

Università degli Studi di Torino  
Facoltà di Biotecnologie Molecolari  
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Corso di Immunologia Molecolare

# IL-2R & IL-15R

**Alice Praduroux**

# Classificazione

- **Recettori appartenenti alla famiglia I o delle eritropoietine**
  - motivo caratteristico **WSXWS**
  - cisteine conservate
- **Esistono in due forme:**
  - ancorati alla membrana
  - solubili

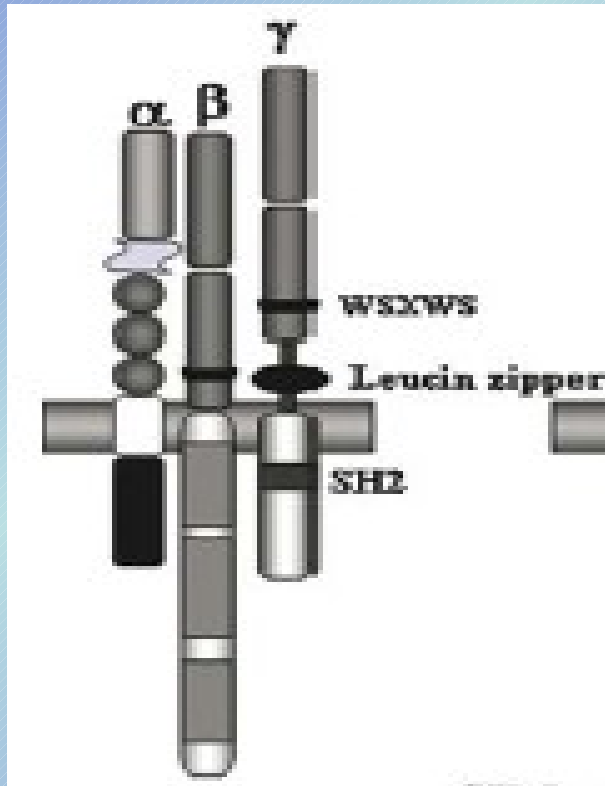
# Struttura

**Eterotrimero:**

**IL-2R $\alpha$  ( CD25 o Tac )**

**IL-2 $\beta$  ( p75 )**

**$\gamma$ C**



**IL-15R $\alpha$**

**IL-15R $\beta$**

**$\gamma$ C**

# Affinità di legame

## IL-2R

| IL-2 affinity         | High                                          | Intermediate                | Low              |
|-----------------------|-----------------------------------------------|-----------------------------|------------------|
| Subunit composition   | IL-2R $\alpha$<br>IL-2R $\beta$<br>$\gamma$ c | IL-2R $\beta$<br>$\gamma$ c | IL-2R $\alpha$   |
| Dissociation constant | $K_d = 10-75$ pM                              | $K_d = 0.5-2$ nM            | $K_d = 10-20$ nM |
| Ability to signal     | Complete                                      | Complete                    | None             |

## IL-15R

|                      |                    |                                                                                       |                     |
|----------------------|--------------------|---------------------------------------------------------------------------------------|---------------------|
| IL-15R $\alpha$      | $K_d = 10^{-11}$ M |  | affinità elevata    |
| IL-15R $\beta\gamma$ | $K_d = 10^{-9}$ M  |  | affinità intermedia |

Gaffen S.L and Liu K.D, Overview of interleukin-2 function, production and clinical applications. Cytokine 28: 109, 2004  
 Budagian V. et al, Natural soluble interleukin-15R $\alpha$  is generated by cleavage that involves the tumor necrosis factor- $\alpha$ -converting enzyme ( TACE/ADAM17 ). J. Biol. Chem 279: 40368, 2004.

# Ruolo delle subunità recettoriali

CATENA  $\alpha$



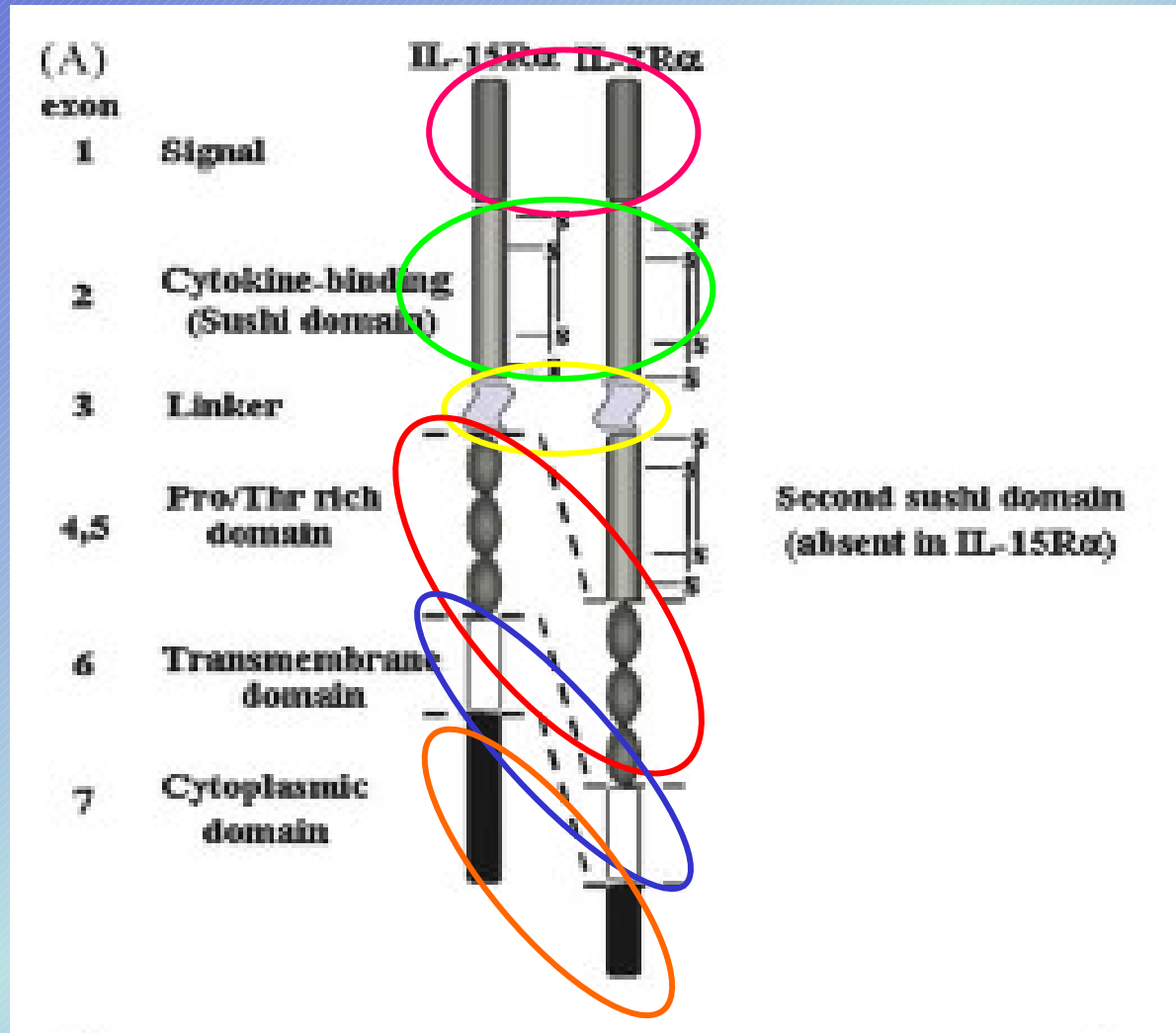
- legame con la citochina
- incapacità di trasduzione del segnale

COMPLESSO  $\beta\gamma$

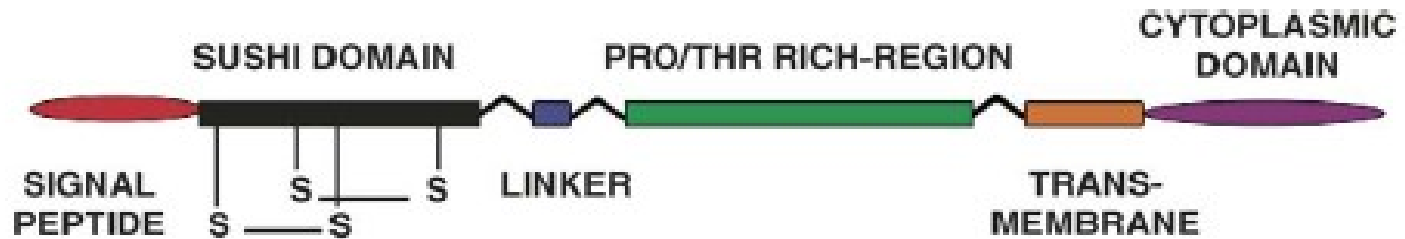


- trasduzione del segnale
- agisce anche in assenza della subunità  $\alpha$

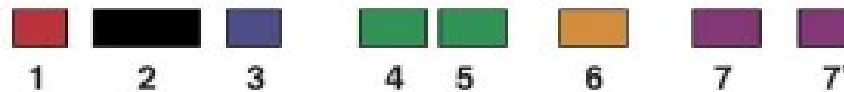
# IL-2R $\alpha$ & IL-15R $\alpha$



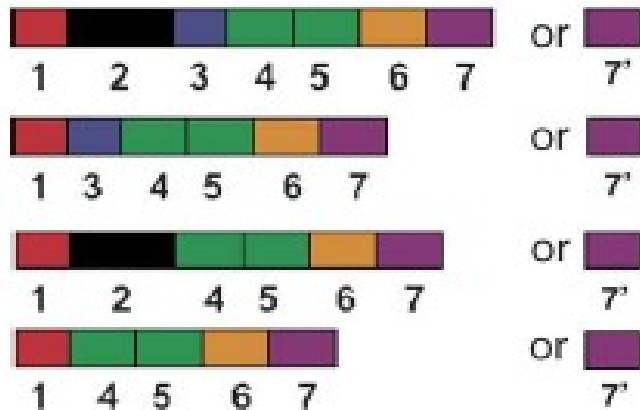
# Isoforme IL-15Ra



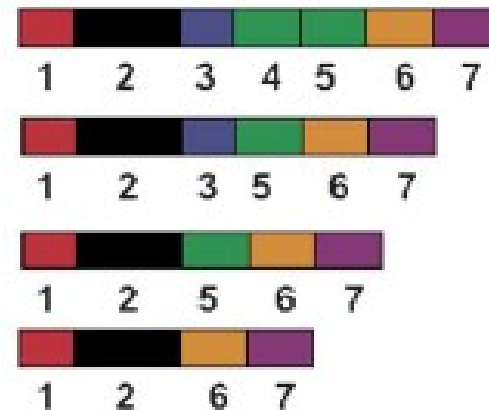
Exons



Human Isoforms



Murine Isoforms



# Complesso $\beta\gamma$

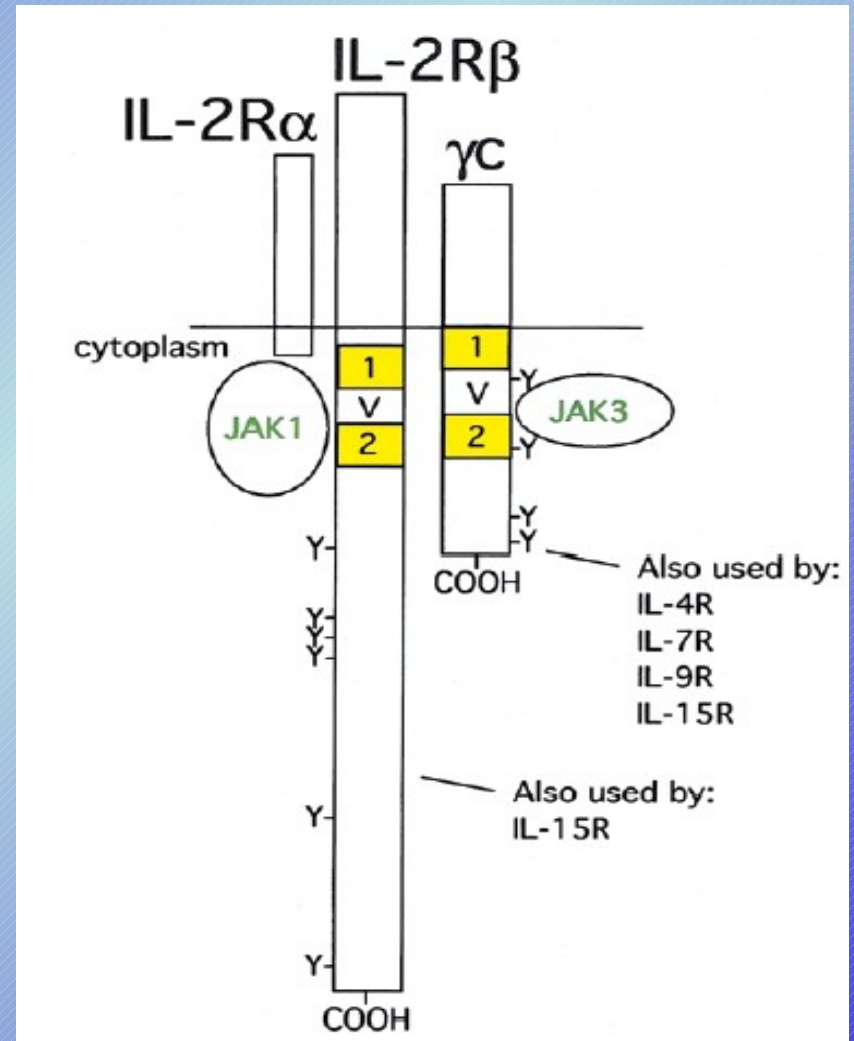
- Famiglia recettoriale delle ematopoietine

## Dominio extracellulare:

- 4 cys conservate
- motivo WSXWS

## Dominio intracitoplasmatico:

- domini Box1 e Box2
- porzione variabile





# Espressione IL-2R & IL-15R

## IL-2R

- linfociti T
- linfociti B
- cellule NK
- DCs

## IL-15R

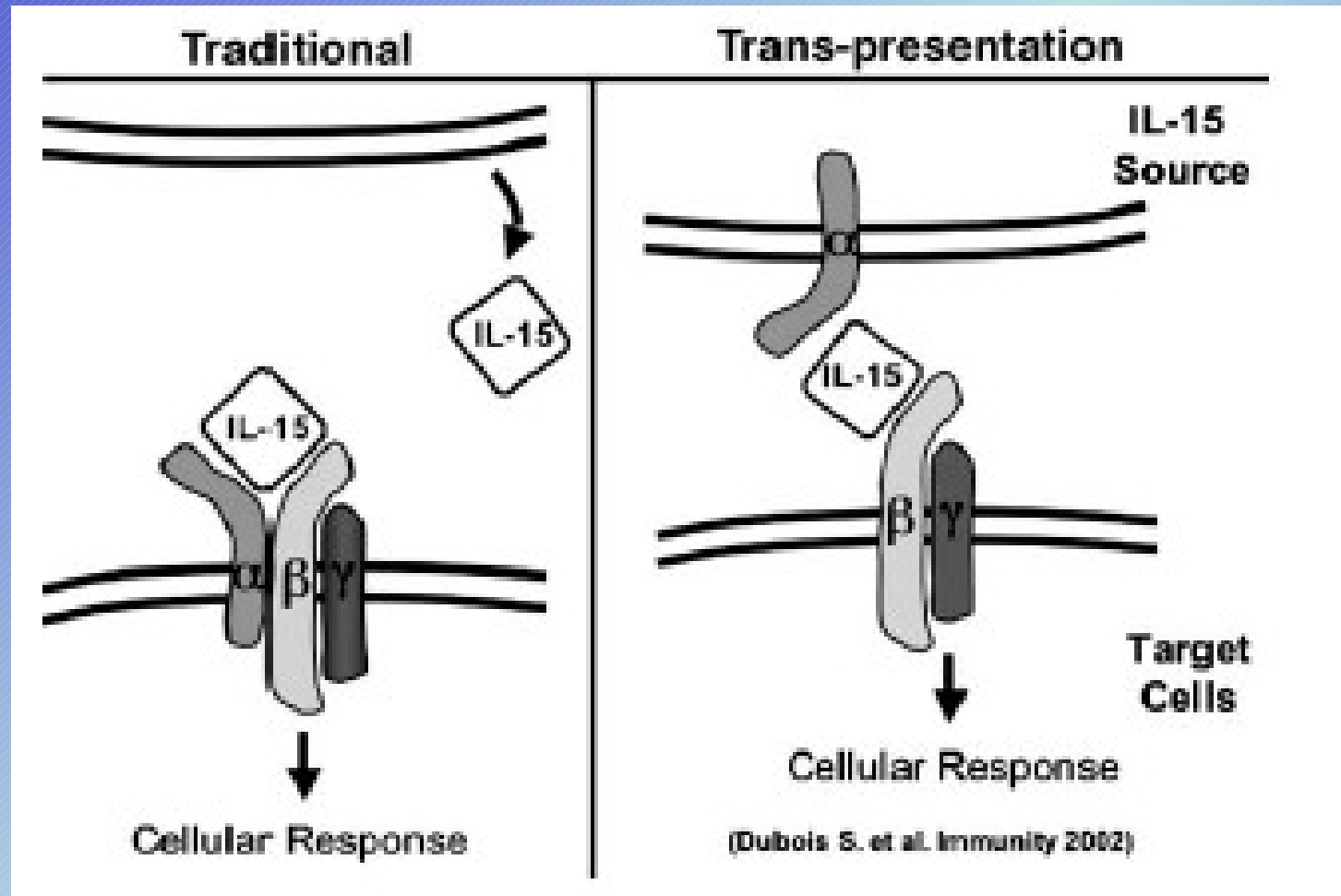
Nel sistema immunitario:

- linfociti T
- linfociti B
- cellule NK
- neutrofili e eosinofili
- DCs
- mastociti e macrofagi

In altre cell:

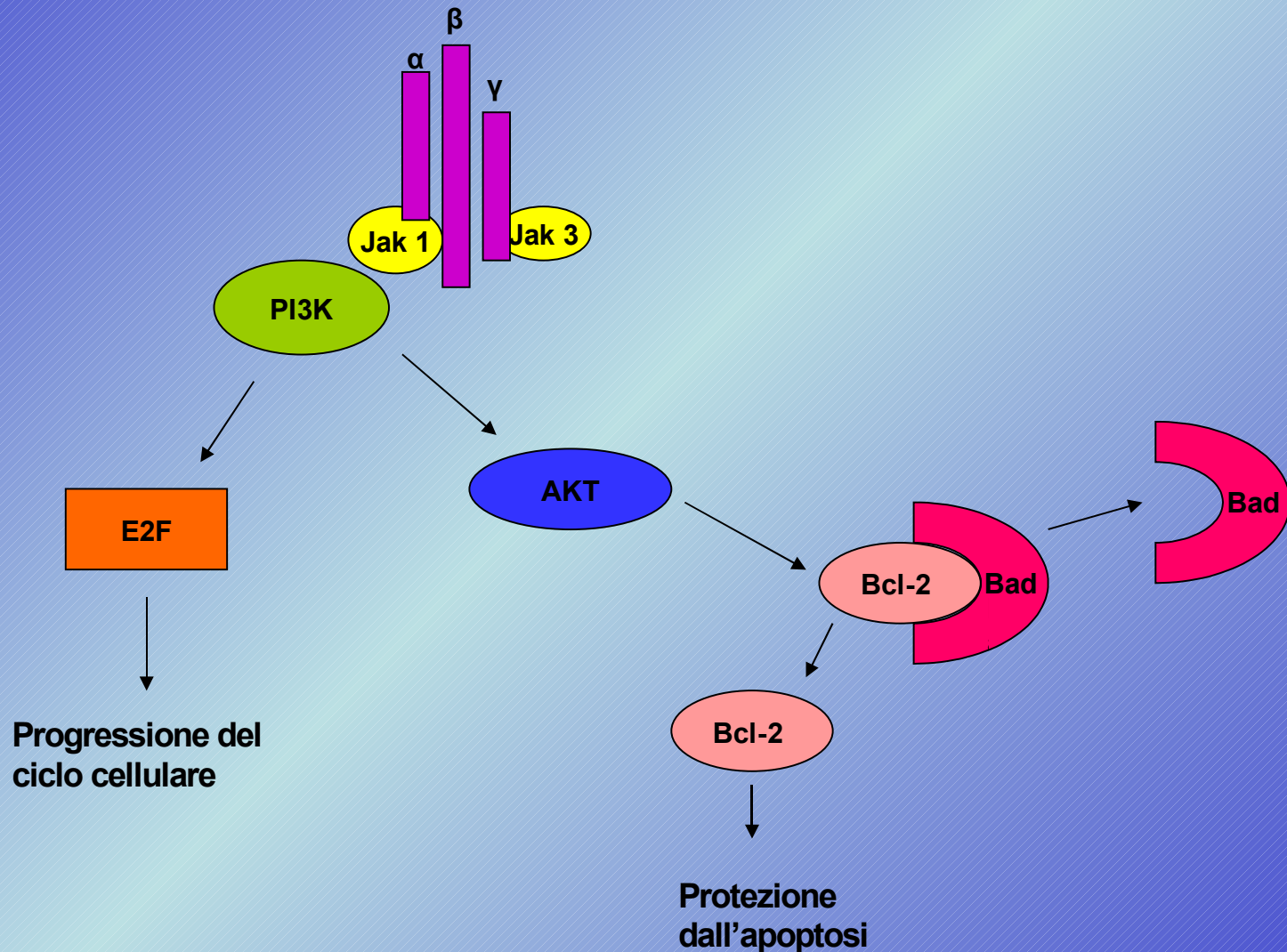
- fibroblasti
- osteoclasti
- cell epiteliali
- cell endoteliali
- cell neuronali e della glia
- adipociti

# Modelli di espressione del IL-15R

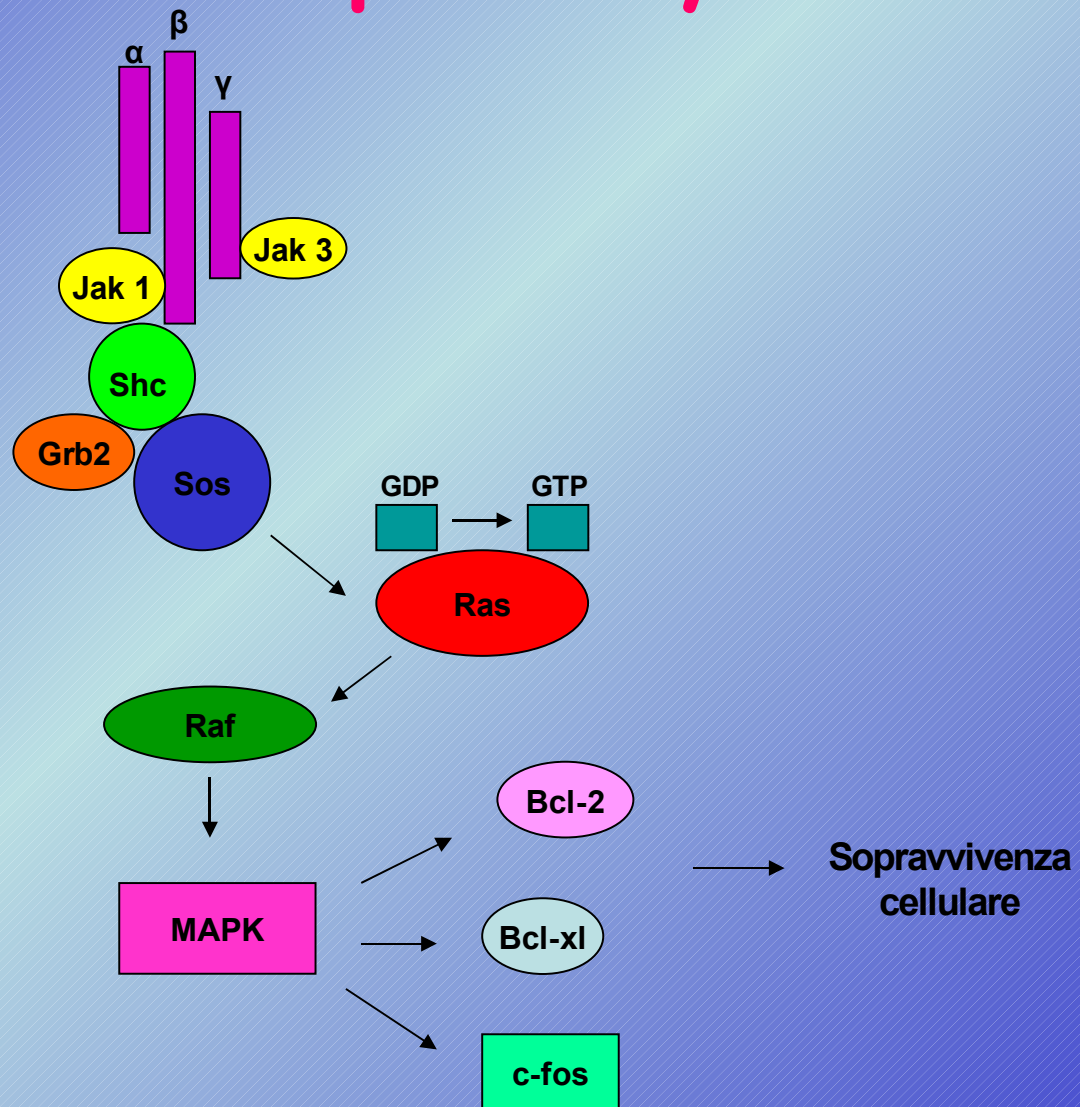


# **Vie di trasduzione del segnale**

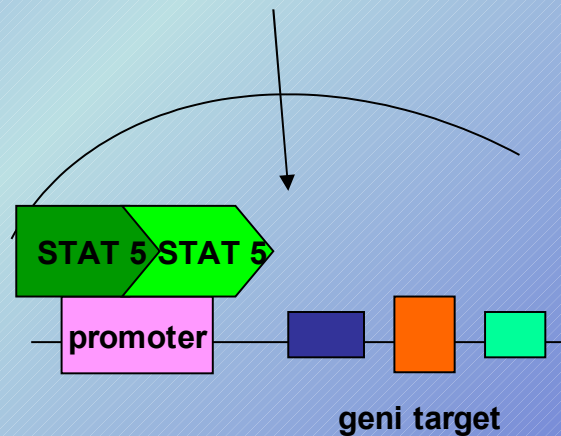
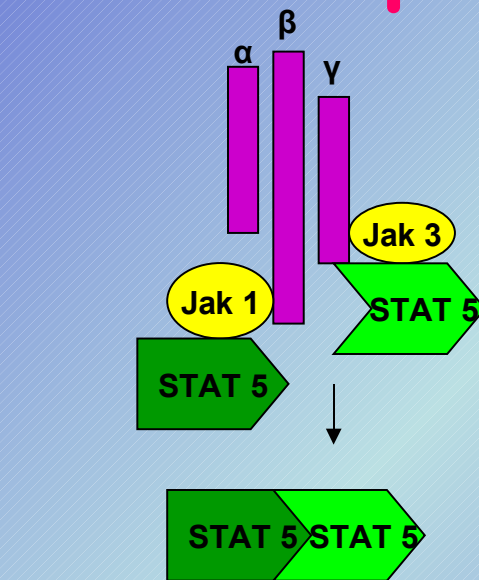
# 1. PI3K pathway



## 2. MAPK pathway



# 3. STAT pathway



IL-2: - IL-2R $\alpha$  e IL-2

- FasL

IL-15: - Bcl-xl

- IL-4

# Inibizione STAT pathway

## JAB/SOCS1/SSI-1

- scoperto come inibitore del signaling di IL-6
- azione sull' IL-2 signalling:

IL-2 promuove espressione di SOCS1  
inibizione della fosforilazione di STAT



blocco dello STAT pathway



blocco trascrizione dell' IL-2



**FEEDBACK NEGATIVO**

# Recettori solubili

Hanno origine a partire da 2 meccanismi principali:

1. Splicing alternativo dell'mRNA

2. Receptor shedding

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Vol. 279, No. 39, Issue of September 24, pp. 40368–40375, 2004  
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## Natural Soluble Interleukin-15R $\alpha$ Is Generated by Cleavage That Involves the Tumor Necrosis Factor- $\alpha$ -converting Enzyme (TACE/ADAM17)\*

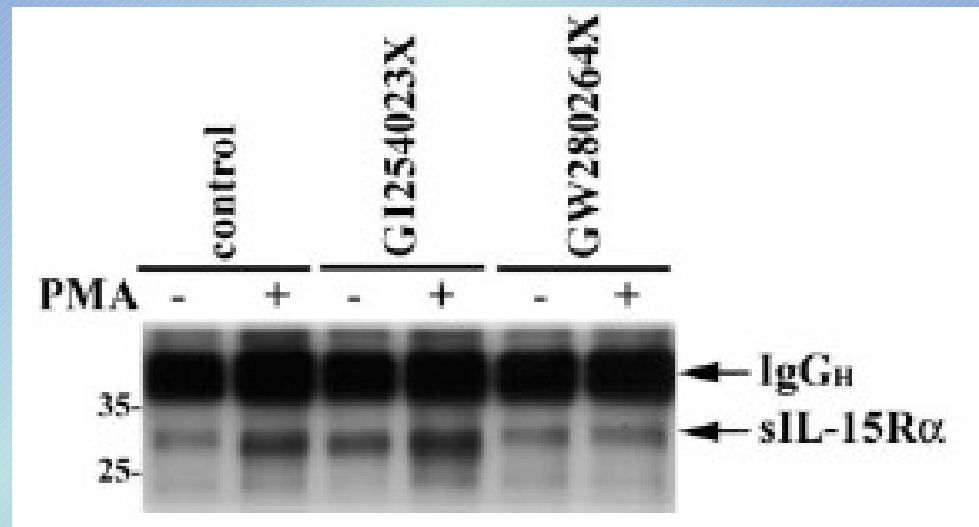
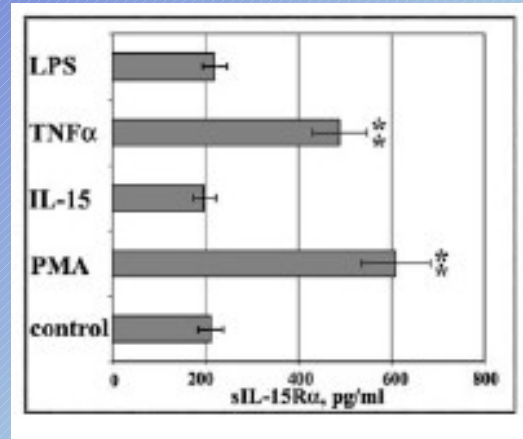
Received for publication, April 14, 2004, and in revised form, June 21, 2004  
Published, JBC Papers in Press, June 23, 2004, DOI 10.1074/jbc.M404125200

Vadim Budagian $\ddagger$  $\S$  $\P$ , Elena Bulanova $\S$  $\P$ , Zane Orinska $\S$ , Andreas Ludwig $^{**}$ , Stefan Rose-John $^{**}$ , Paul Saftig $^{**}$ , Ernest C. Borden $\ddagger$ , and Silvia Bulfone-Paus $\S$

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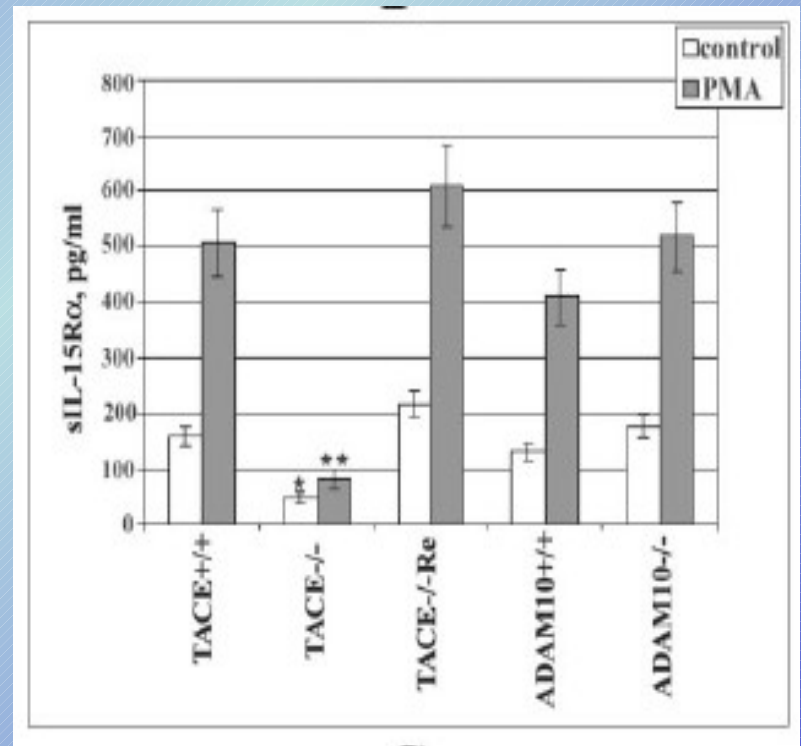
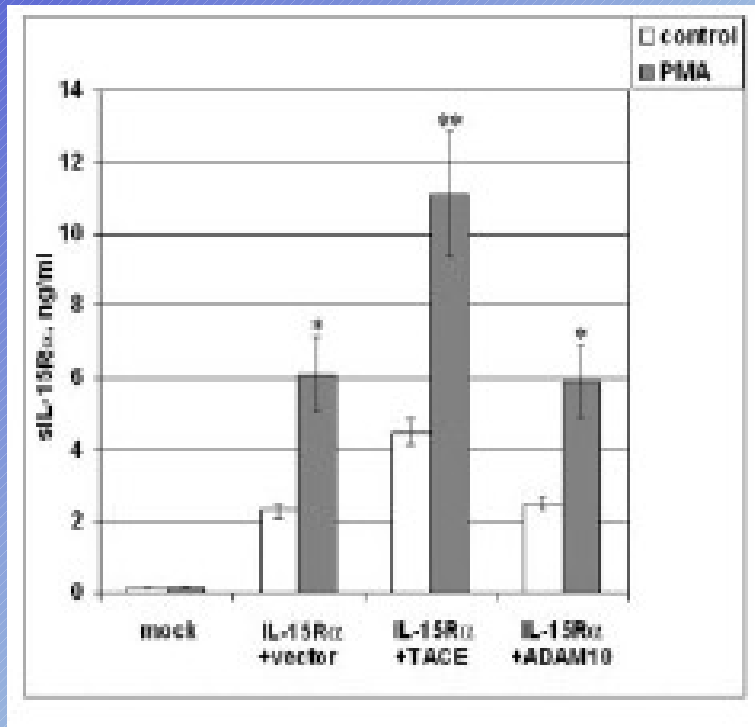


# IL-15R $\alpha$ soluble



Budagian V. et al, Natural soluble interleykin-15R $\alpha$  is generated by cleavage that involves the tumor necrosis factor- $\alpha$ -converting Enzyme ( TACE/ADAM10 ). J. Biol. Chem, 279: 40368, 2004.

# IL-15R $\alpha$ soluble



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# IL-2R $\alpha$ e cancro

## **Direct Inhibition of Interleukin-2 Receptor $\alpha$ -Mediated Signaling Pathway Induces G<sub>1</sub> Arrest and Apoptosis in Human Head-and-Neck Cancer Cells**

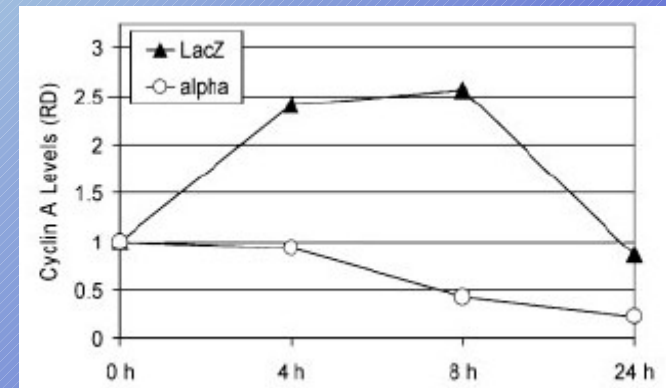
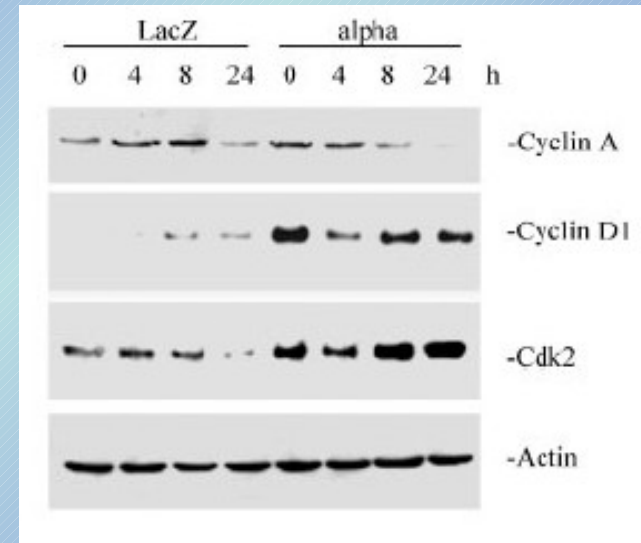
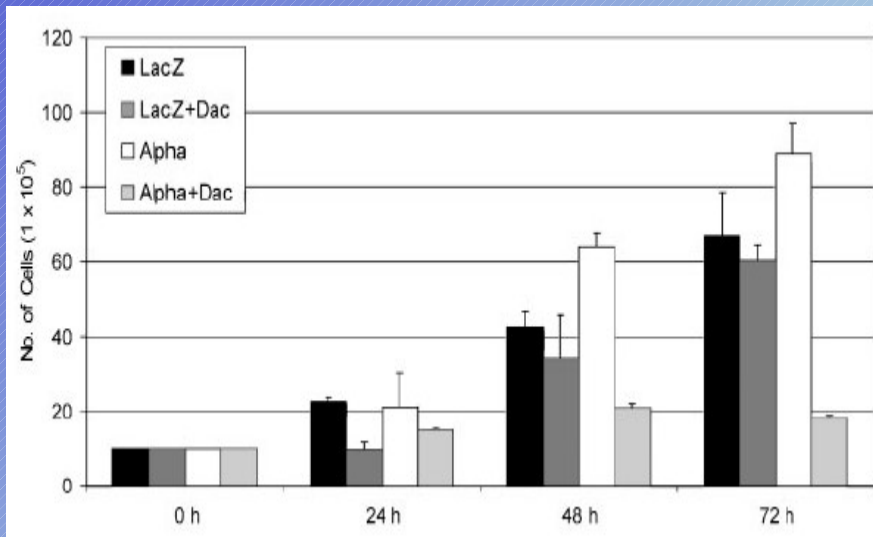
Deborah J. Kuhn and Q. Ping Dou\*

The Prevention Program, Barbara Ann Karmanos Cancer Institute, and Department of Pathology, School of Medicine, Wayne State University, Detroit, Michigan



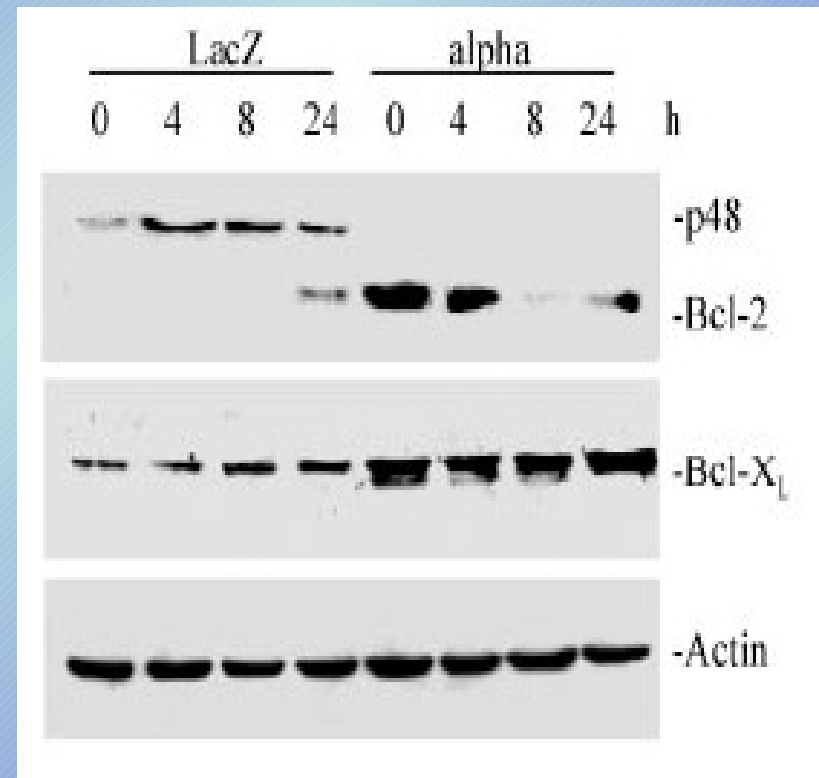
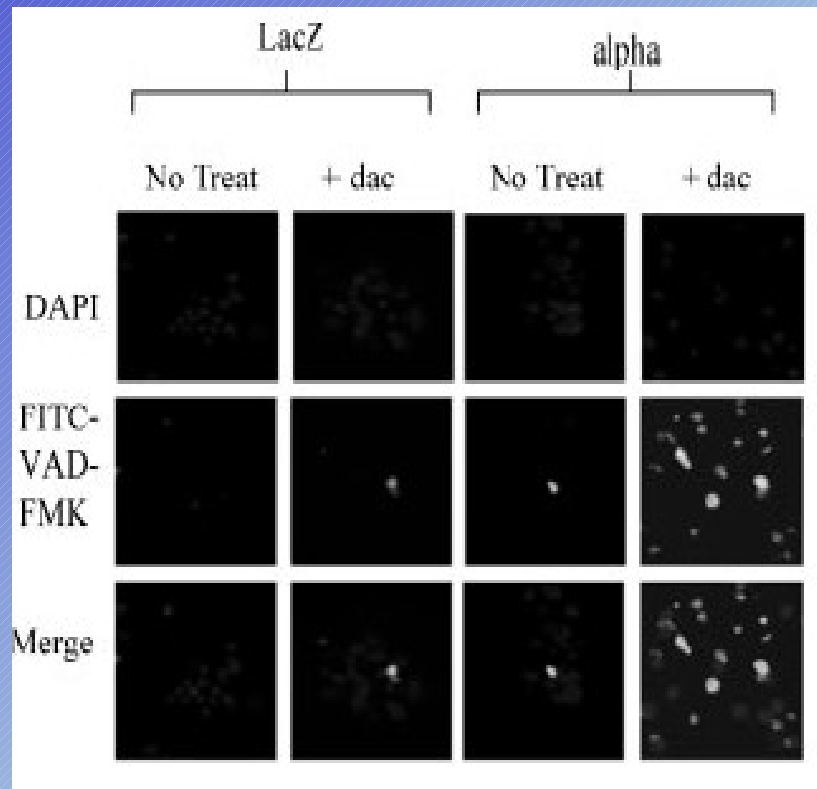
**Uso mAb daclizumab per definire il ruolo dell' IL-2R $\alpha$  nella tumorigenesi**

# IL-2R $\alpha$ e cancro



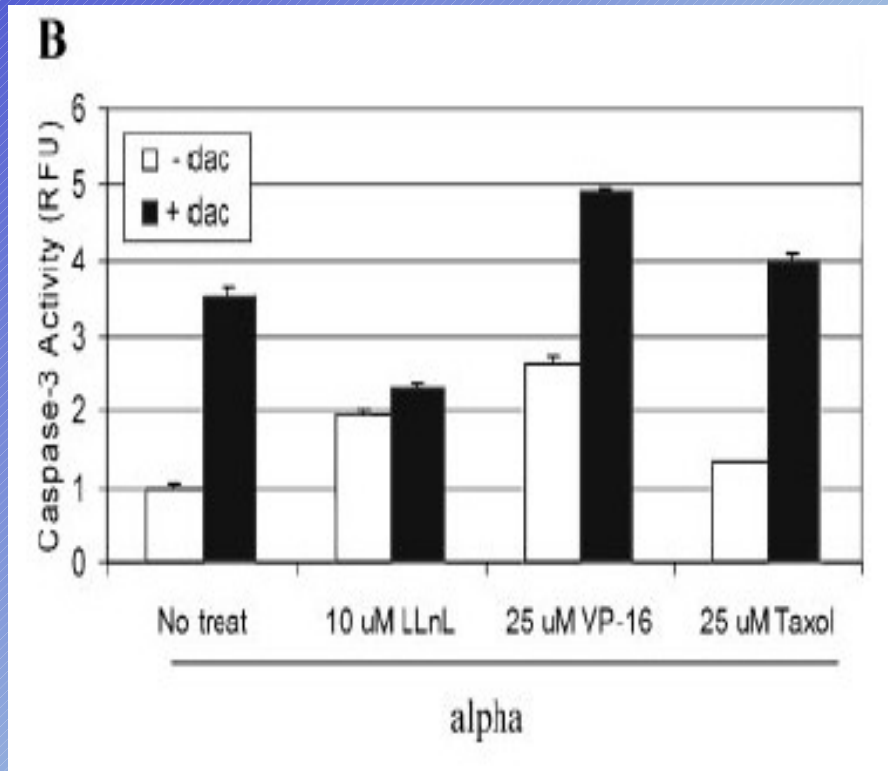
Khun D.J. And Ping Dou Q. Direct inhibition of interleukin-2 receptor  $\alpha$ -mediated signaling pathway induces G1 arrest and apoptosis in human head-and-neck cancer cells. J. Cell. Biochem, 95: 379, 2005.

# IL-2R $\alpha$ e cancro



Khun D.J. And Ping Dou Q. Direct inhibition of interleukin-2 receptor  $\alpha$ -mediated signaling pathway induces G1 arrest and apoptosis in human head-and-neck cancer cells. J. Cell. Biochem, 95: 379, 2005.

# IL-2R $\alpha$ e cancro



**Overespressione IL-2R $\alpha$**



- Attivazione pathway per Bcl-2
- Attivazione costitutiva ciclina A



**TRASFORMAZIONE  
NEOPLASTICA**

**Problema: resistenza ai farmaci e  
chemoterapici**

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