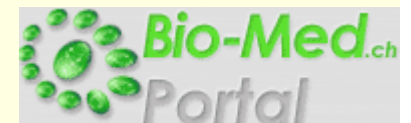


# Cytotoxic T Cell Action Against Tumor Cells

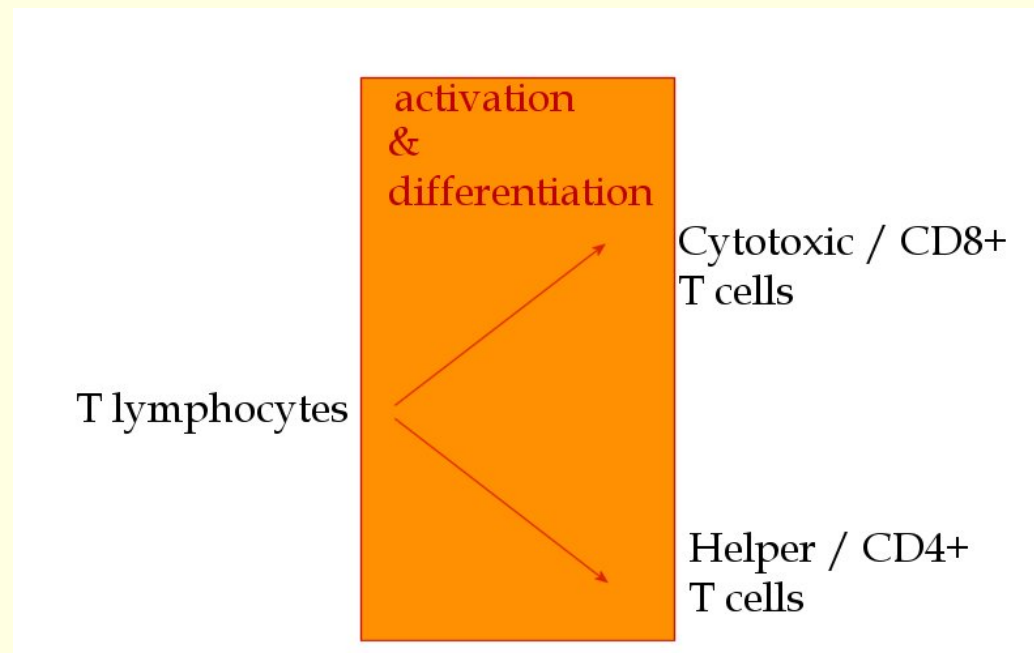
{Guillaume.Bonnier, Christopher.Burger, Kremena.Diatchka  
Saurabh.Indra, Jean-christophe.Fillion-Robin, Alexei.Kounine}@epfl.ch

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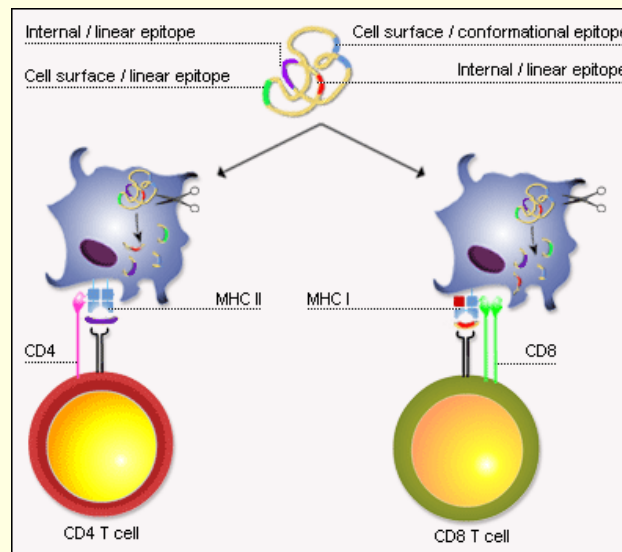
# Cytotoxic T Cells

- One of the cell types which constitutes the Adaptive Immune System
- Can recognize and eliminate cells infected or tumor cells infected by specific target antigen



# Recognition Mechanism

- T-cell receptors (TCR's) are surface proteins which help the T-cell detect the presence of target cells
- Target cells present fragments of antigens using major histocompatibility molecules (MHC)

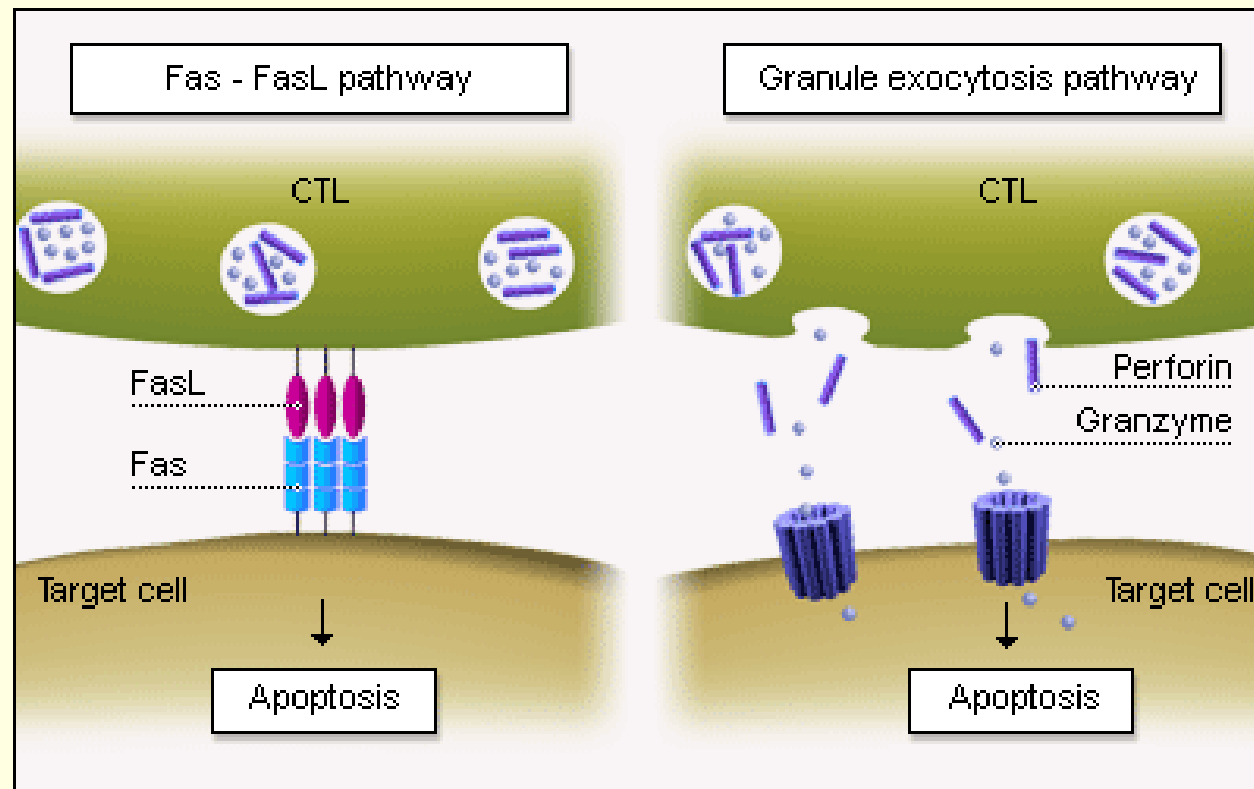


# Two Pathways for Destruction of Infected Cells

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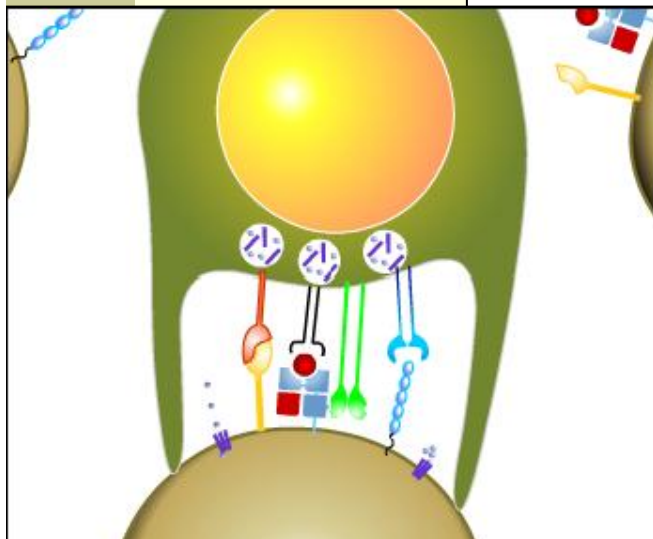
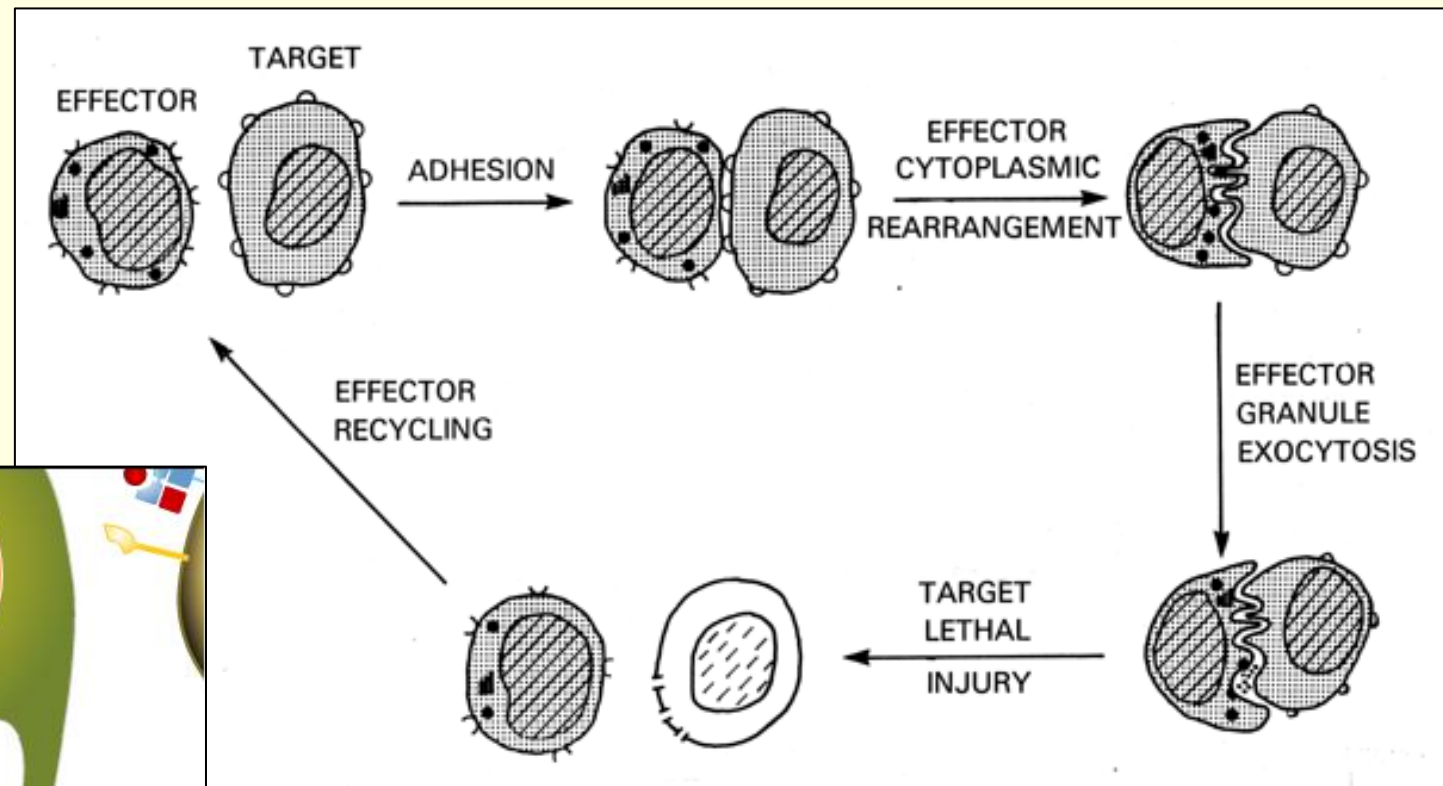
- Two possible methods for killing infected cells
  - Granule exocytosis pathway : Target cell death by cytotoxic granule proteins
  - FasL/Fal pathway : Non-inflammatory programmed cell death (Apoptosis)

# Target cell death pathways



# The Granule Exocytosis Pathway


- Illustration of the steps involved:




# The FasL/Fal Pathway

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- Cytotoxic T cells express Fas Ligand (FasL) on their cell surface
  - FasL is a TNF cytokine
- FasL binds to Fas (TNF Receptor), which leads to reorganization of Fas complex
- This allows formation of death-inducing signaling complex (DISC). DISC contains:
  - Fas
  - Fas-associated death domain protein (FADD)
  - Pro-caspase-8
- FasL-induced clustering -> initiation of **apoptosis**



# Role of STAT-1 in Enabling Destruction of Tumor Cells by the Adaptive Immune System





# Role of STAT-1 in Enabling Destruction of Tumor Cells

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The Adaptive Immune System may fail to kill tumor cells in the absence of STAT-1 due to :

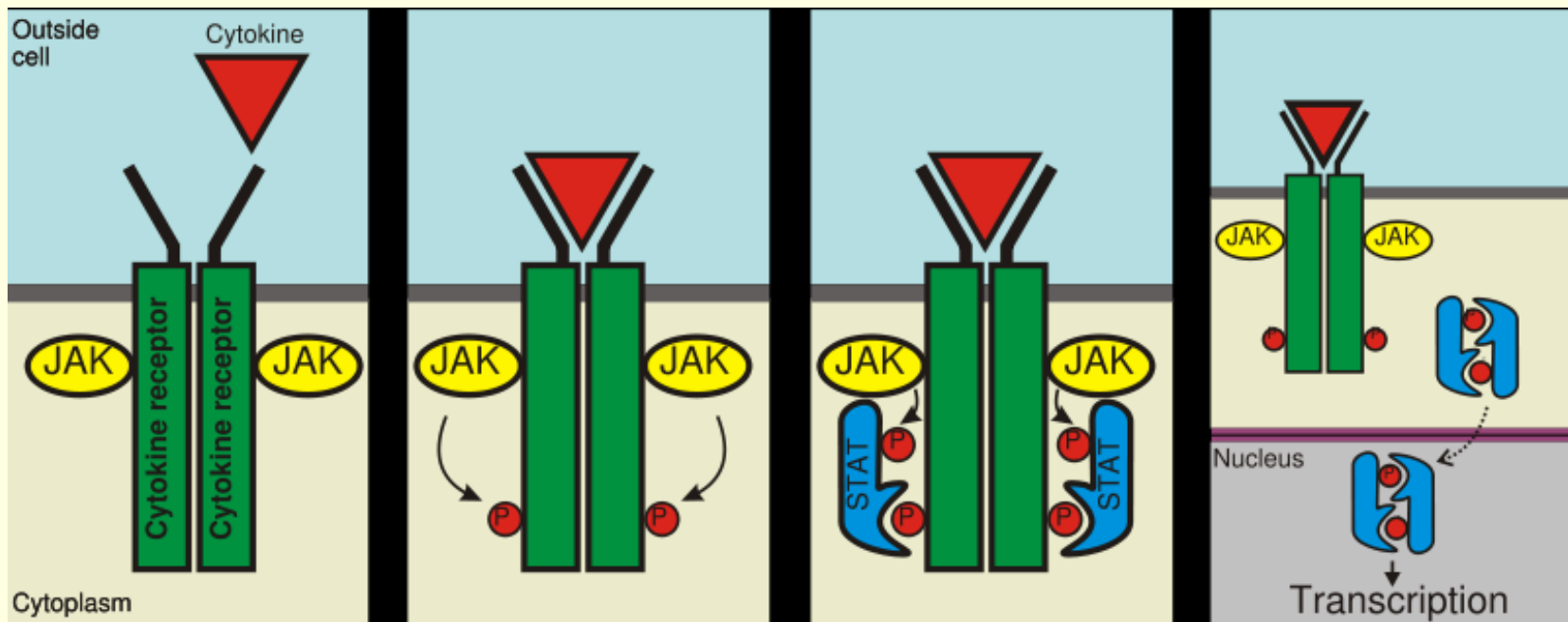
- Reduced Cytolytic activity
- Impaired recognition of Tumor cells

# Reduced Cytolytic Activity

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- IFN signaling through STAT-1 could be needed for the acquisition of a cytolytic phenotype by T cells (**differentiation** stage)
- Stat-1 dependent transcription could be vital for the expression of genes encoding cytotoxic granule proteins required in the exocytosis pathway (**effector** stage)

# Cytokine Induced Signaling Leading to Transcription



# Decreased Recognition of Tumor Cells

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- IFN- $\gamma$  acts to activate STAT-1 signal transduction within the tumor, so that tumor cells are more likely recognized by T cells for destruction
- IFN signaling may also be involved in up-regulating the expression of MHC molecules – also needed for recognition by T cells

# Application to Cancer Therapy

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- Immunological approaches to cancer treatment aim to utilize the power and specificity of the immune system
- These methods aim to aid the immune system – for example by artificially stimulating the differentiation of T lymphocytes

# References

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- "Distinct Requirements for IFNs and STAT1 in NK Cell Function" Chien-Kuo Lee, Dharma T. Rao, Rachel Gertner, Ramon Gimeno, Alan B. Frey, and David E. Levy. *J. Immunol.* 2000;
- Fallarino, F., and T. F. Gajewski. 1999. Differentiation of antitumor CTL in vivo requires host expression of Stat1. *J. Immunol.*

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■ Thanks !

■ Questions and comments are welcome