

# Molecular Mechanisms of Multi Drug Resistance & Its Reversal in Cancer

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[www.yusufbaran.net](http://www.yusufbaran.net)

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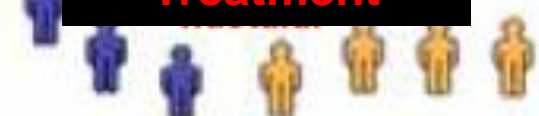
Ist International Conference of TWAS Young Affiliates Network

22-14 August 2017 Rio De Janerio, Brasil

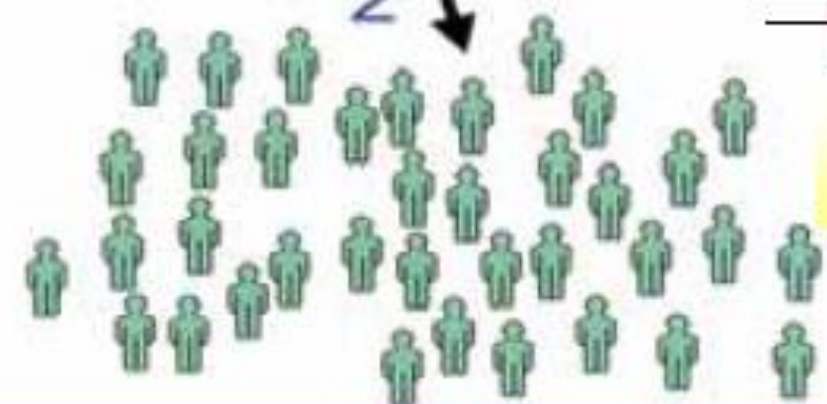
**Patients with the same disease**



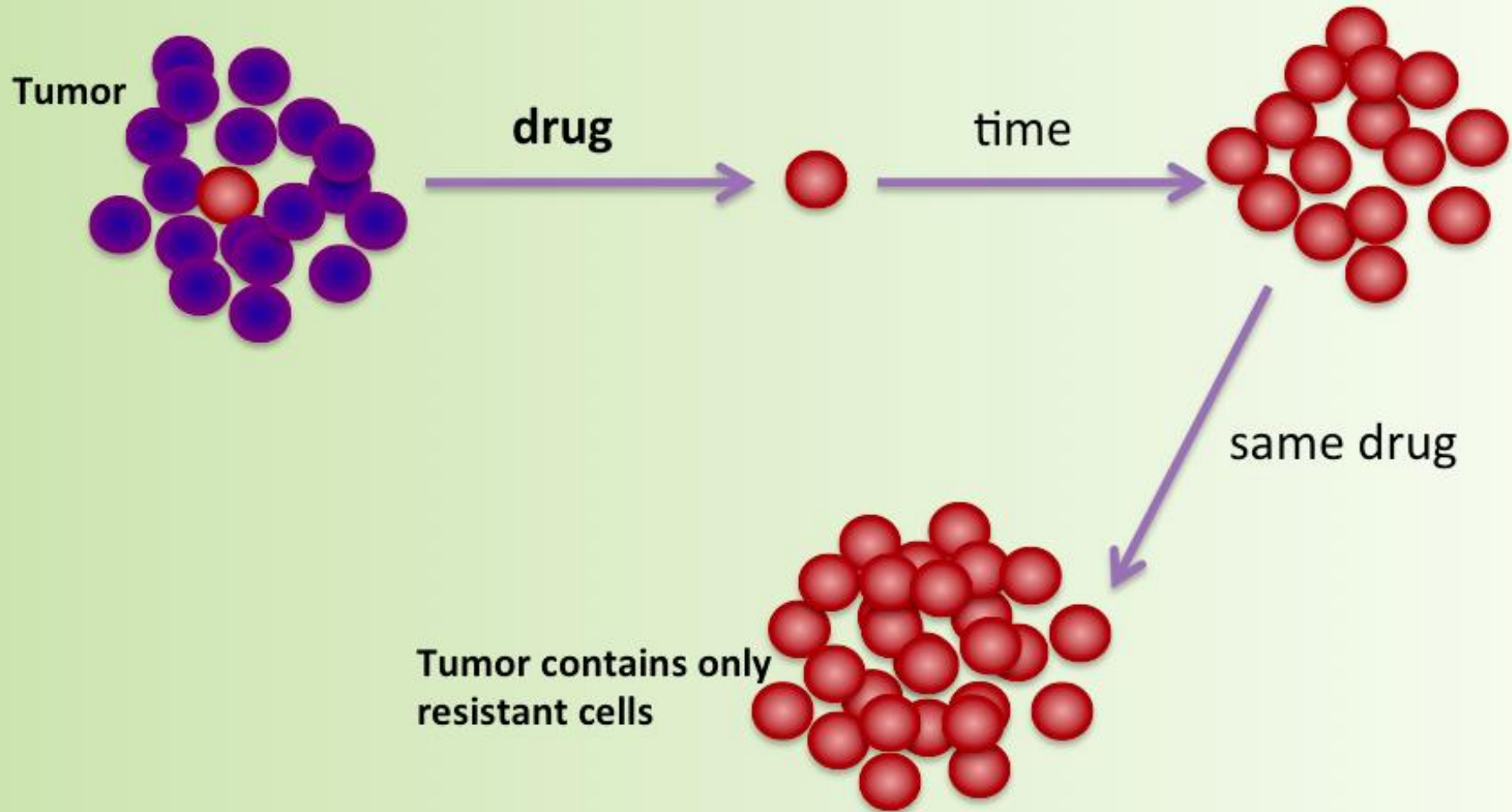
**No response to Treatment**



**Good response to Treatment**



# DRUG RESISTANCE



# Mechanisms of resistance to anti-cancer drugs

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**Decreases in intracellular concentrations of anticancer agents resulting from increased efflux or decreased influx**



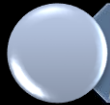
**Alterations in drug target**



**Increases in drug targets or removal of drug targets**



**Changes in expression levels of apoptotic and antiapoptotic genes**



**Aberrations in ceramide metabolism**



**Increases in DNA repair**



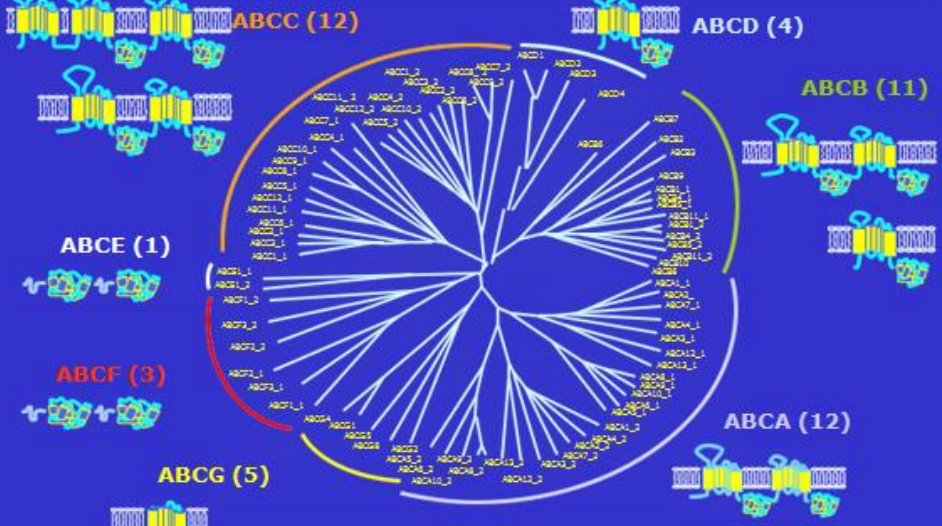
**Epigenetic differences**



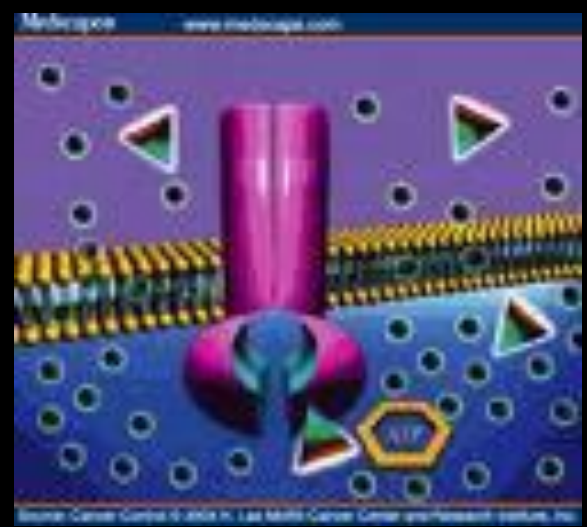
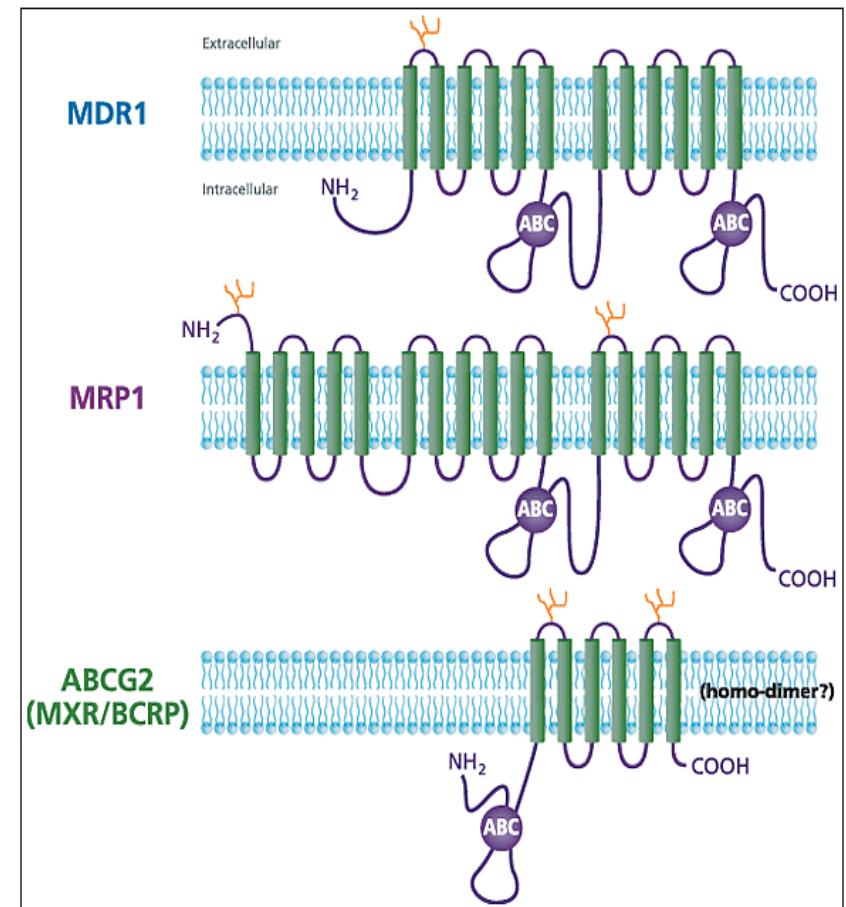
**MicroRNAs**

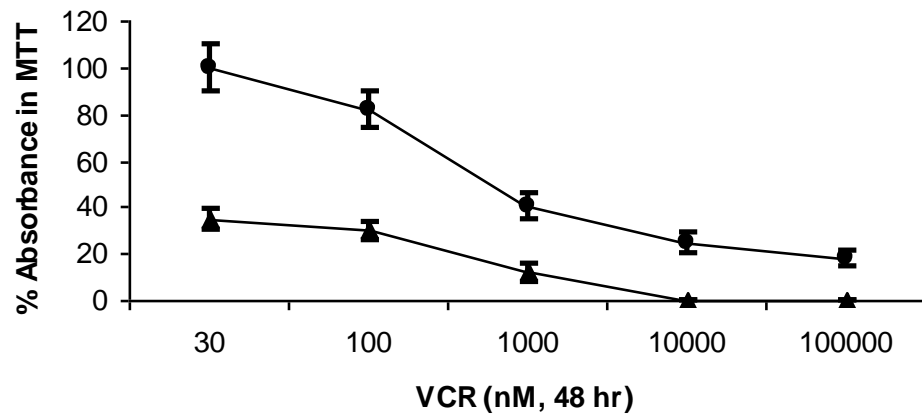


# Human ABC Genes

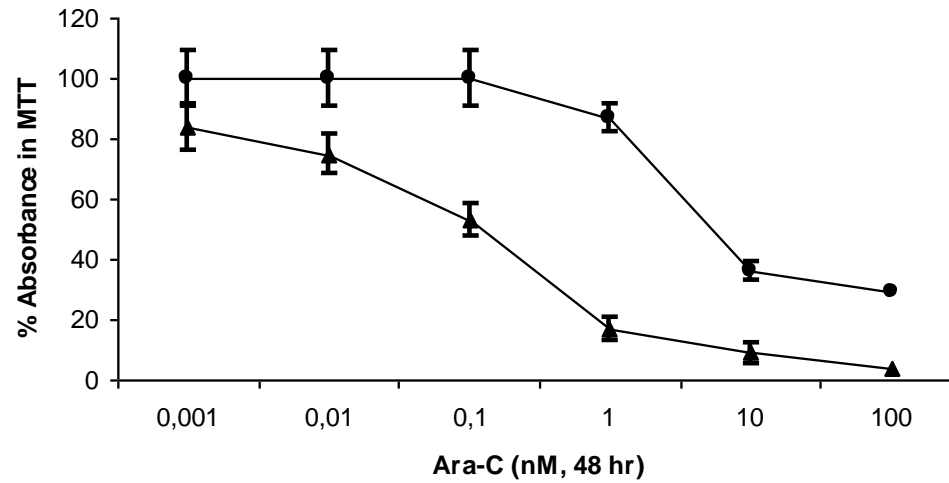


The Clustal W program was used to make the alignment of the NBDs and the tree was built by using the MEGA program – By Mike Dean, NCI

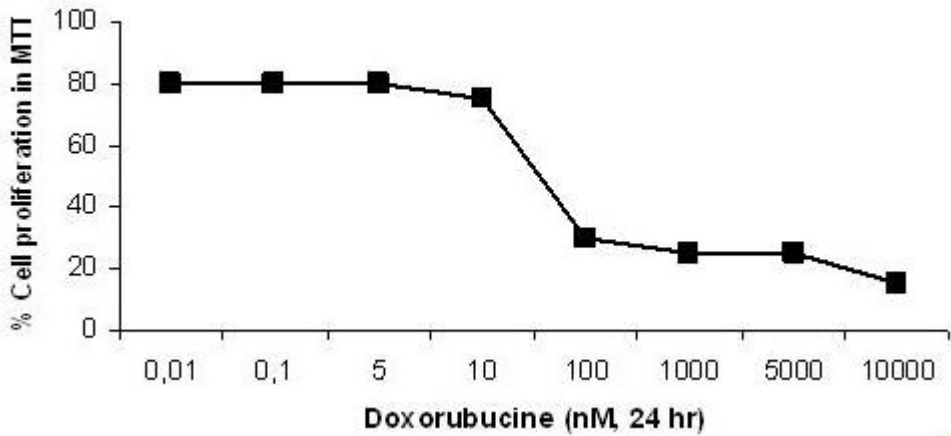




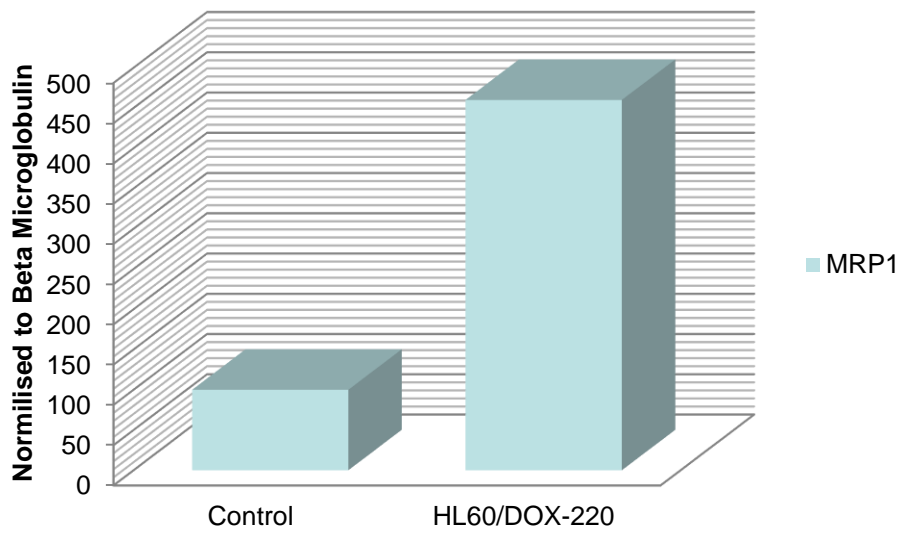
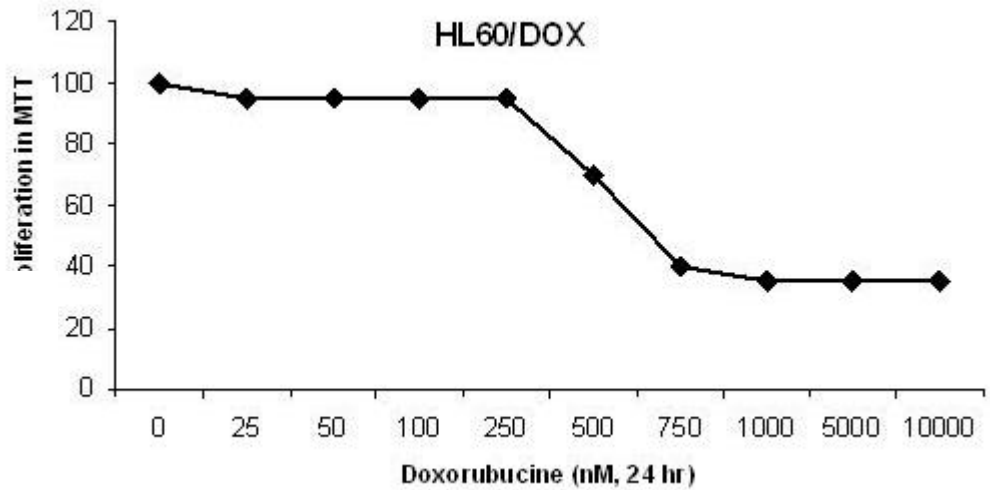
HL60 4 nM  
HL60/VINC 300 nM



HL60



HL60 62 nM  
HL60/DOX 666 nM



# Mechanisms of resistance to anti-cancer drugs

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Decreases in intracellular concentrations of anticancer agents resulting from increased efflux or decreased influx

## Alterations in drug target

Increases in drug targets or removal of drug targets

Changes in expression levels of apoptotic and antiapoptotic genes

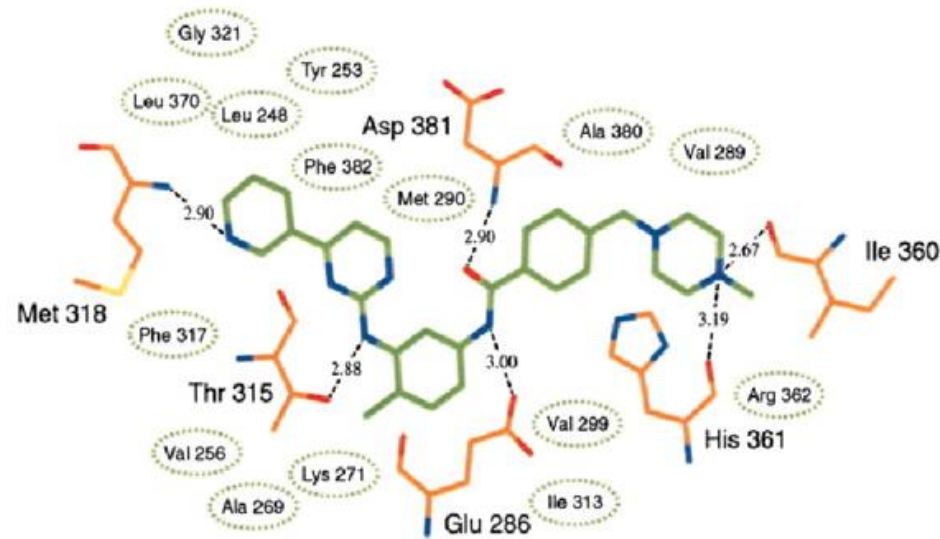
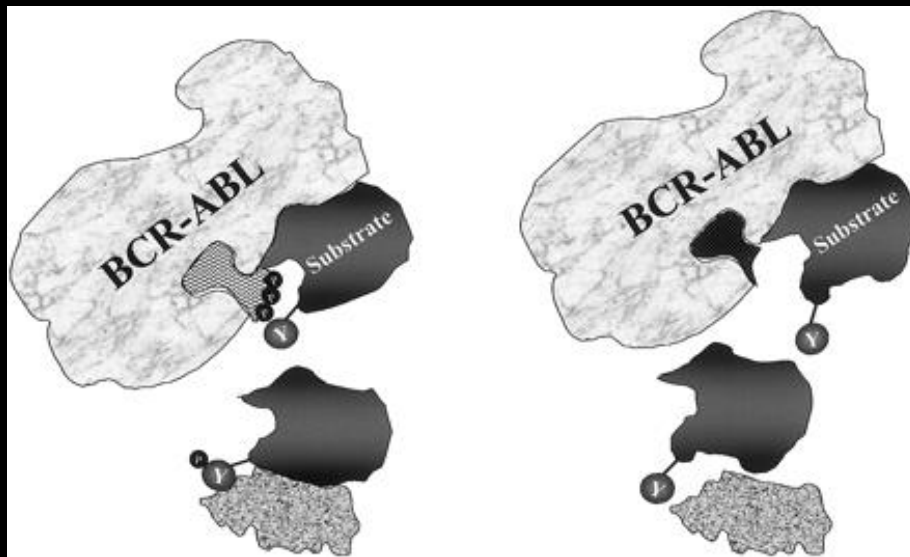
Aberrations in ceramide metabolism

Increases in DNA repair

Epigenetic differences

MicroRNAs





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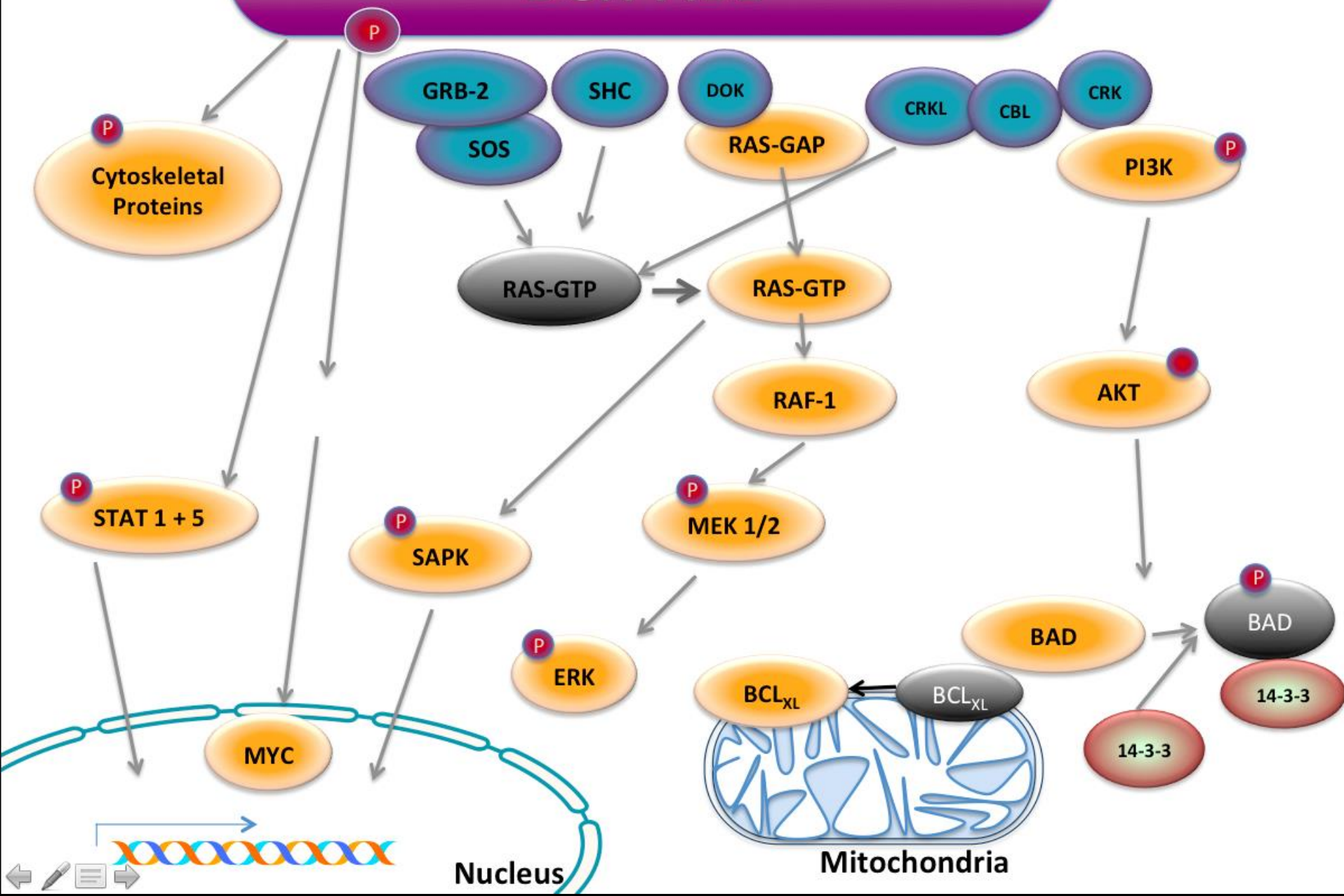
Aberrations in ceramide metabolism

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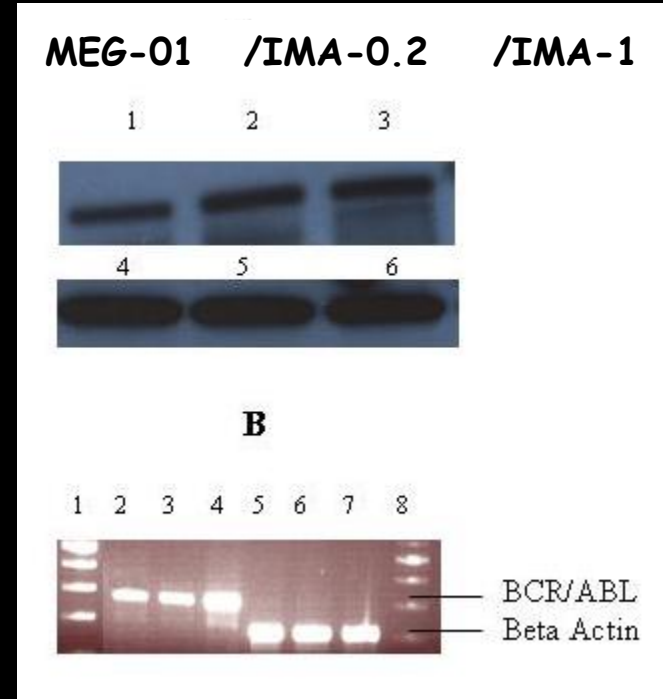
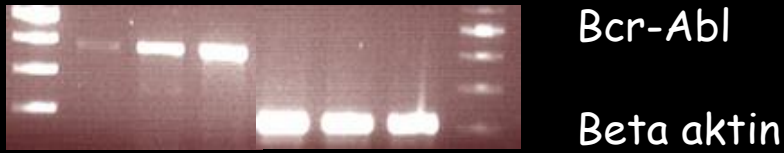
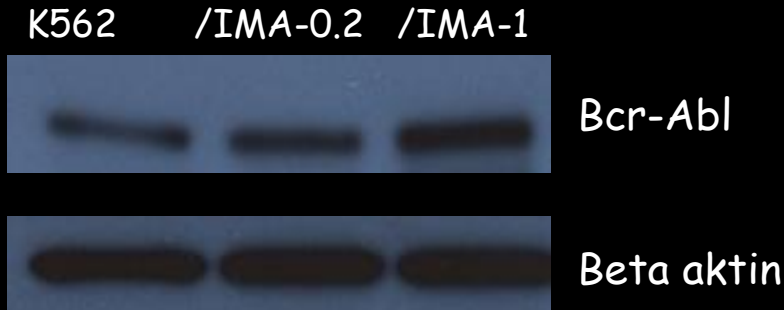
Epigenetic differences

MicroRNAs

# BCR-ABL

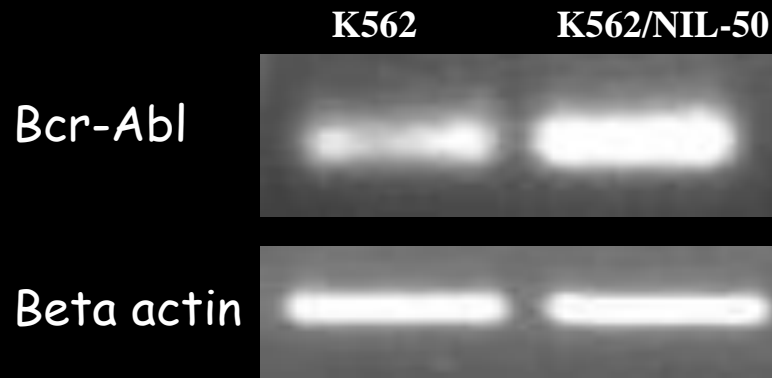
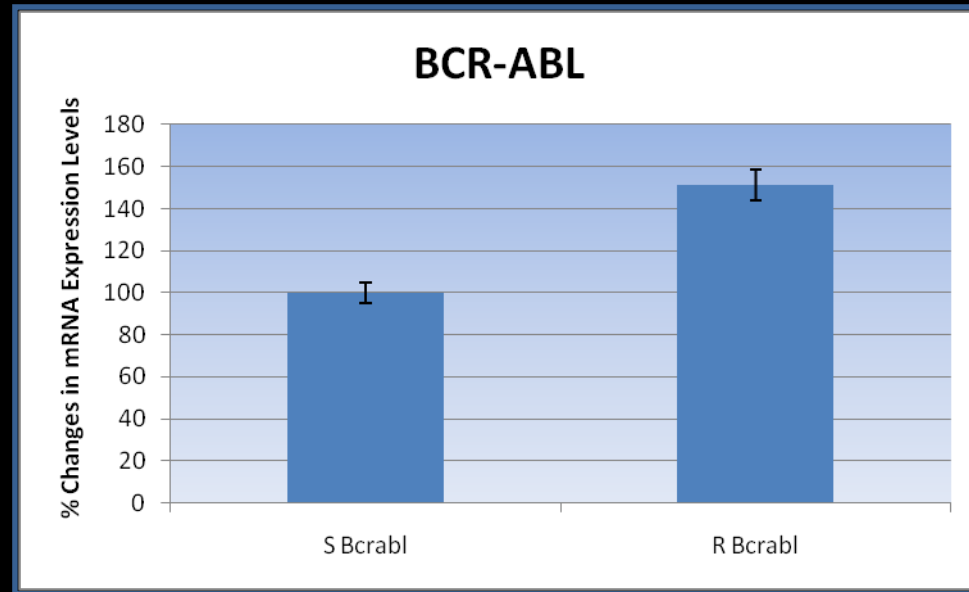


# BCR-ABL



Baran Y. Et al  
 Journal of Biological  
 Chemistry, 2007 282(15);  
 10922-10934.

Baran Y. Et al  
 Hematology, 2007 12(6);497-503.



Baran Y. Et. al.  
Leukemia and Lymphoma, 2013; 54(6): 1279-1287.

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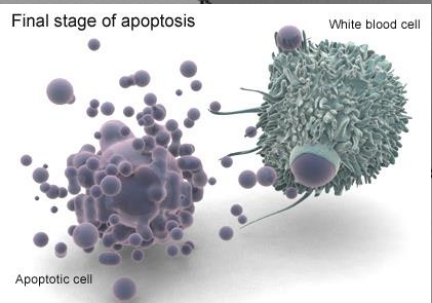
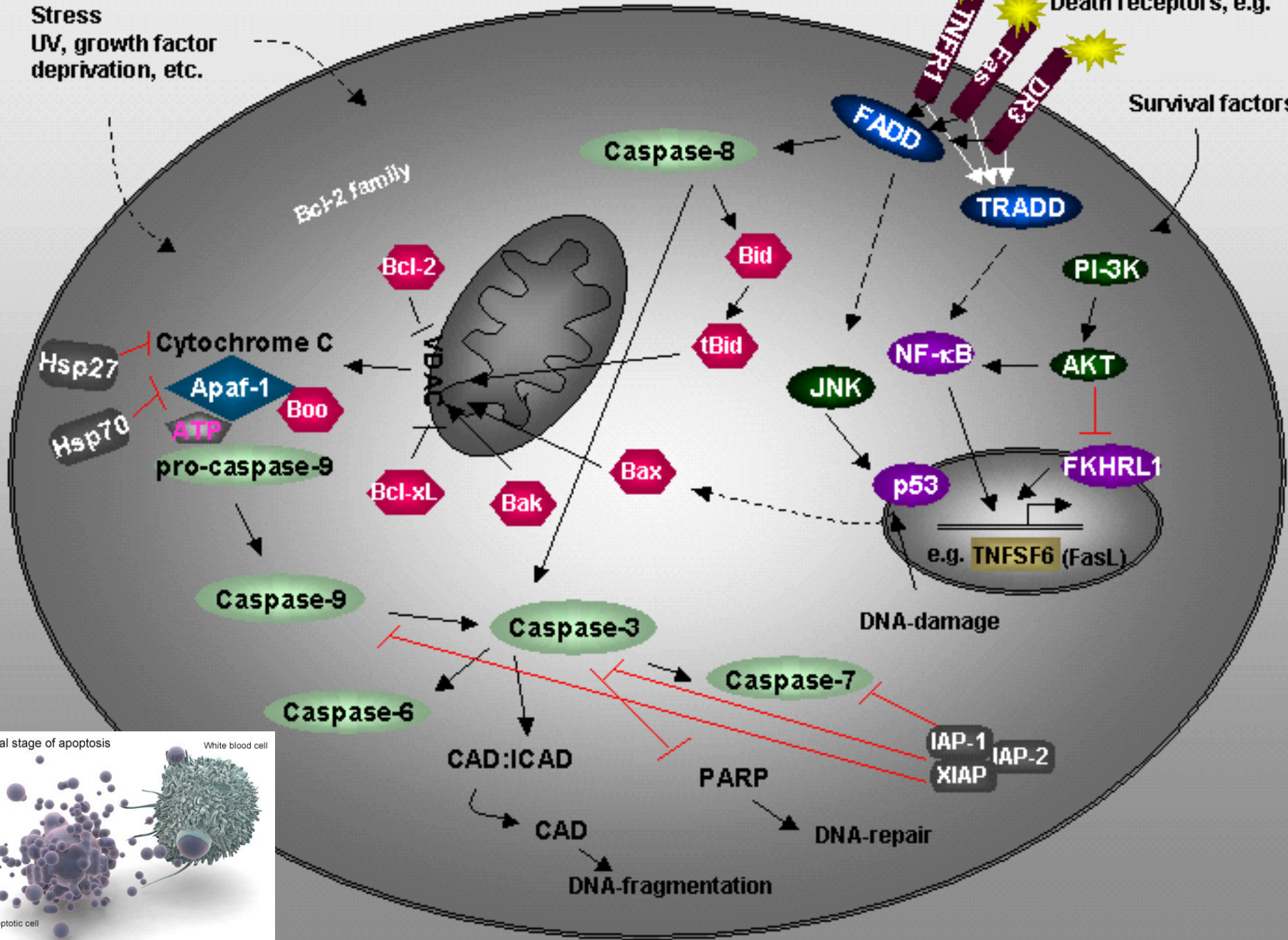
MicroRNAs

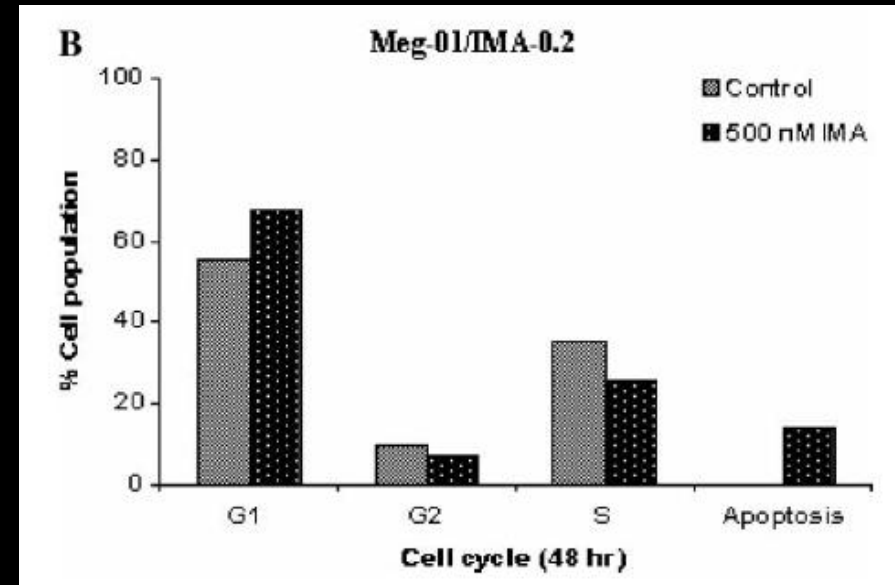
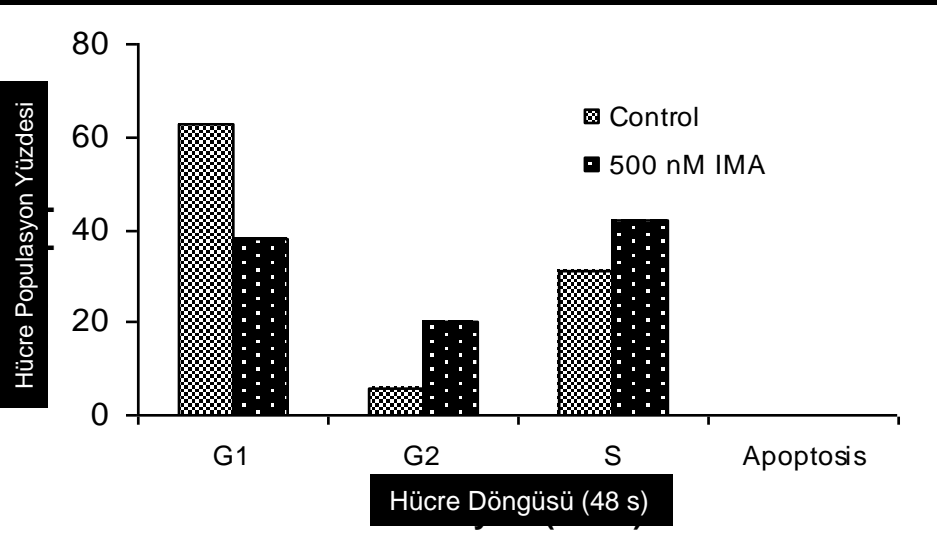
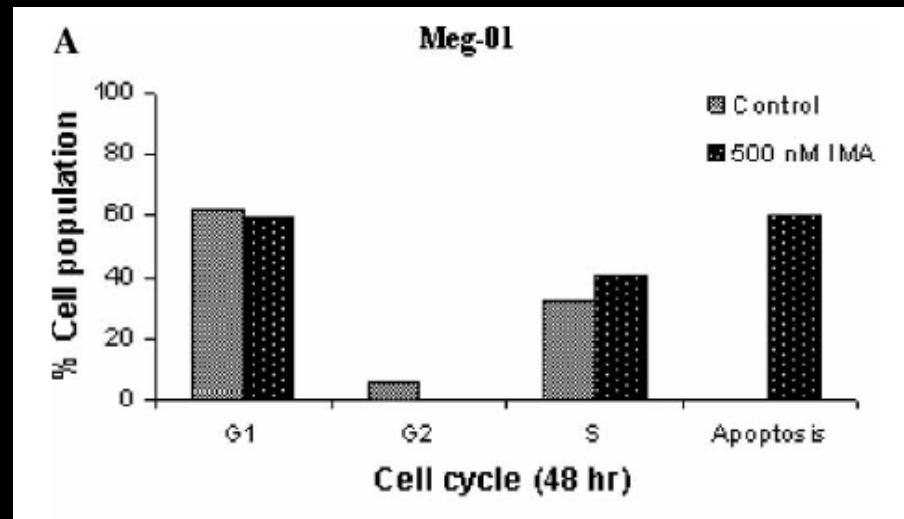
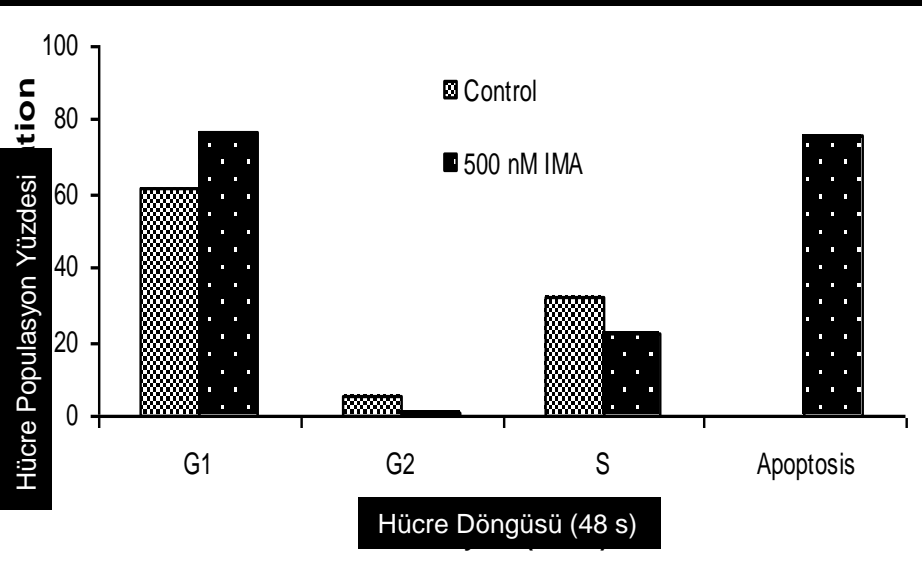


Stress  
UV, growth factor  
deprivation, etc.

Death receptors, e.g.

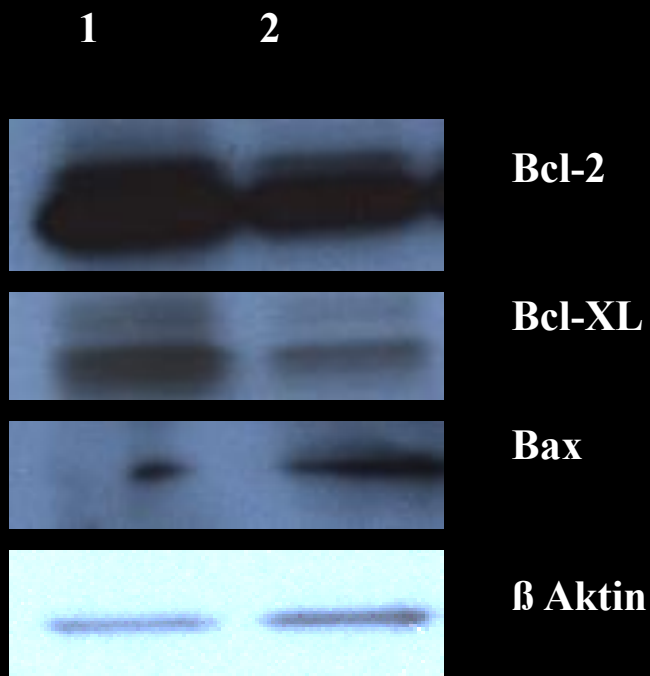
Survival factors:



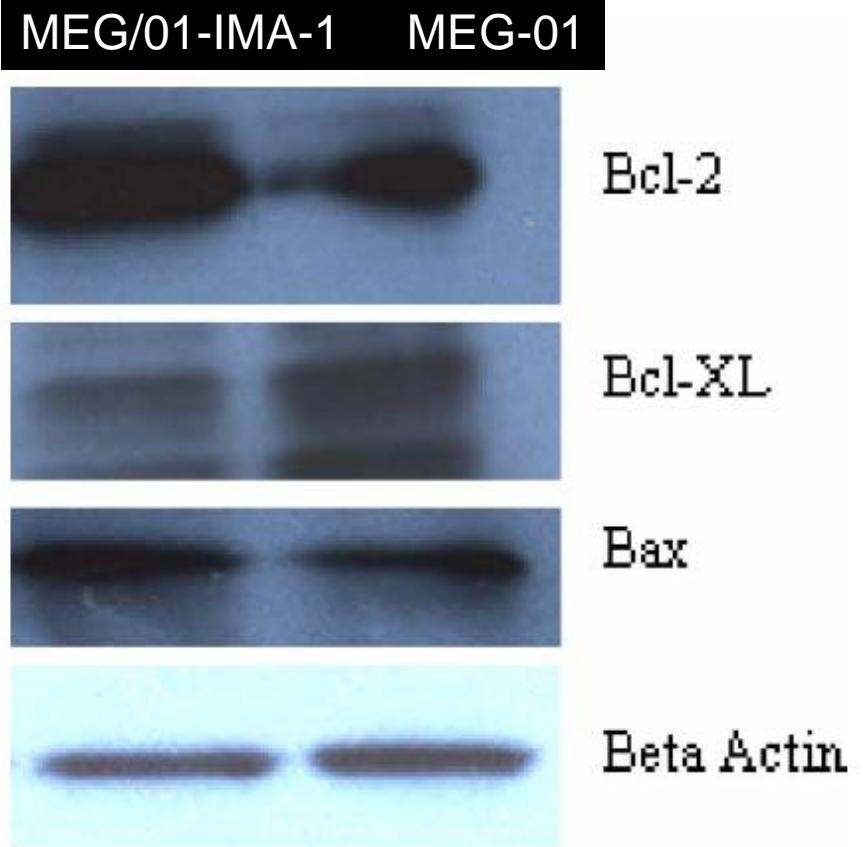


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Baran Y. Et al  
 Hematology, 2007 12(6);497-503.



**1- K562/IMA-1 μM**  
**2- K562**



**Baran Y. Et al**

**Journal of Biological Chemistry, 2007 282(15); 10922-10934.**

**Baran Y. Et al**

**Hematology, 2007 12(6);497-503.**

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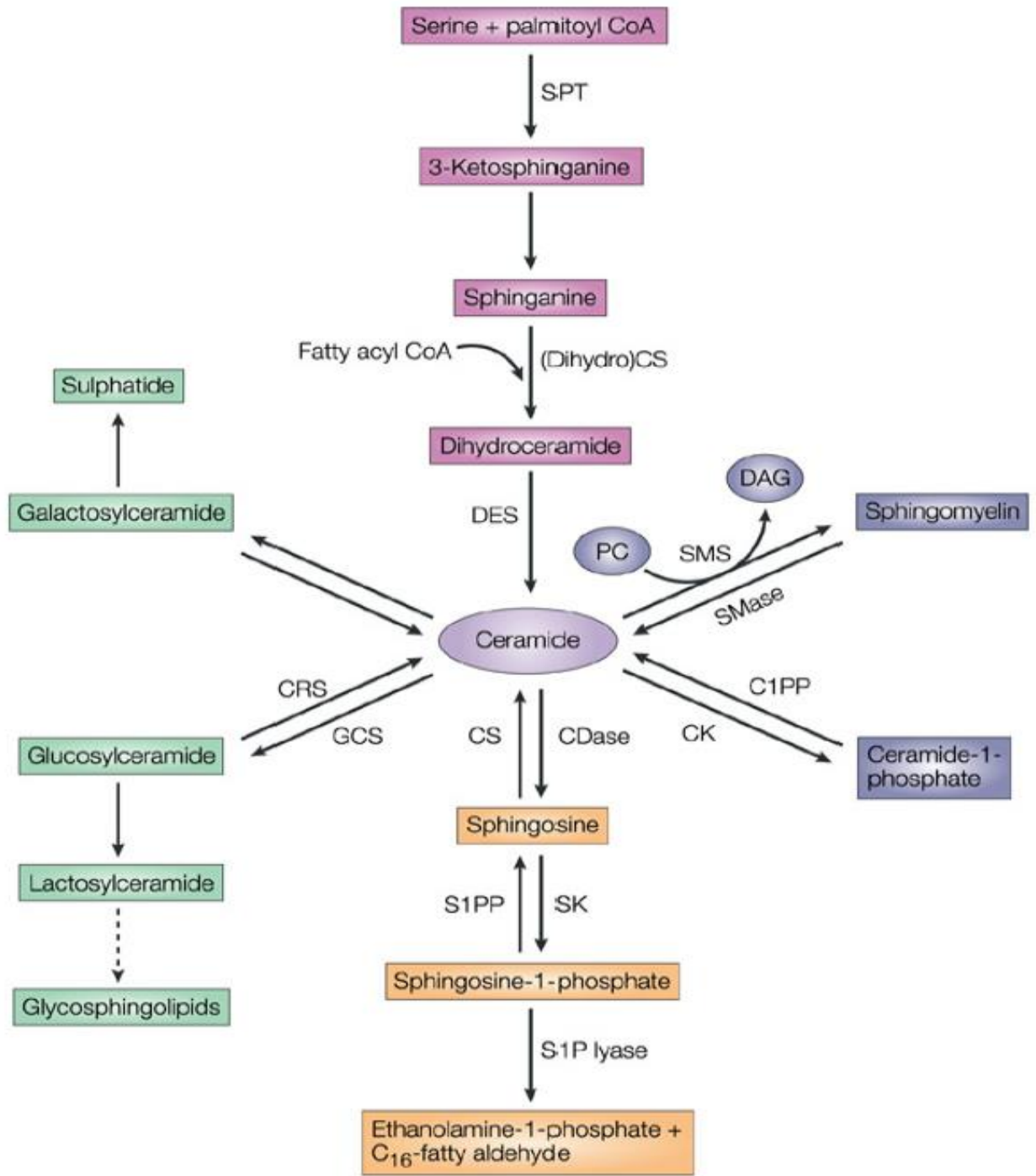
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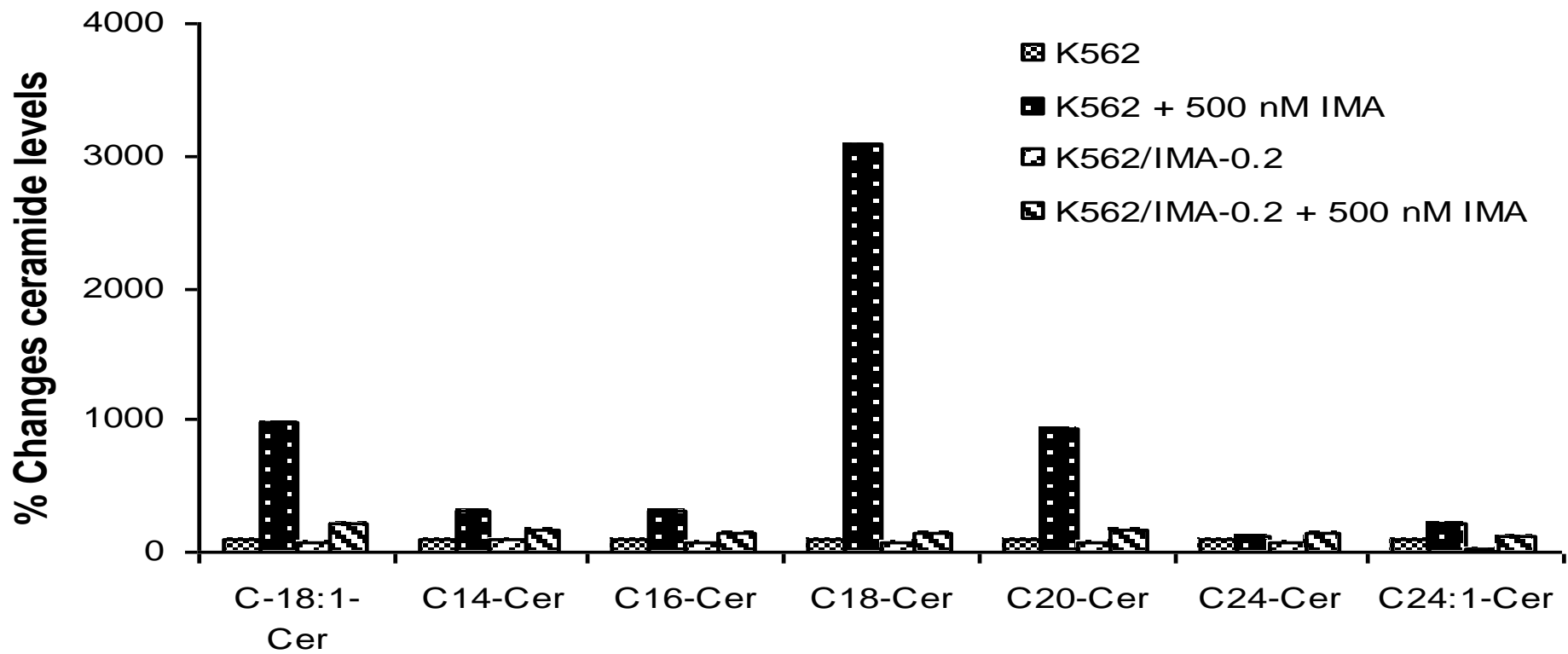
Increases in DNA repair

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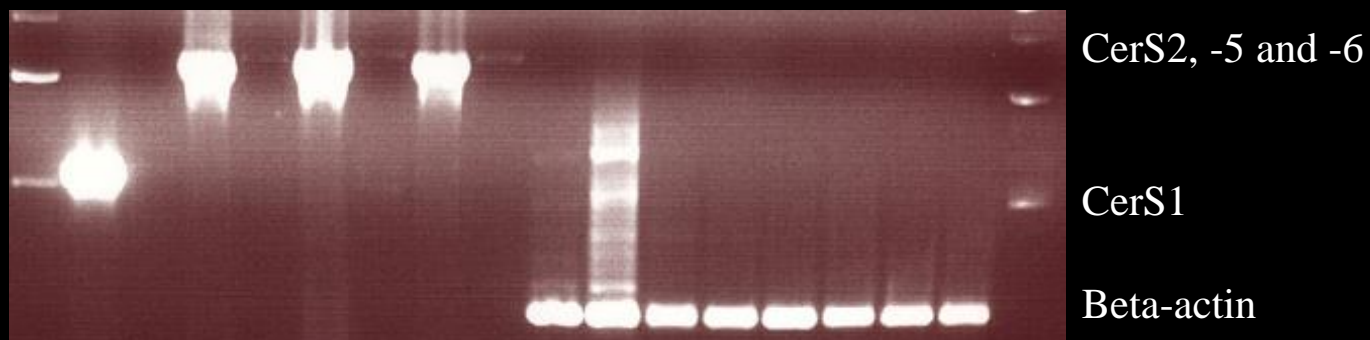
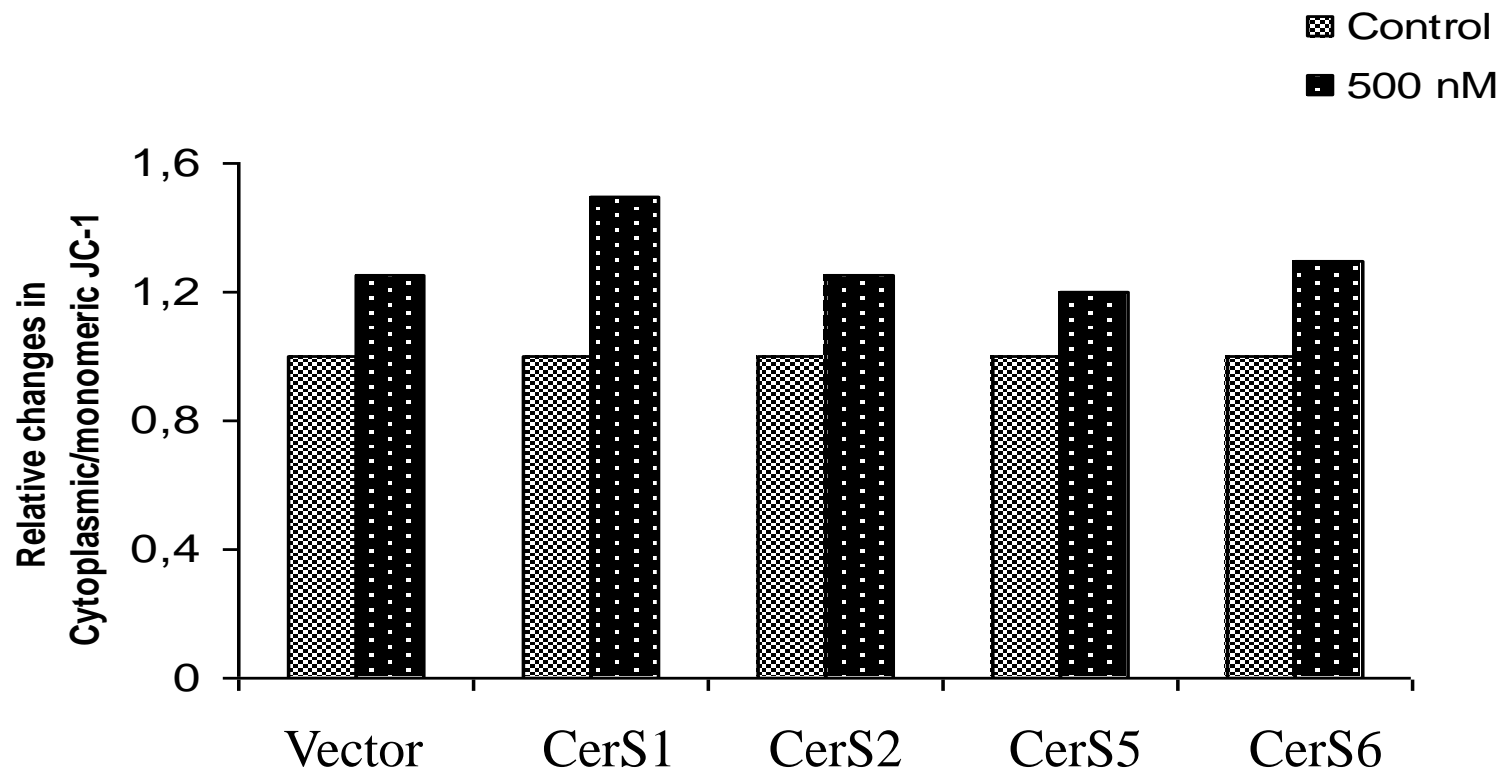
MicroRNAs

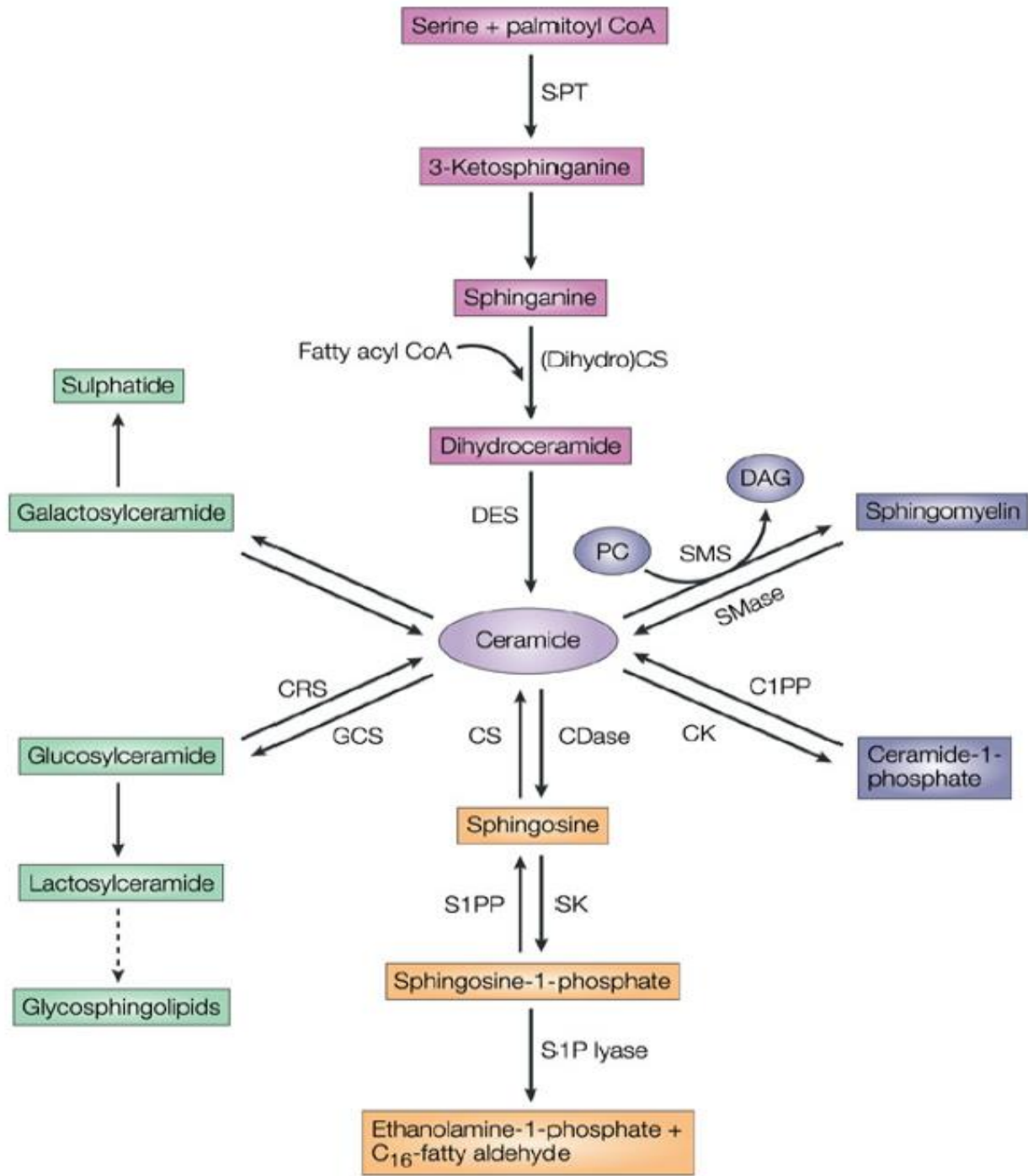


**Baran Y**  
**International Journal of Cancer**  
 2010 Oct 1;127(7):1497-506.

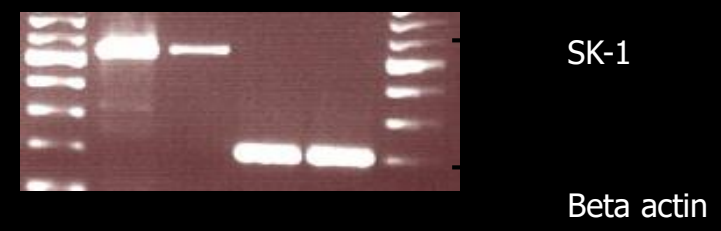
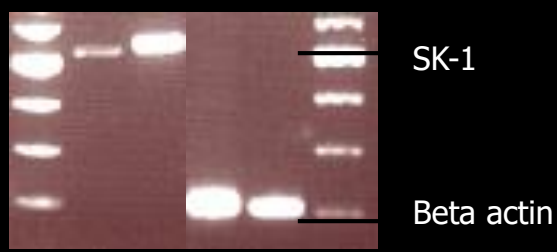
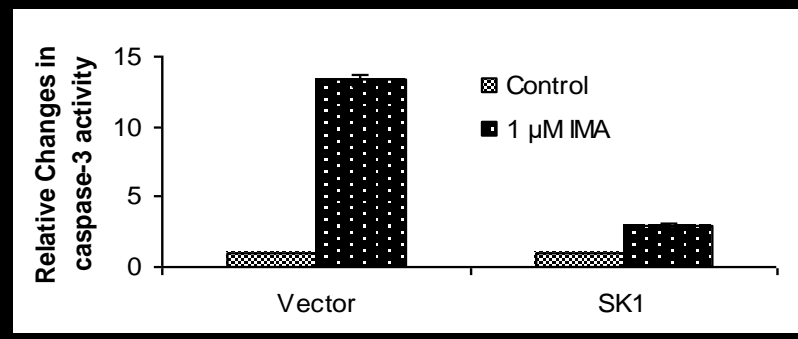
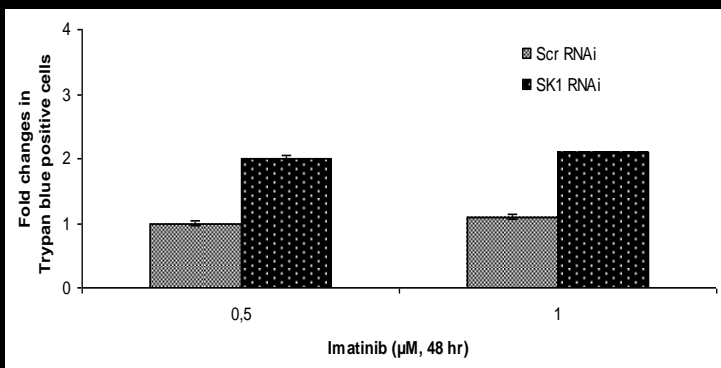
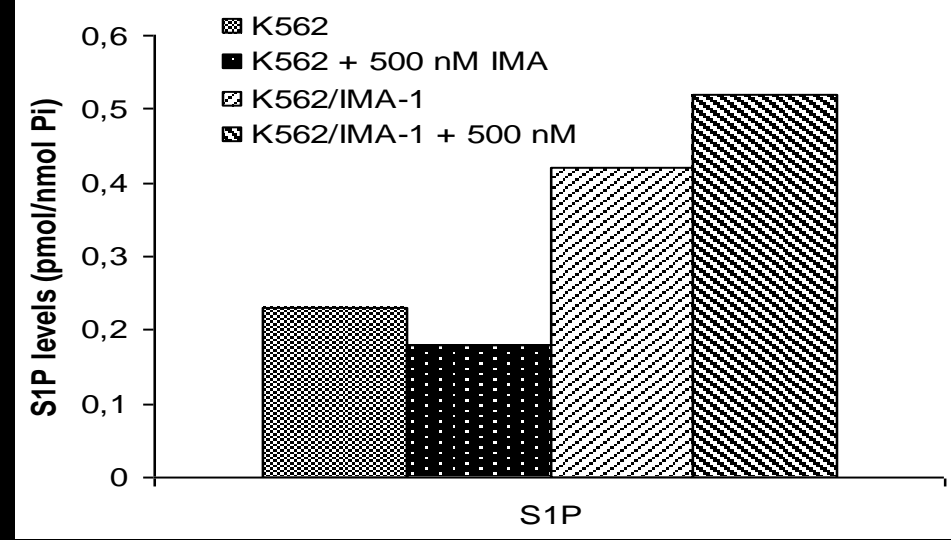
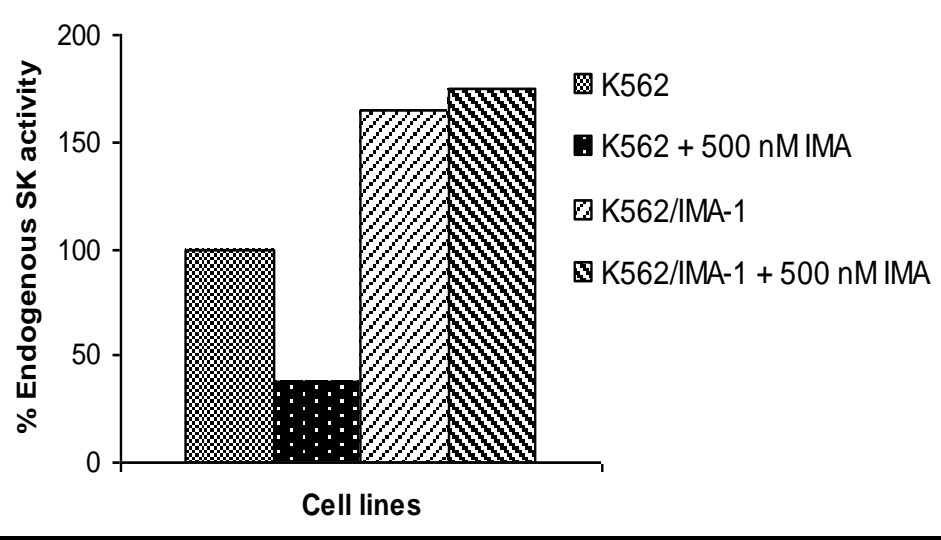




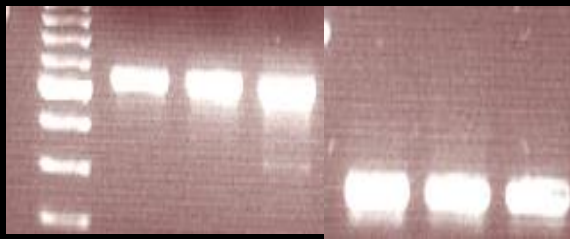




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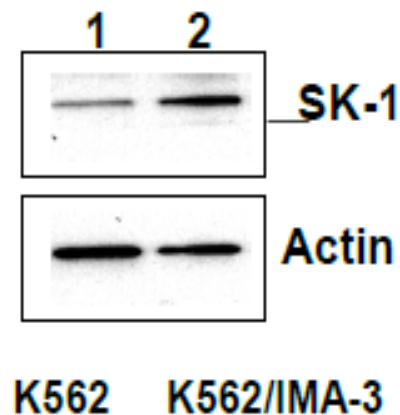
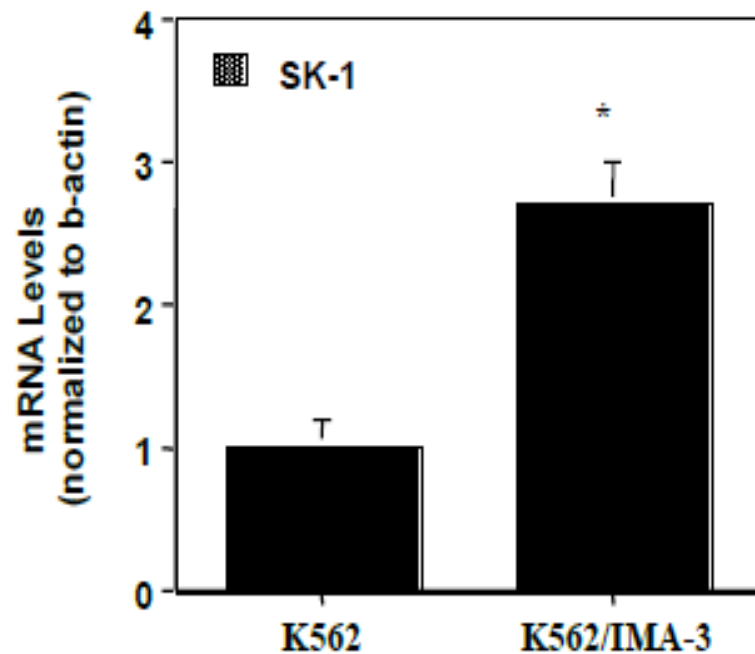
**Baran Y. Et al**  
**Journal of Biological Chemistry,**  
**2007 282(15); 10922-10934.**



SK-1

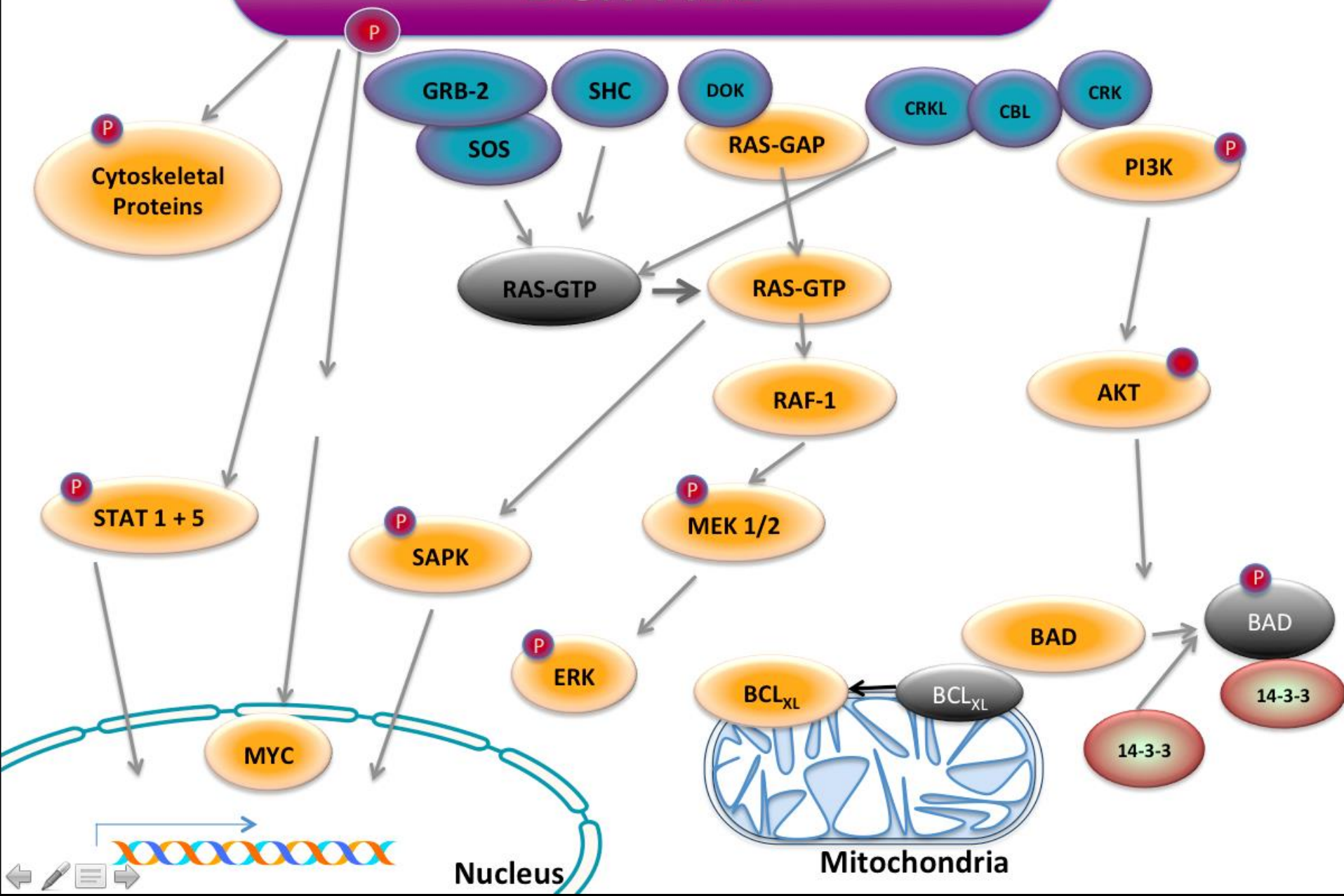
Beta actin

Baran Y. Et al  
Journal of Biological Chemistry,  
2007, 282(15): 10922-10934.



Salas et al. Blood, 2011, 117(22):5941-52.

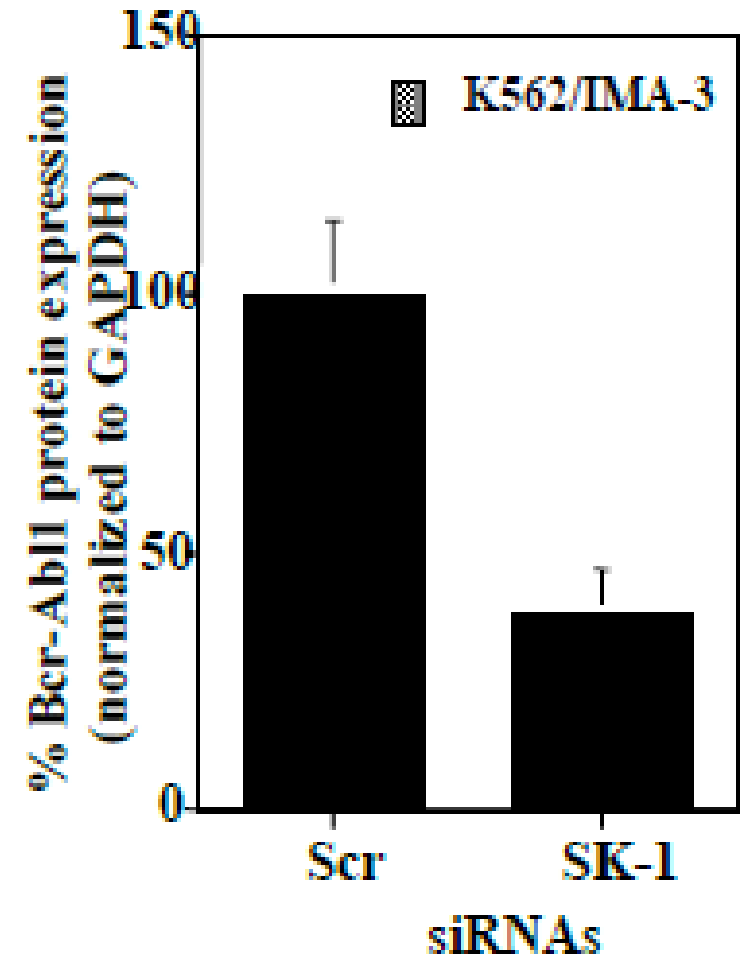
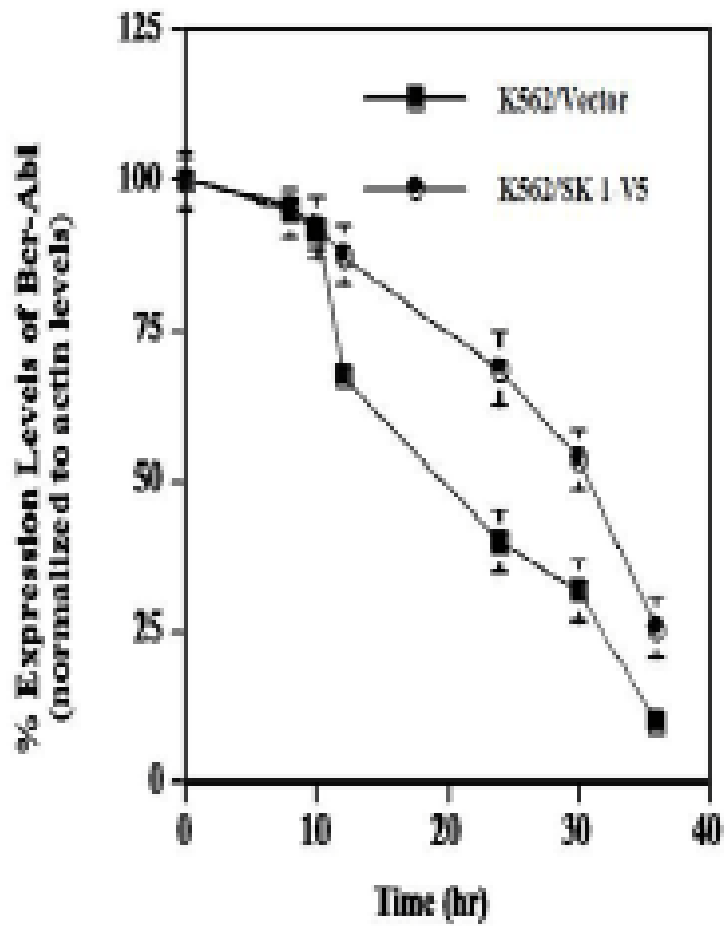
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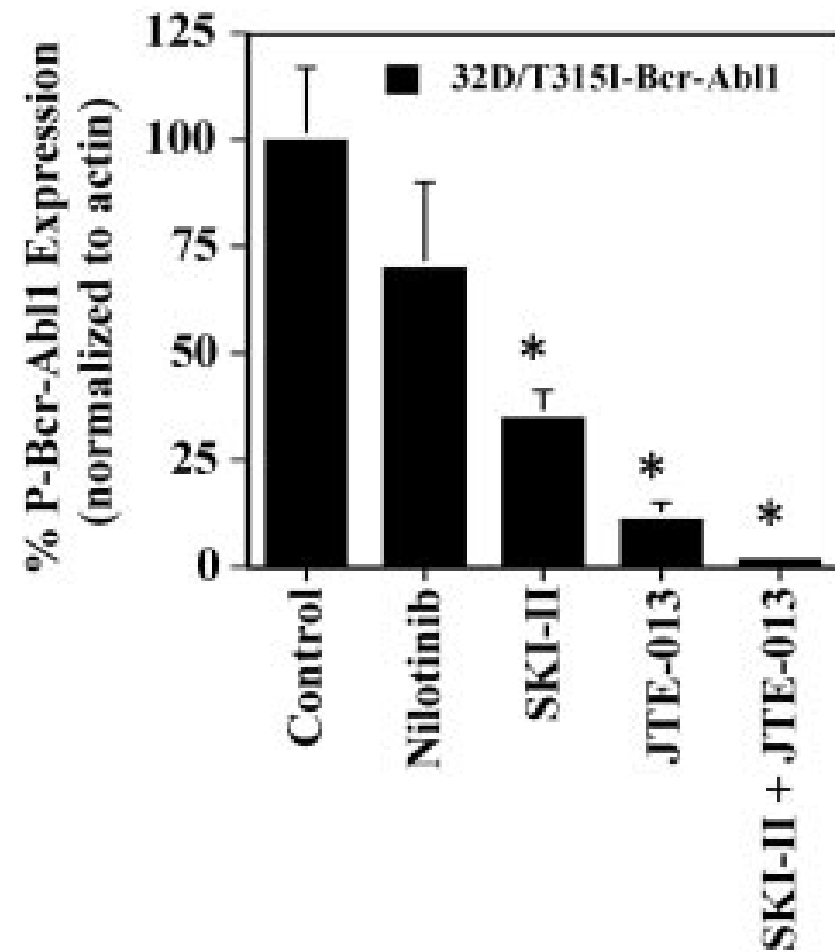
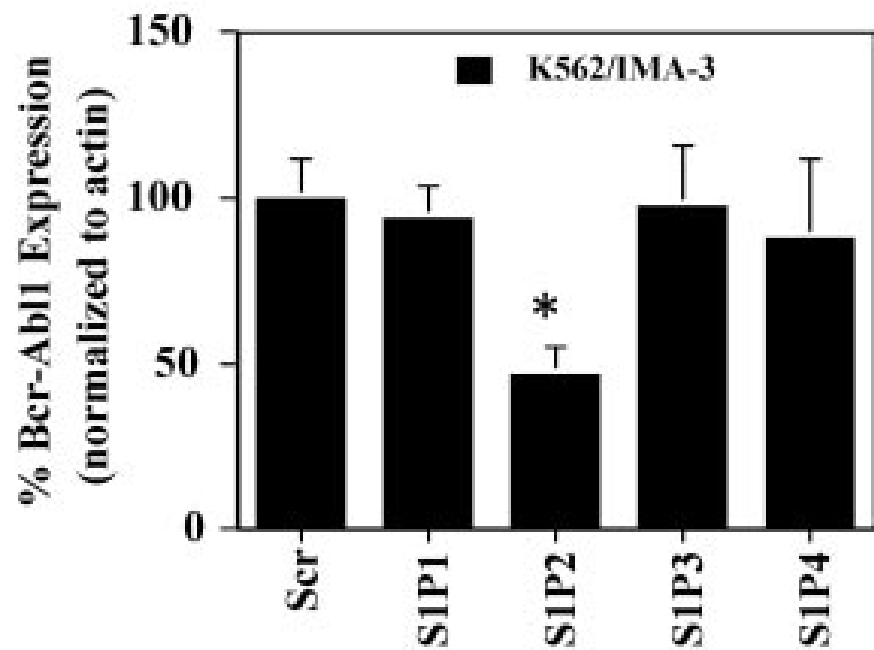


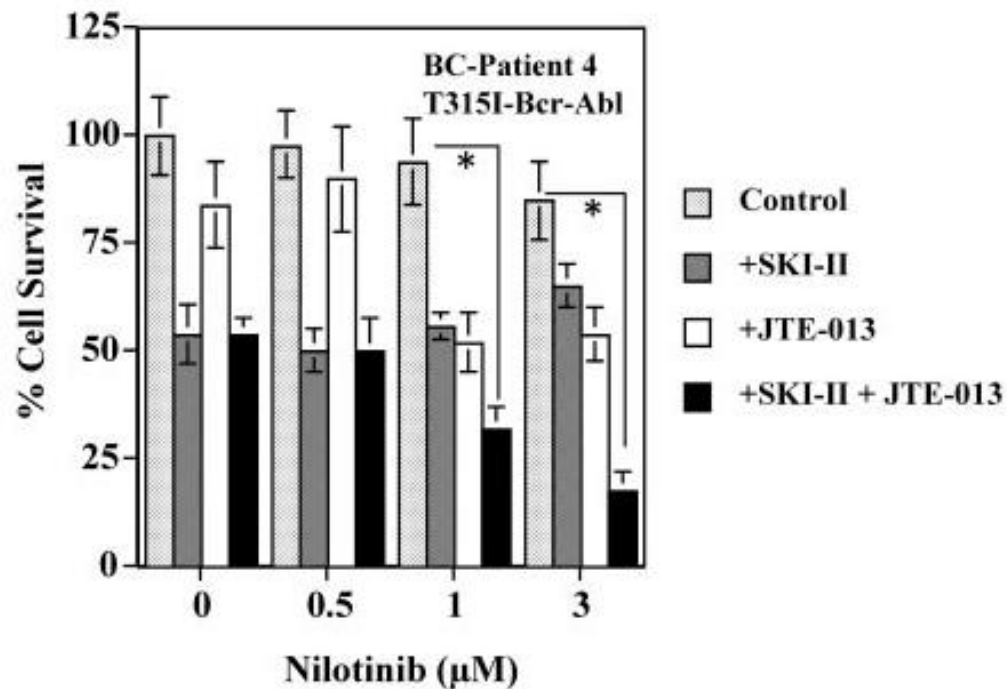




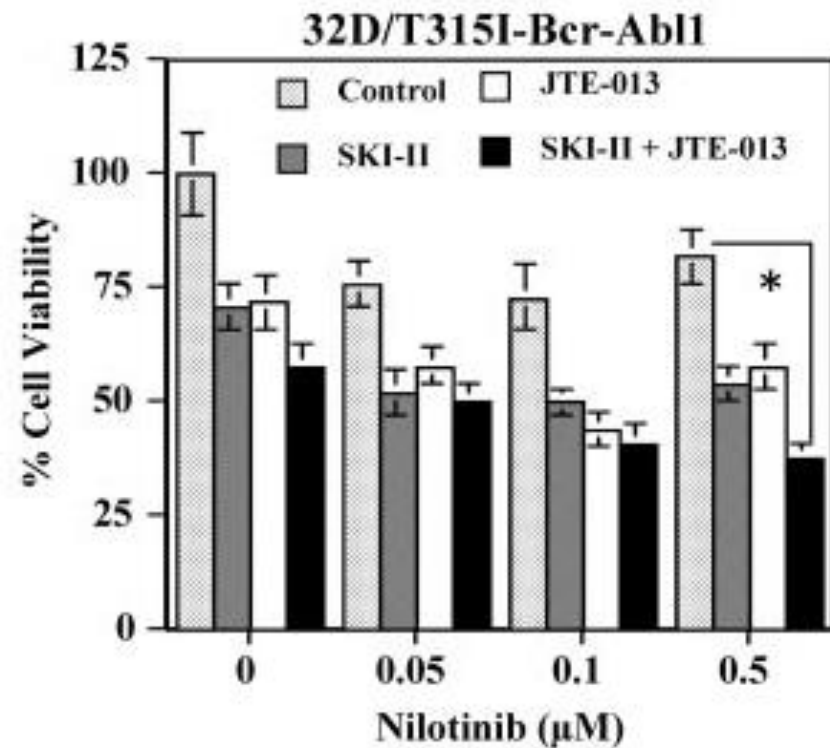


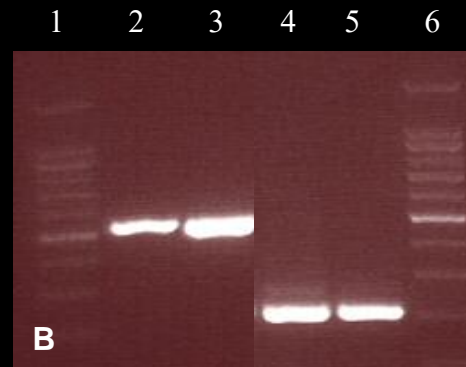
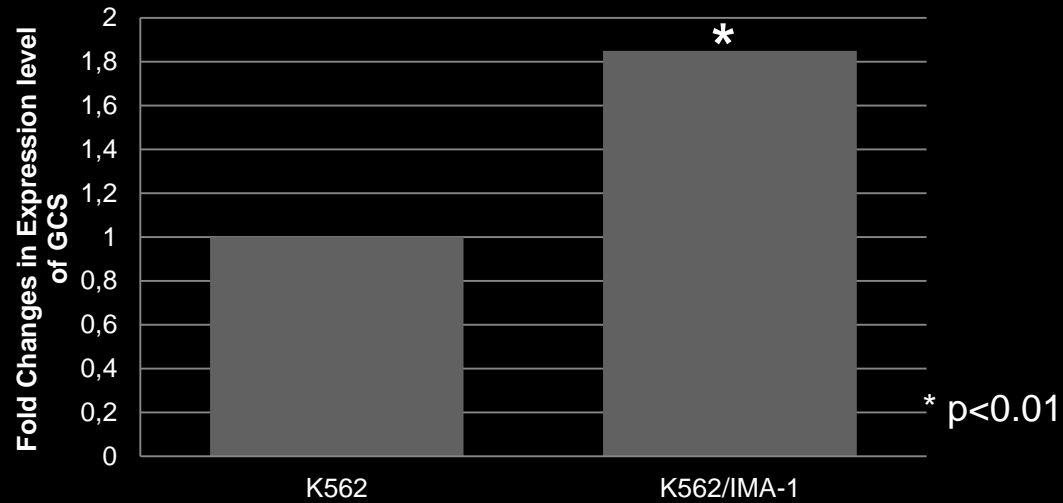




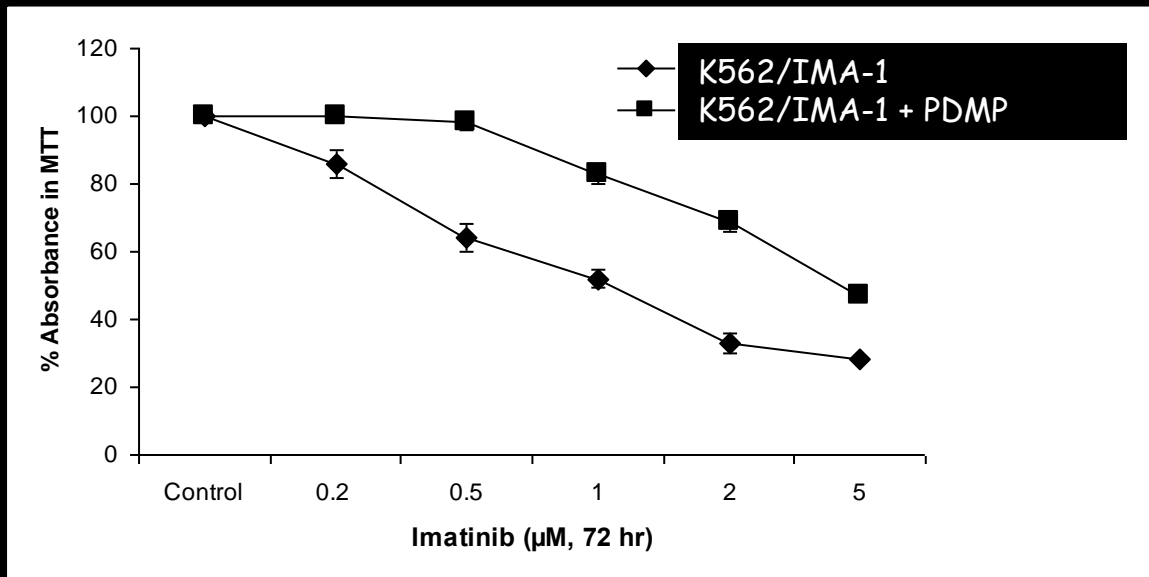


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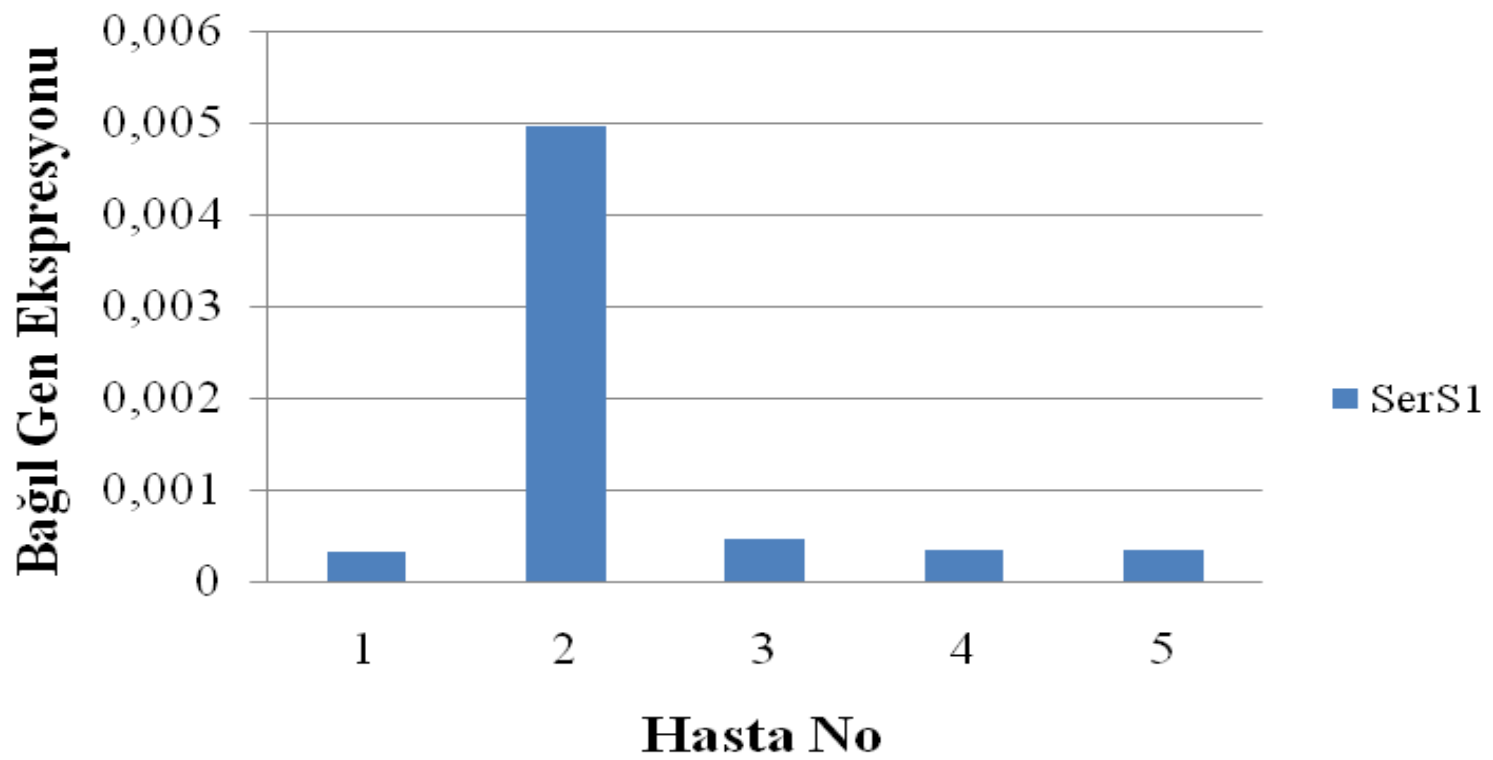




Baran Y. Et al  
 Journal of Cancer Research  
 and Clinical Oncology,  
 2011, 137(10):1535-1544.



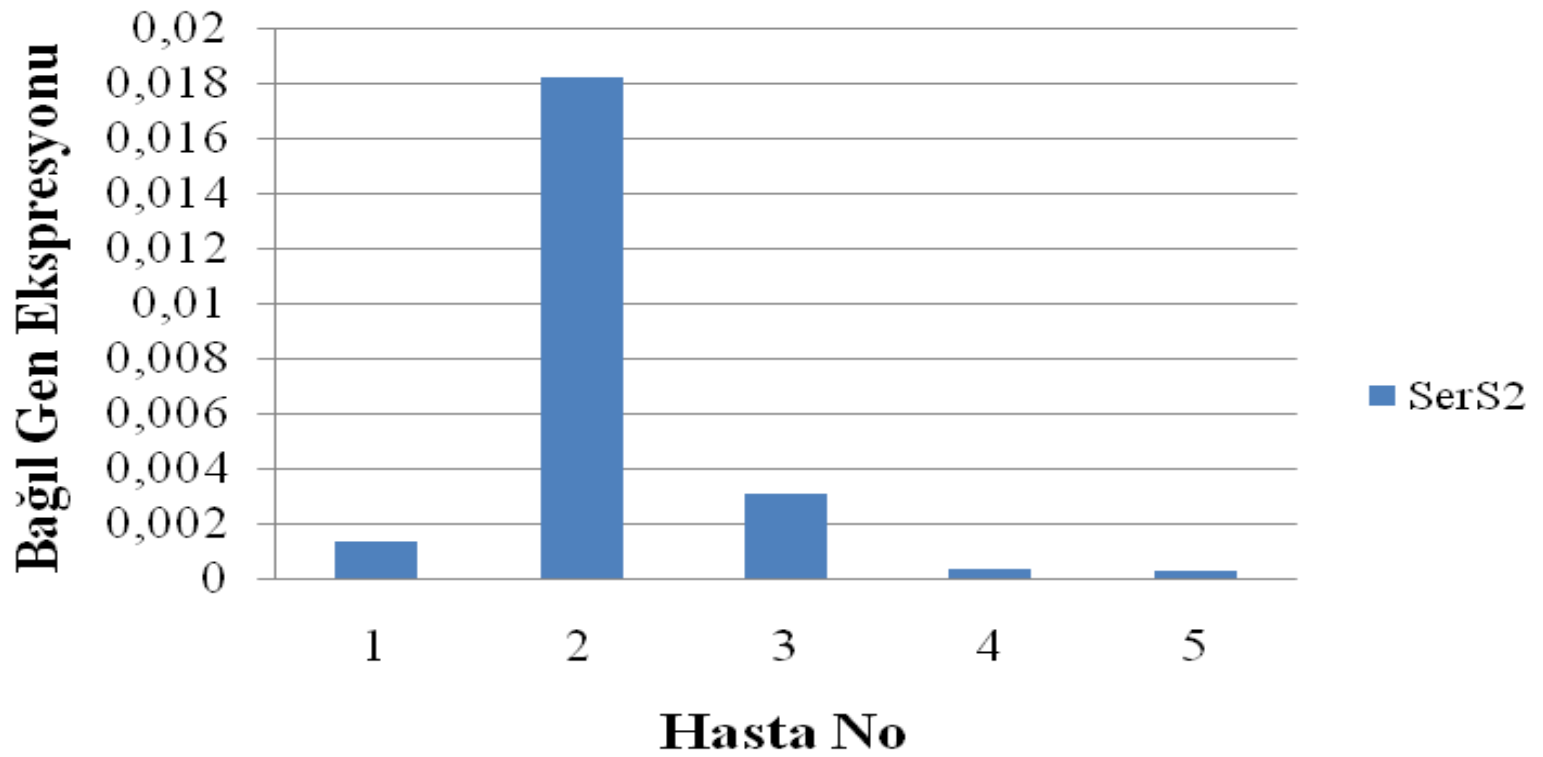
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2011, 137(10):1535-1544.



Patient No	Case
1	Newly Diagnosed
2	Positive response to Nilotinib
3	Newly Diagnosed
4	Loss of Molecular response
5	Newly Diagnosed

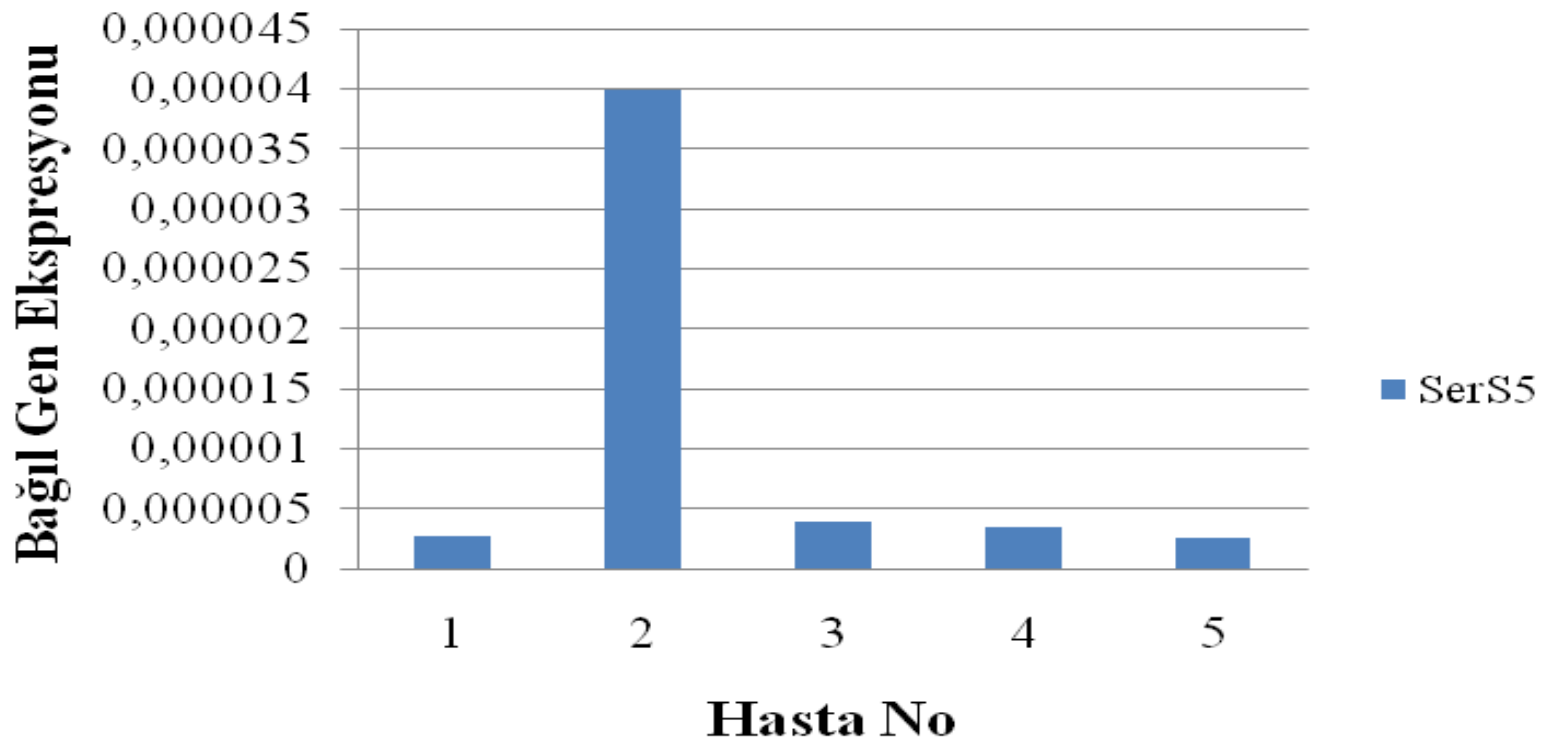
**Cooking!**





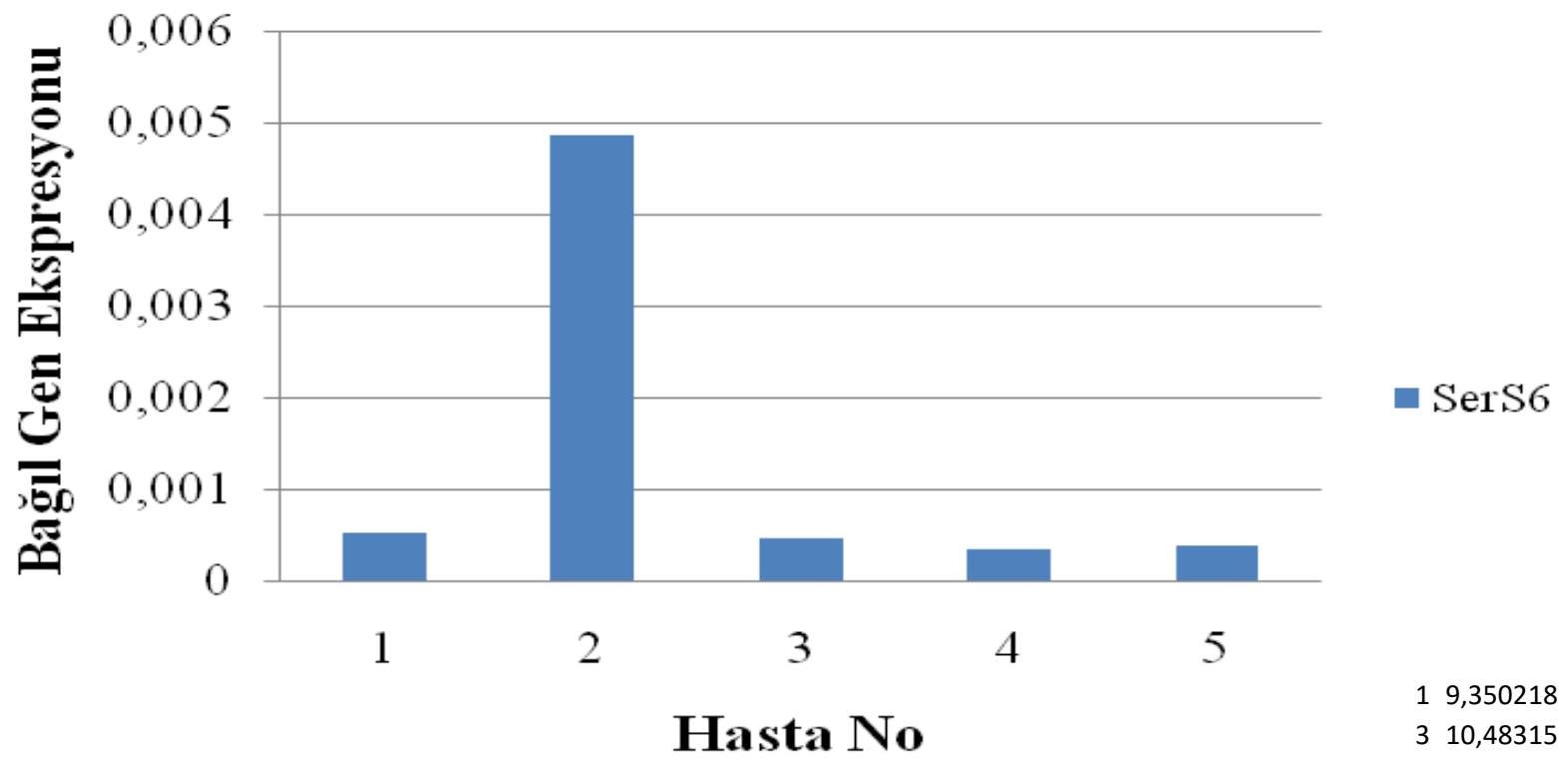
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**Cooking!**



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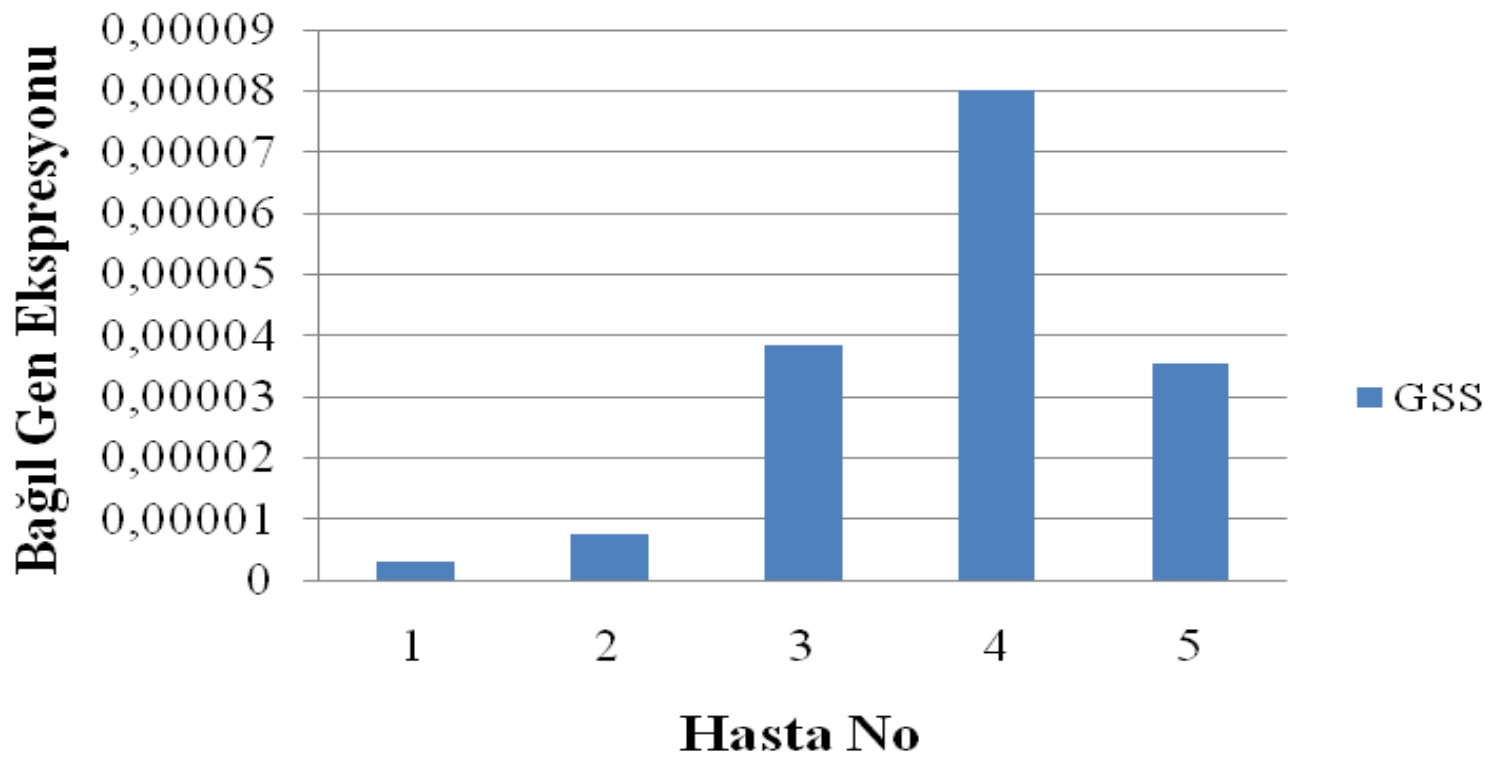
**Cooking!**



1 9,350218  
 3 10,48315  
 4 14,37012  
 5 13,285

Patient No	Case
1	Newly Diagnosed
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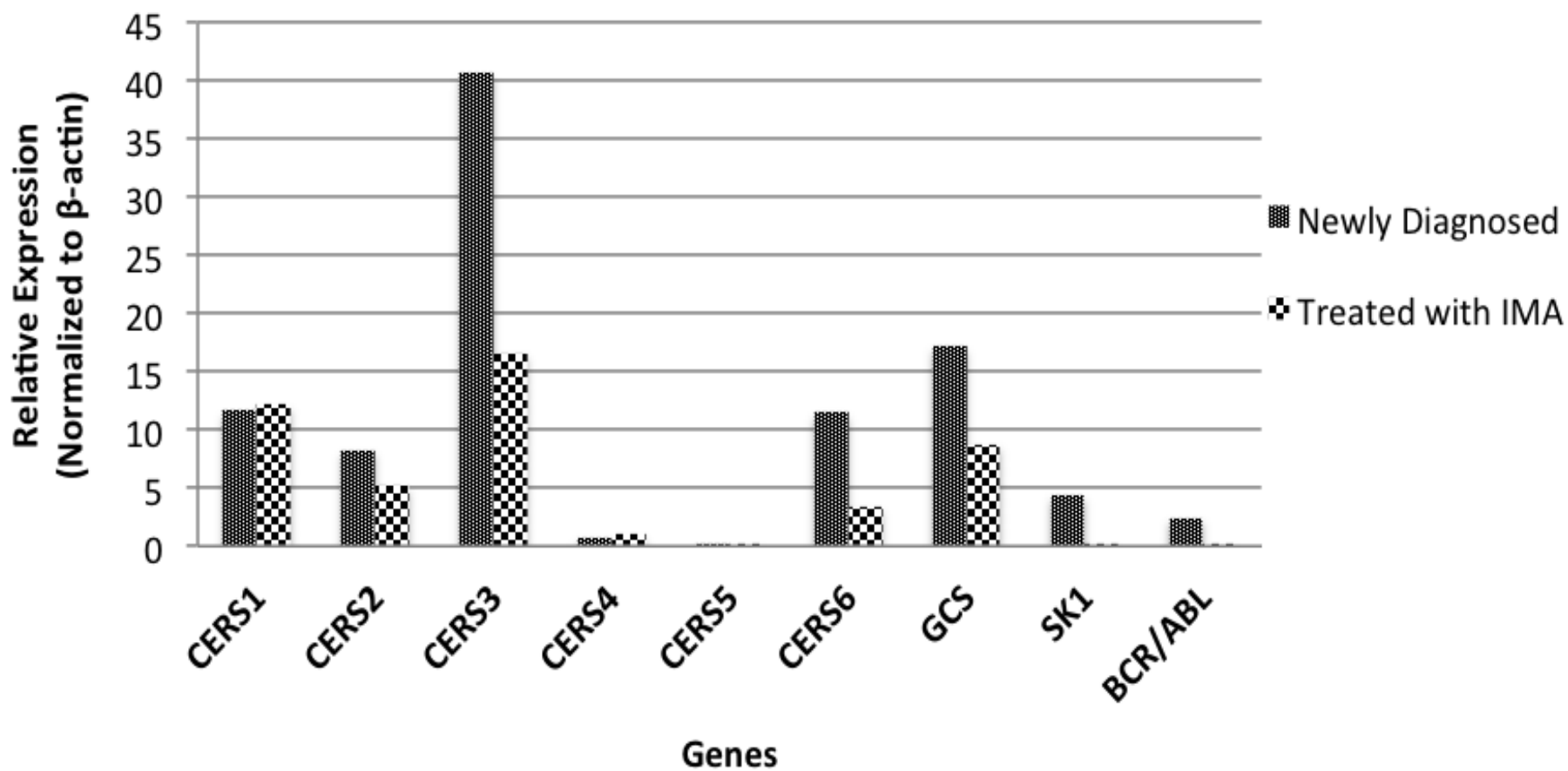
**Cooking!**



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3	Newly Diagnosed
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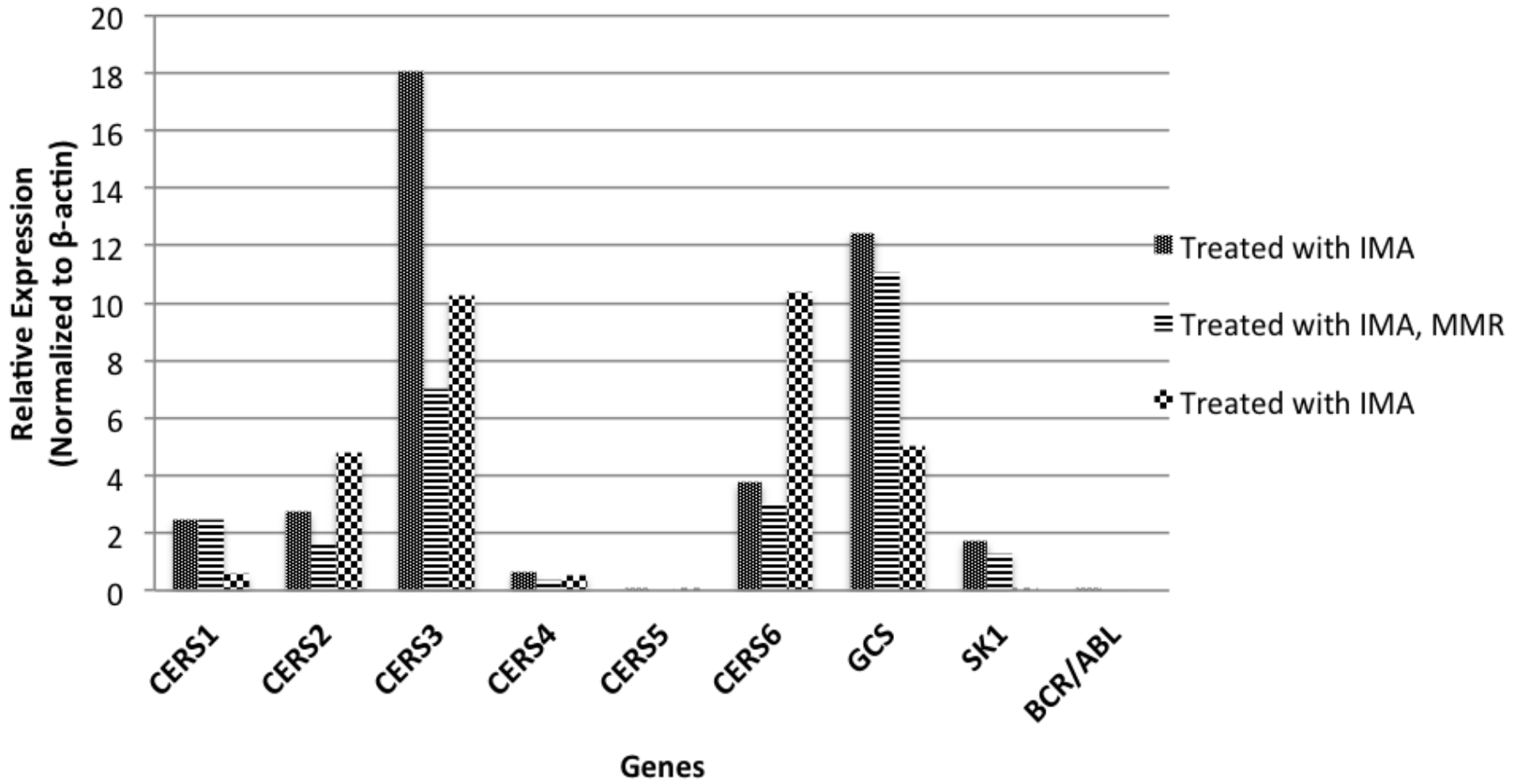
**Cooking!**

# Patient # 25



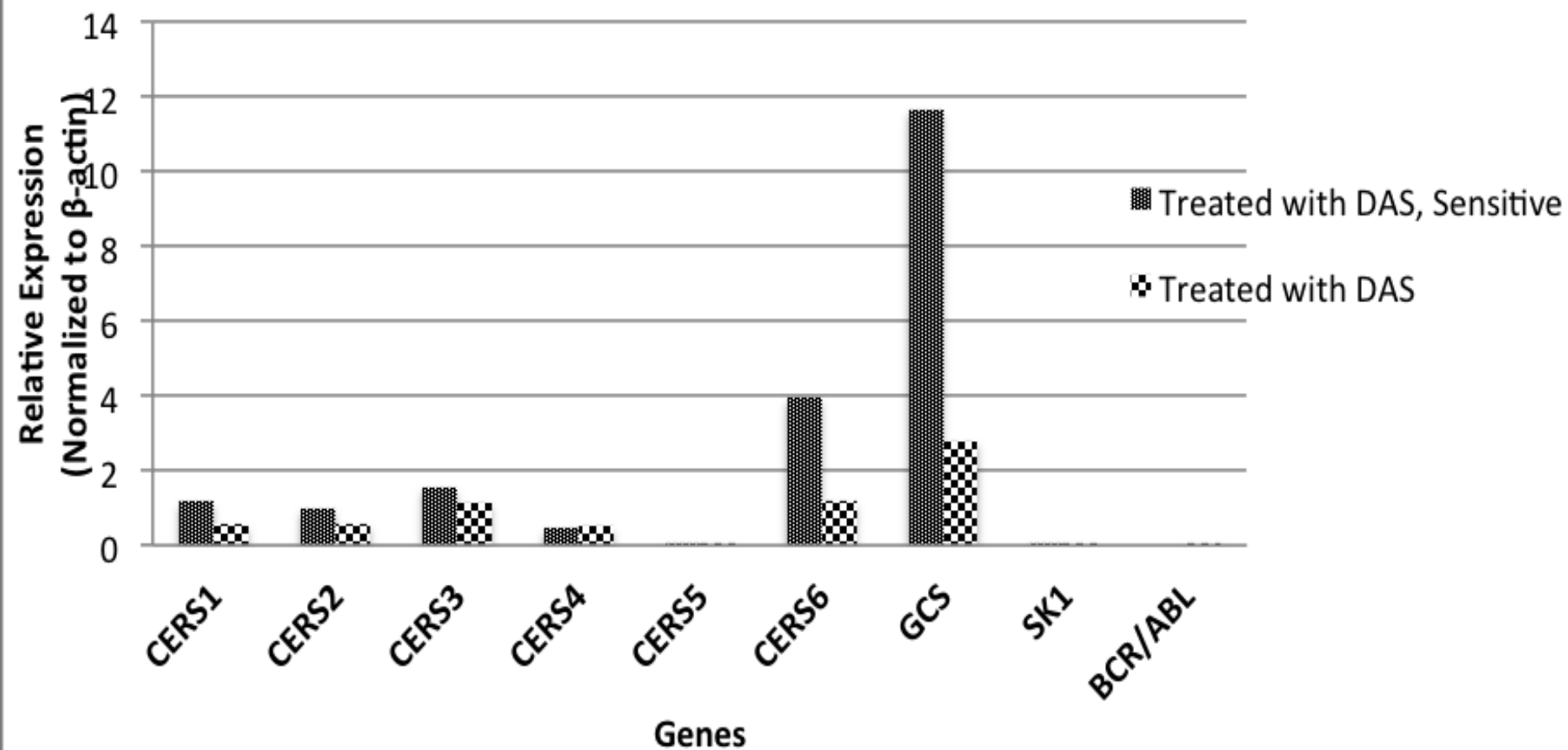
Cooking!

# Patient # 7



Cooking!

# Patient # 29



Cooking!



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The background of the slide features a pattern of blue water ripples, with concentric circles and overlapping waves creating a textured, fluid appearance. The colors range from light sky blue to deeper, darker blues.

Each patient's

cancer is as

unique as

the human

fingerprint





Türkiye Bilimsel ve Teknolojik Araştırma Kurumu

TÜBİTAK

TÜBA



TÜRKİYE BİLİMLER AKADEMİSİ

TÜRKİYE BİLİMLER AKADEMİSİ

Eczacıbaşı



Türk Hematoloji Derneği

Ana Sayfa



ÖZEL ANKARA

GÜVEN  
HASTANESİ



TÜRK KANSER ARAŞTIRMA ve SAVAŞ KURUMU DERNEĞİ

Turkish Association For Cancer Research and Control



Izmir Institute of Technology & Abdullah Gul University





***Thank You.***