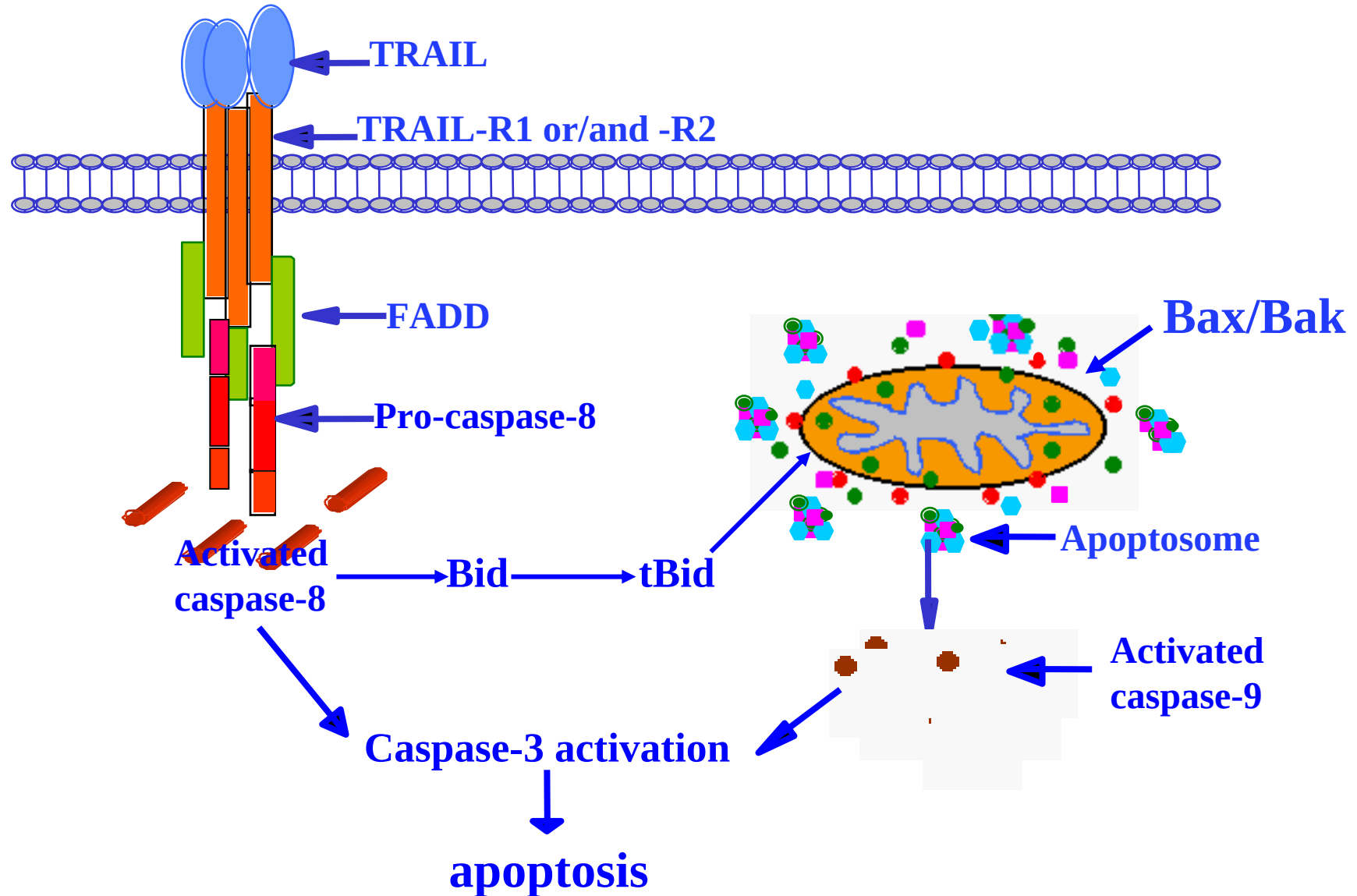
SUMMARY

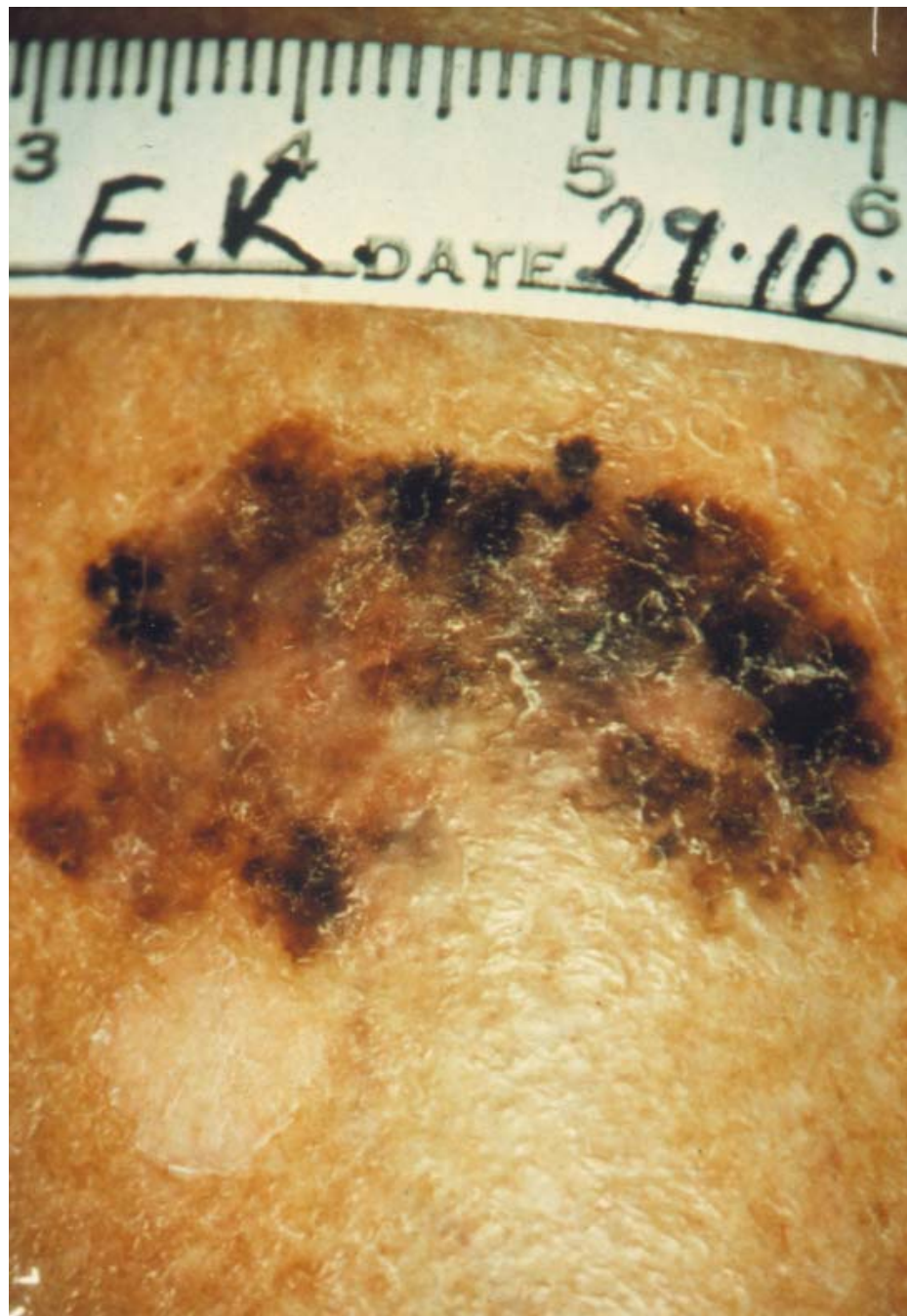
- Vincristine, Cisplatin, SBHA show cross resistance with TRAIL
- Inhibition appears to be upstream of Mitochondria
- Activation of ERK and Akt pathways do not seem to be involved
- Selection of P53 variants possibly involved

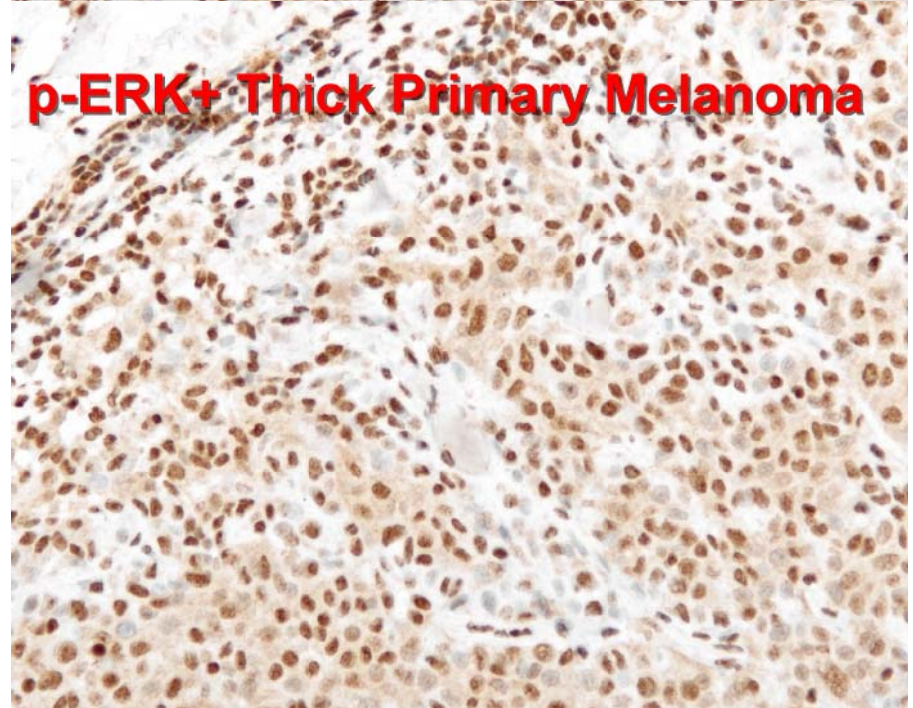
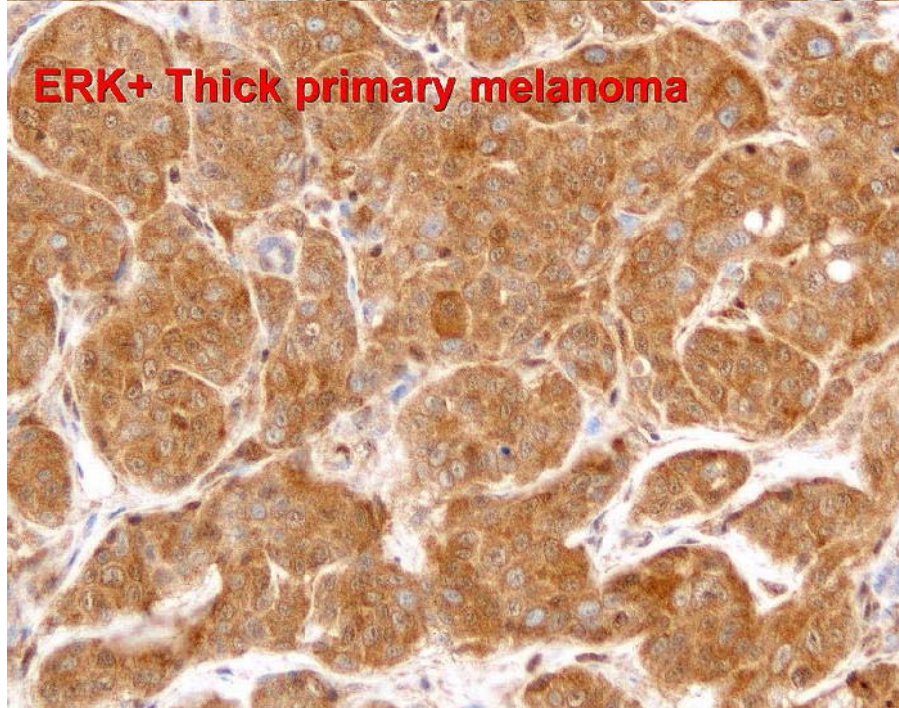
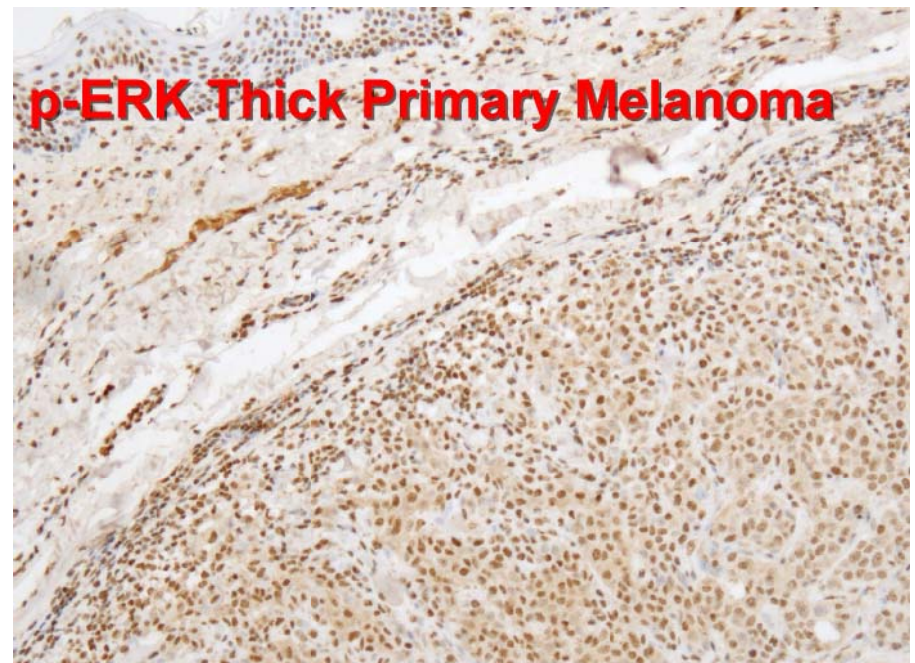
TRAIL death receptor expression is down-regulated in TRAIL-resistant cells



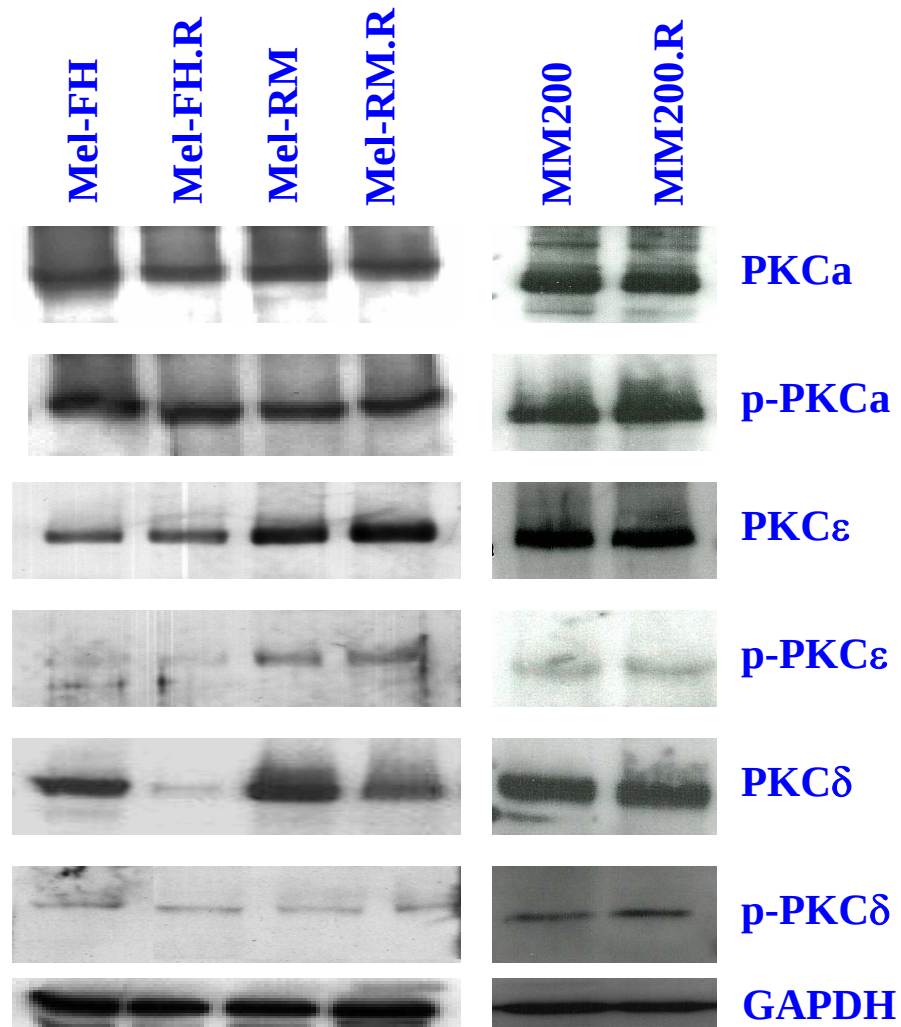
The “Classical” Extrinsic Signaling Pathway Suggested for TRAIL-Induced Apoptosis



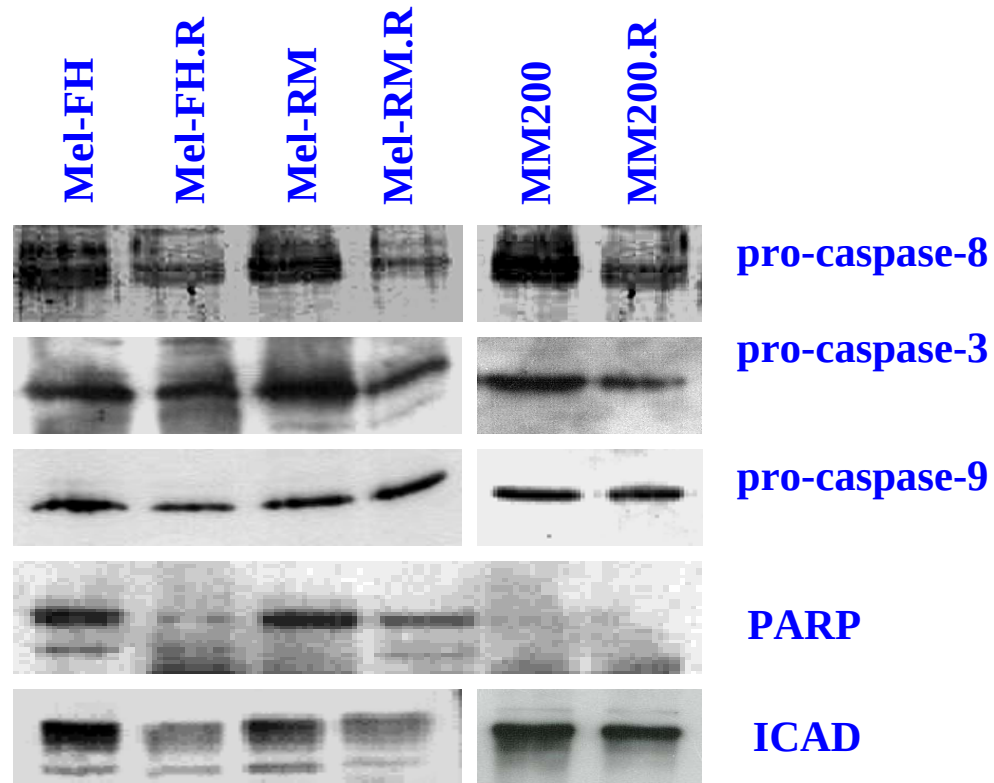




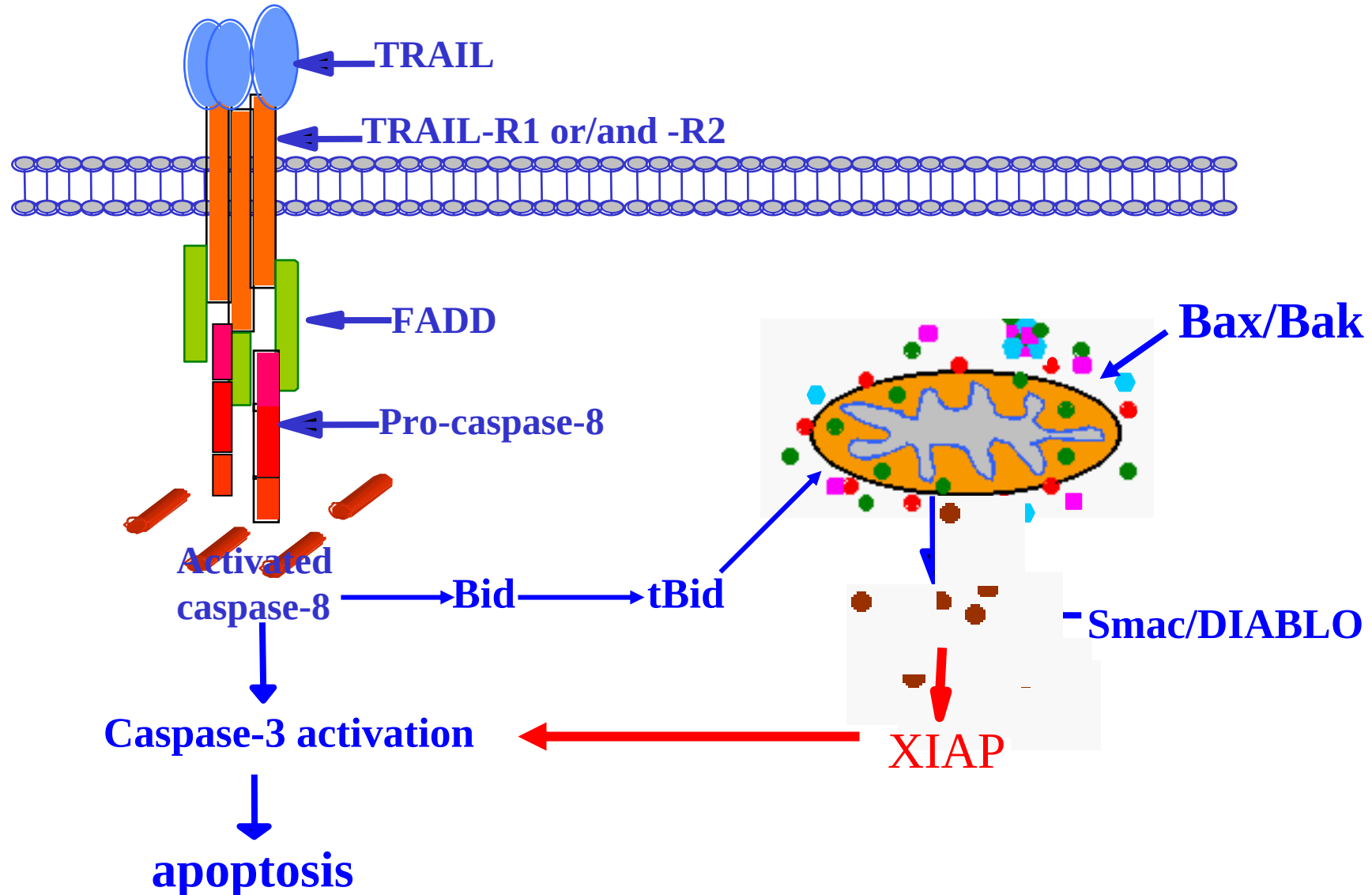
Decreased expression of PKC δ in TRAIL-resistant cells



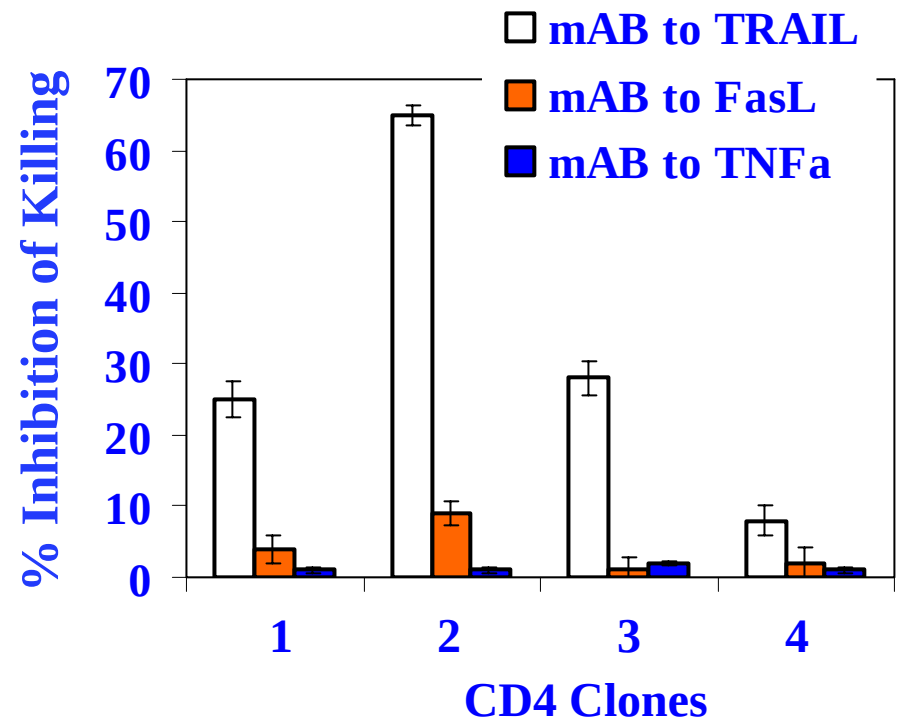
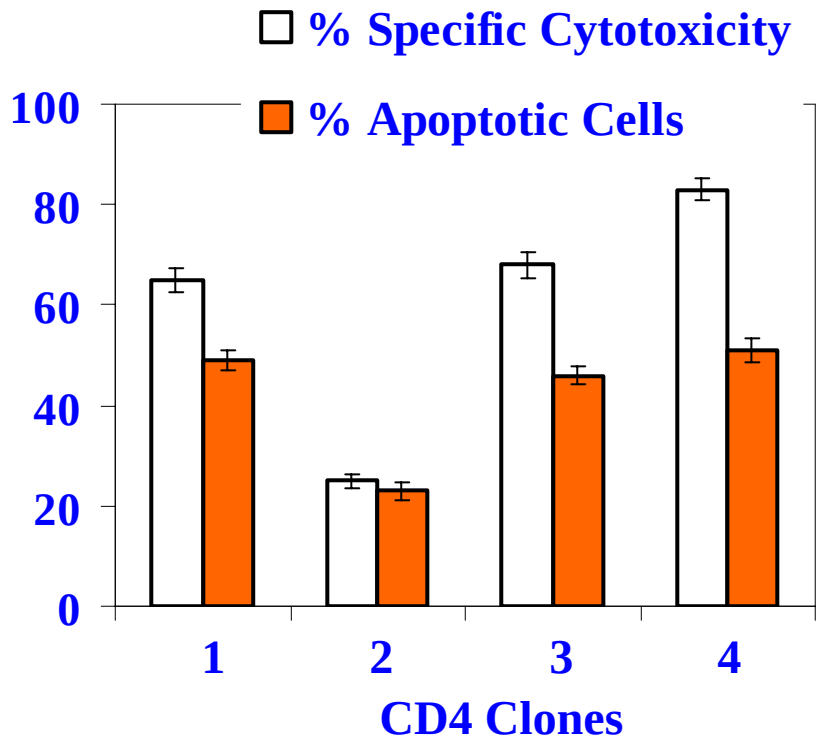
Decreased expression of ICAD and PARP in TRAIL-resistant cells



The Alternative Intracellular Apoptotic Pathway Used by TRAIL in Melanoma Cells



TRAIL Is Involved in Killing of Melanoma Cells by CD4 T Cells



Effects of PKC on TRAIL-Induced Caspase-3 Activation, Cleavage of Its Substrates, and Release of Smac from Mitochondria

