

# Society for Immunotherapy of Cancer (SITC)

Basic Mechanisms of Tumor Immune Suppression

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UT MD Anderson Cancer Center

Advances in Cancer Immunotherapy™ - Texas

June 19, 2015



Society for Immunotherapy of Cancer

# Objectives

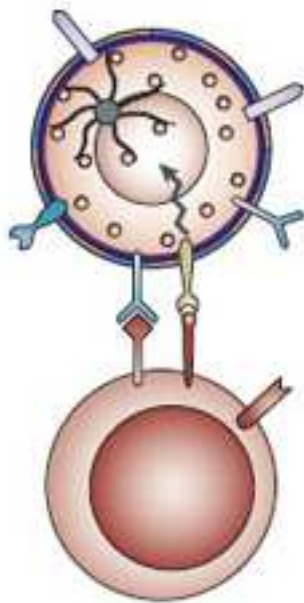
- Understand basic mechanisms by which the immune system recognizes malignancy.
- Describe mechanisms of avoiding immune recognition and the concept of immunoediting
- Discuss approved and experimental approaches for overcoming immune suppression



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# Stages of Immune-Mediated Killing

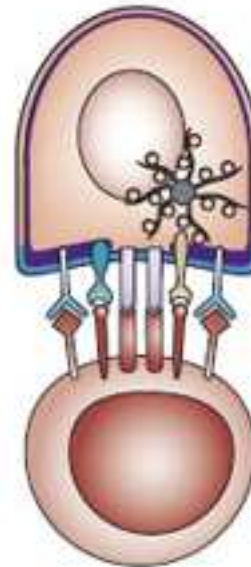
Activation  
signaling



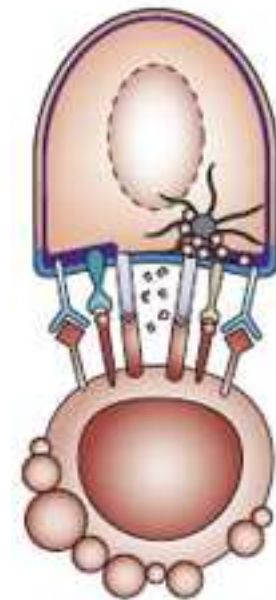
Granule  
clustering



MTOC  
polarization

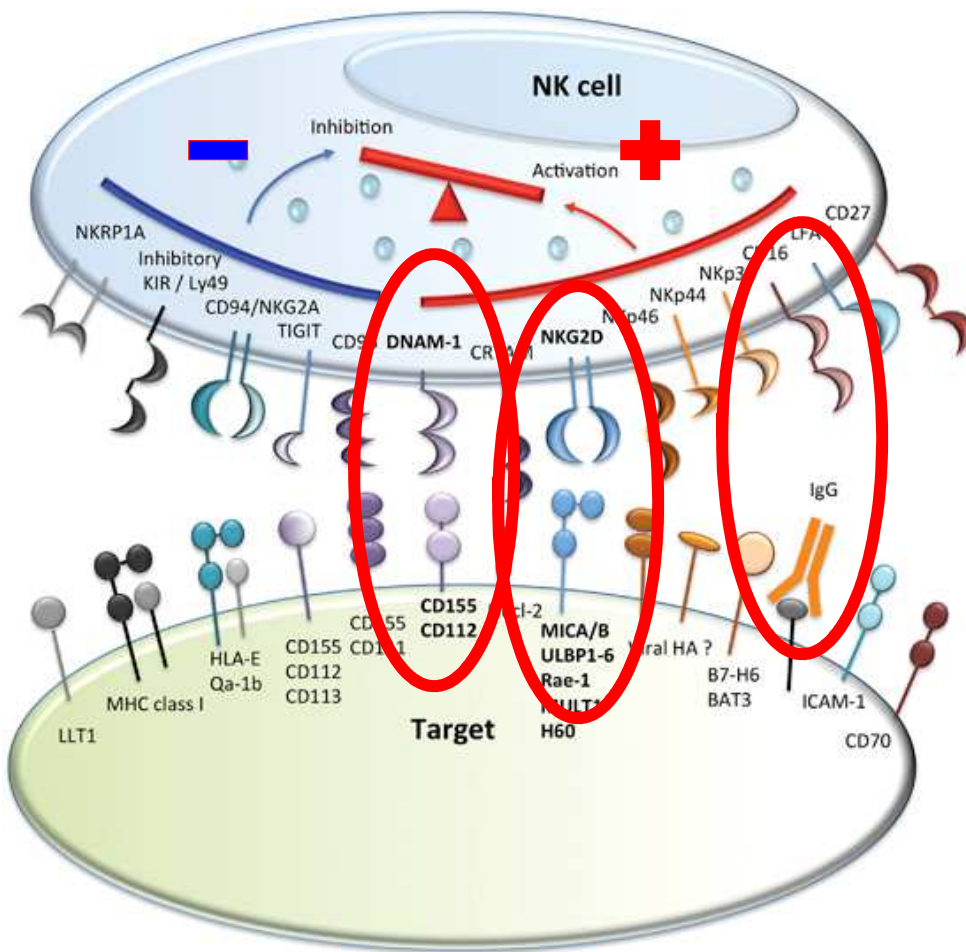


Lytic granule  
release

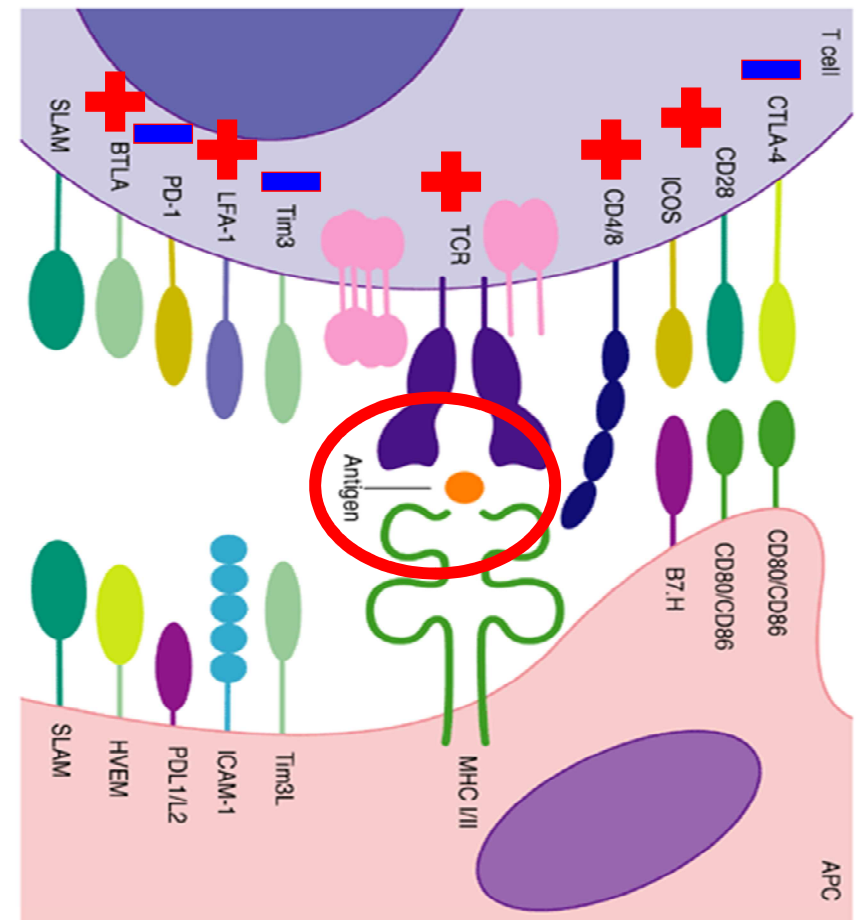


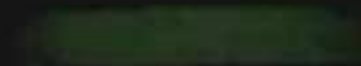
# Receptors and Ligands

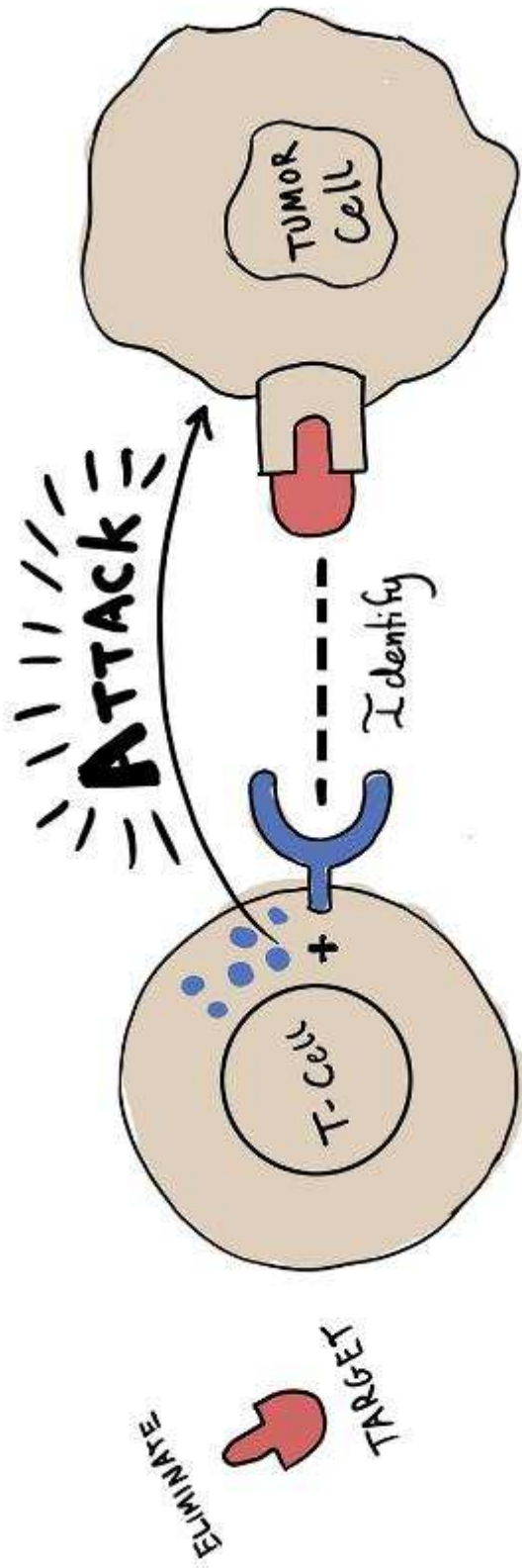
NK cell



T cell

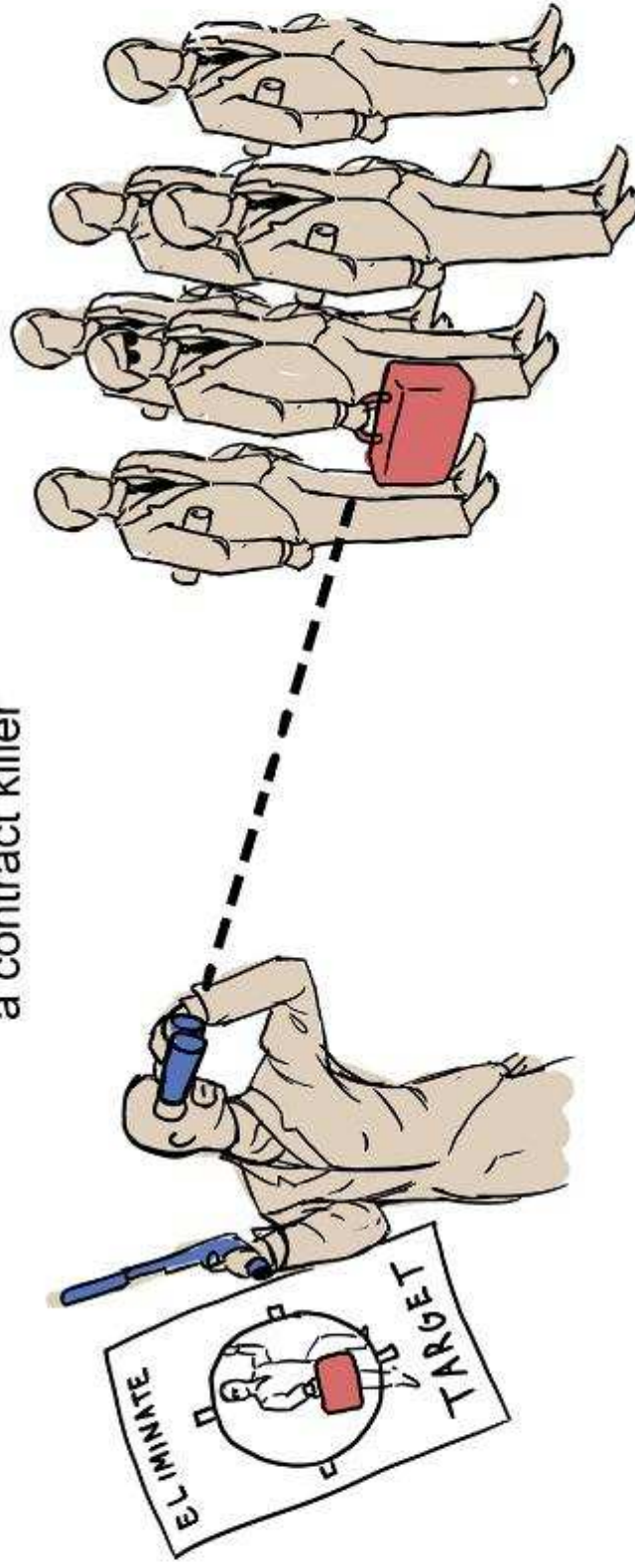






The T-Cell is like...

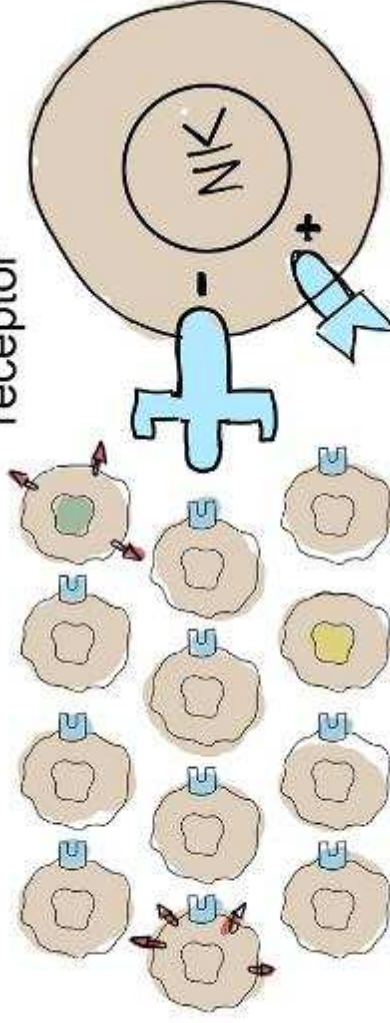
a contract killer







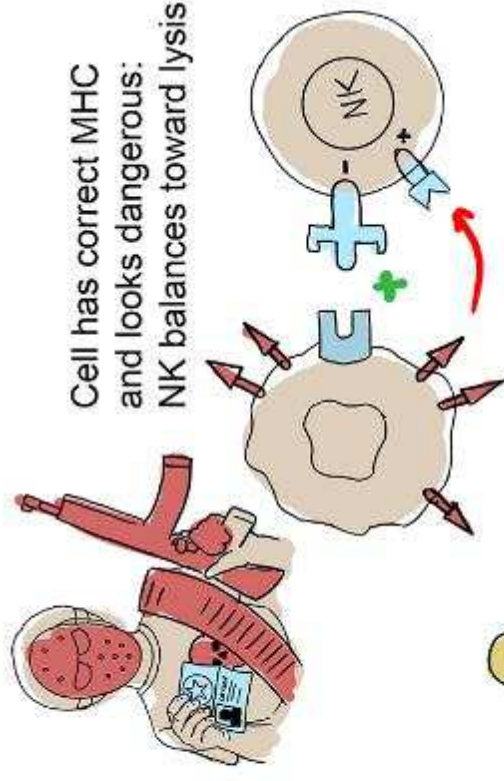
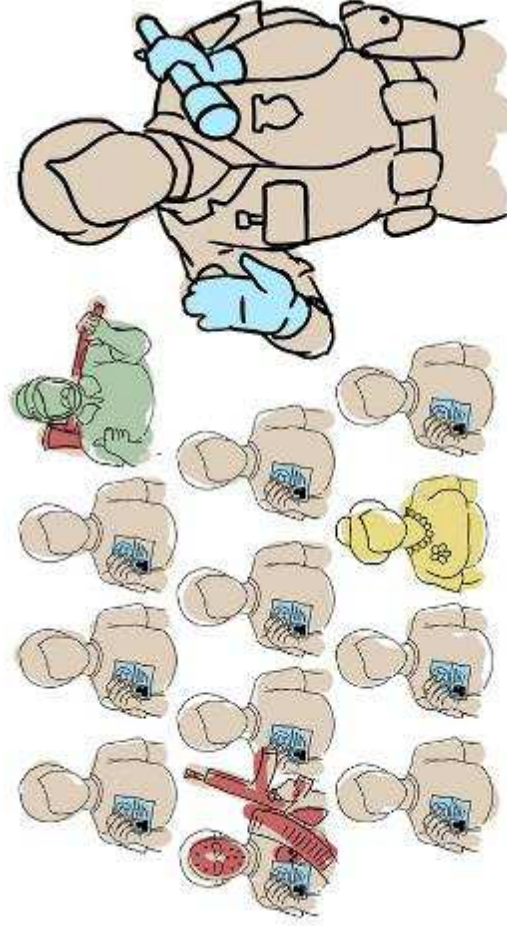
Inhibitory  
receptor



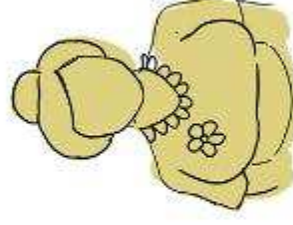
Activating  
receptor

The NK Cell is like...

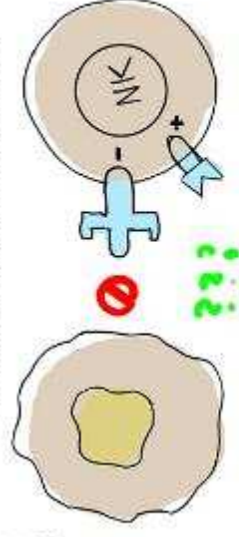
a border patrol agent



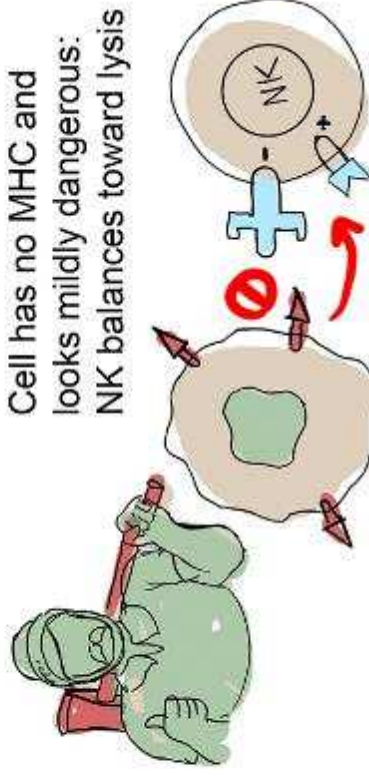
Cell has correct MHC  
and looks dangerous:  
NK balances toward lysis



Cell has no MHC and  
doesn't look dangerous:  
NK activation balanced

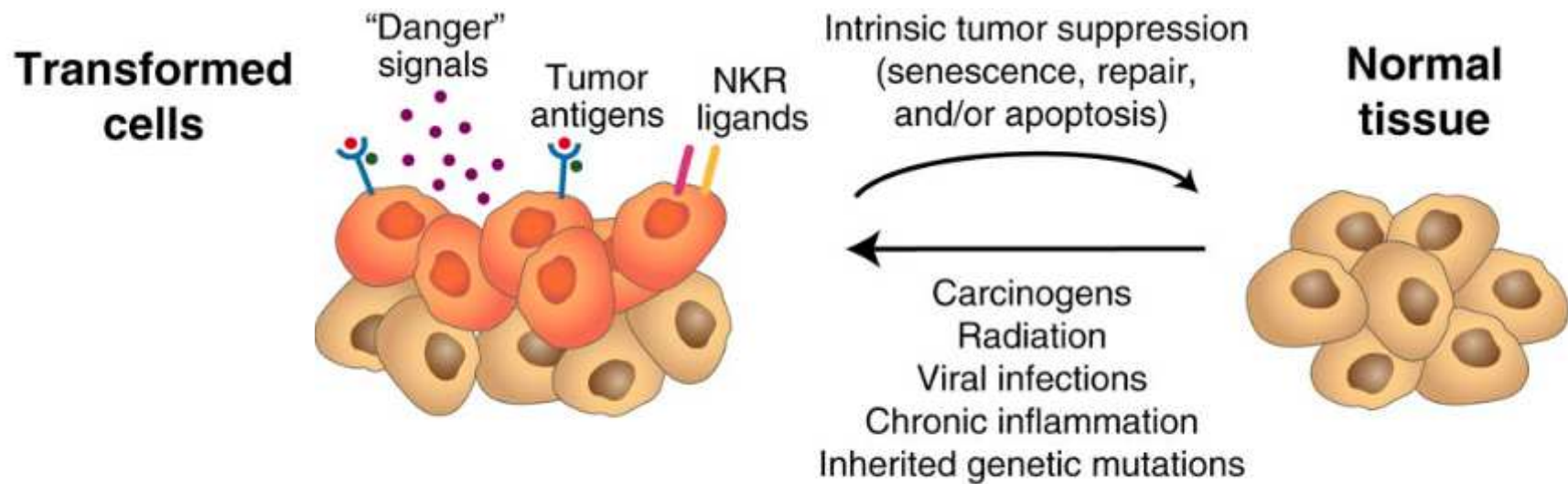


Cell has no MHC and  
looks mildly dangerous:  
NK balances toward lysis

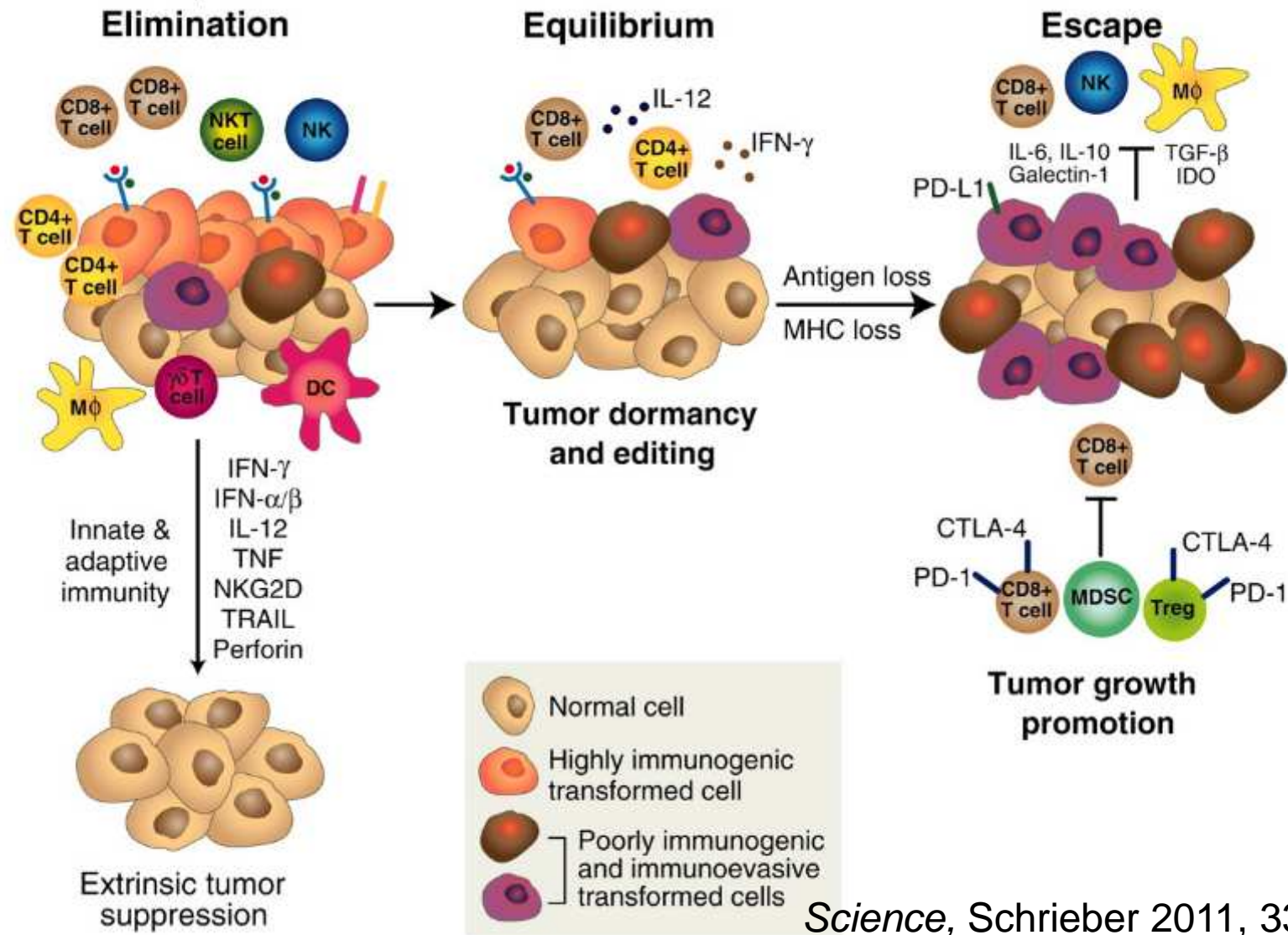




# “Birthmarks” of Cancer

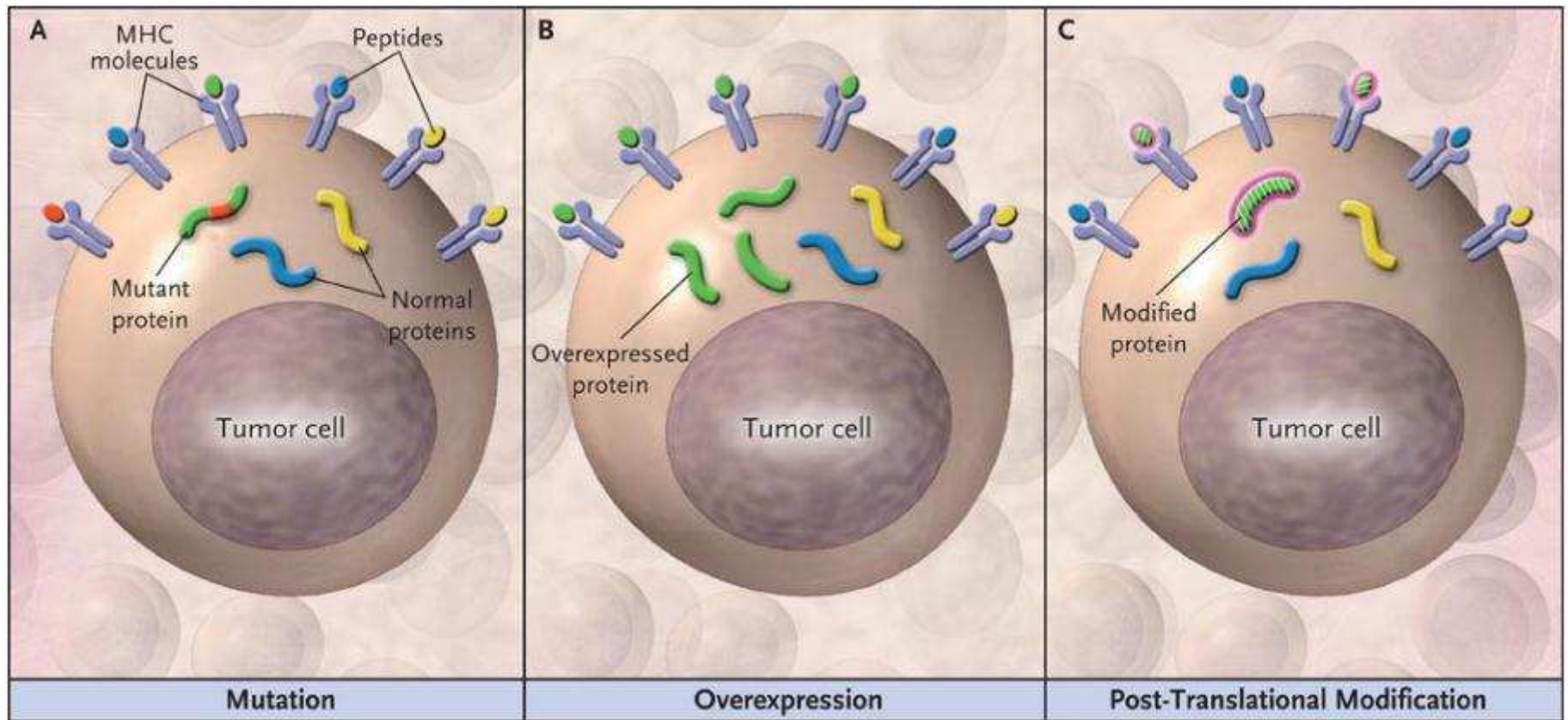


# Immuneediting



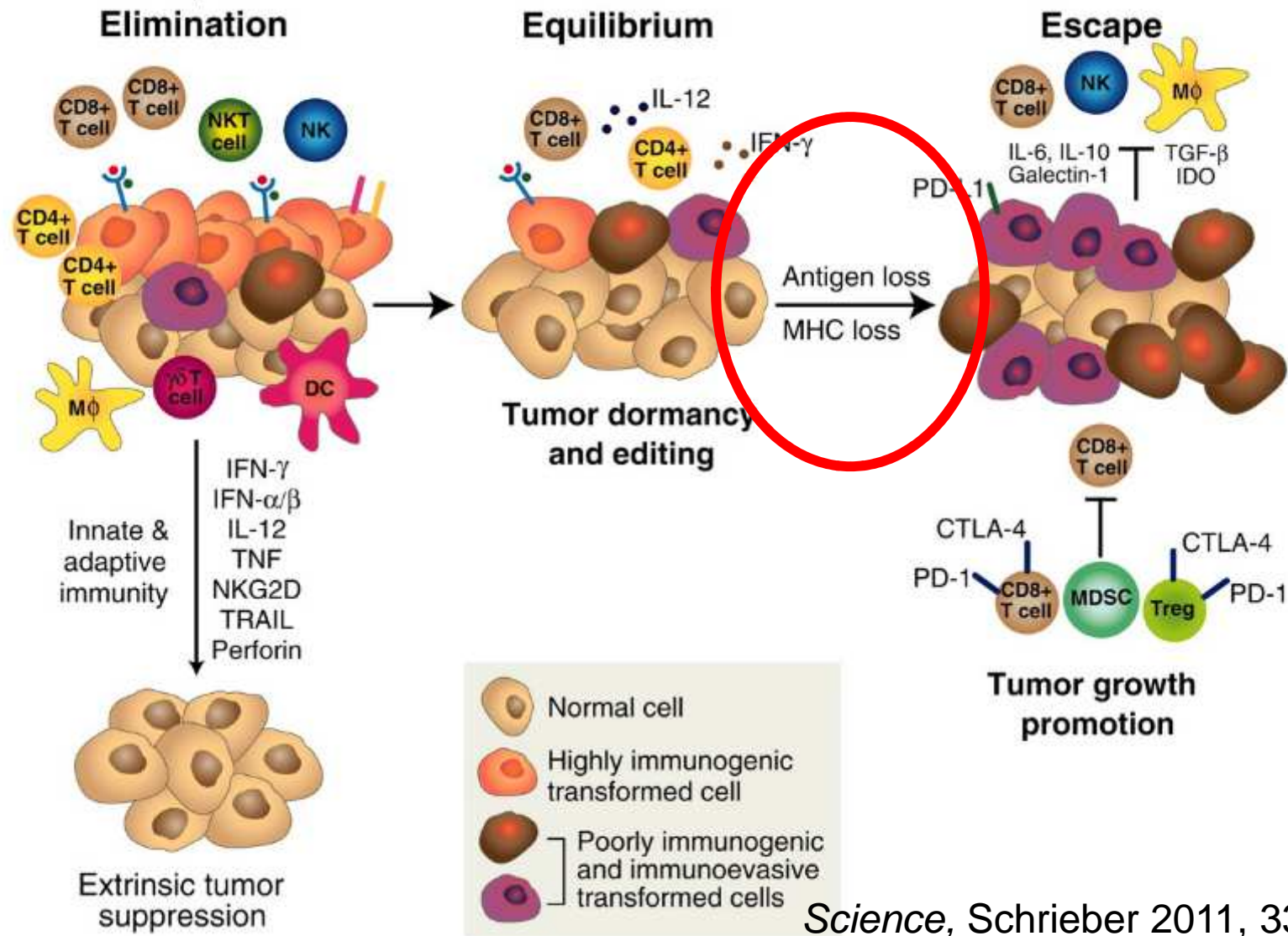
Science, Schreiber 2011, 331:1565

# Origins of tumor antigens



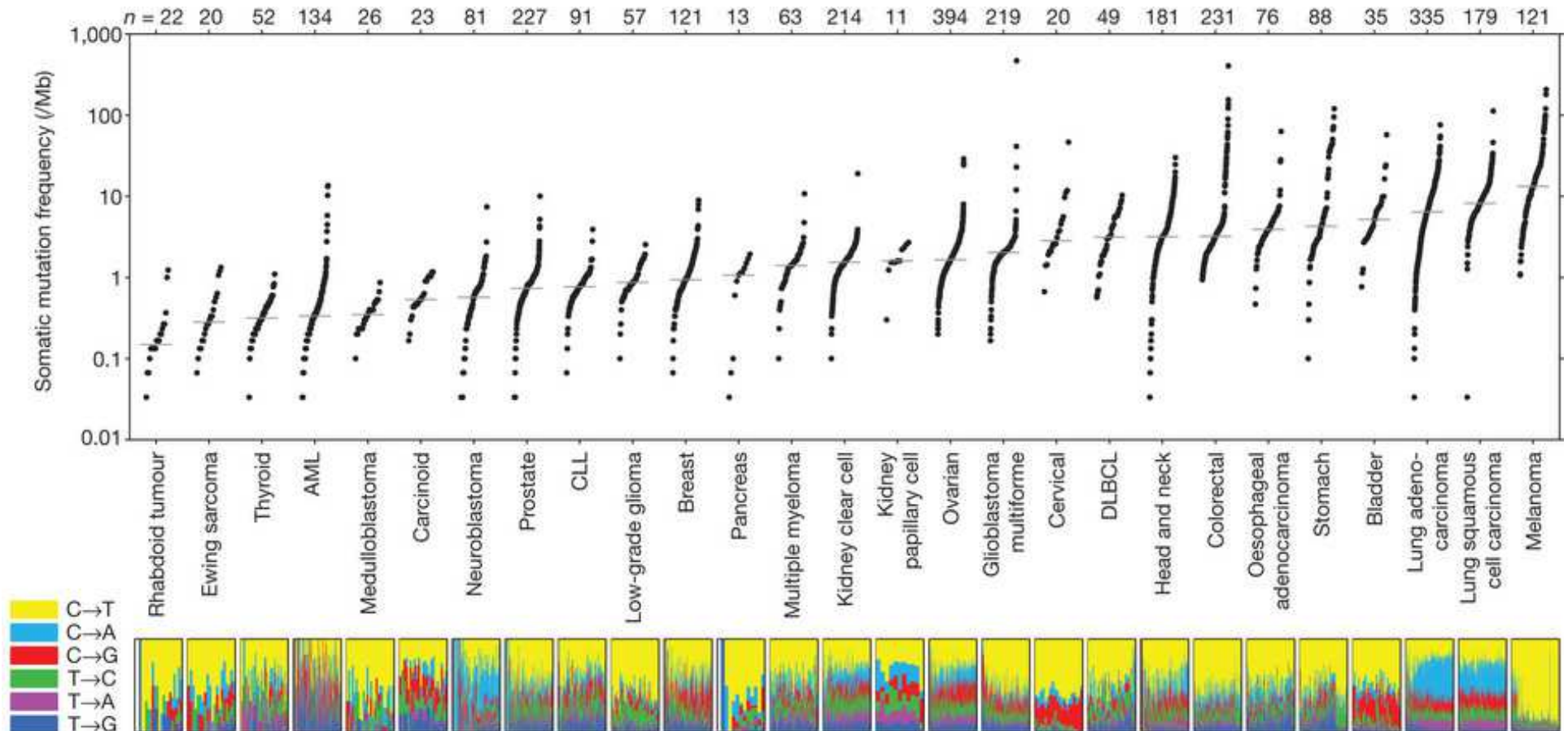


# Antigen Loss



*Science*, Schreiber 2011, 331:1565

# Mutation frequencies in cancer

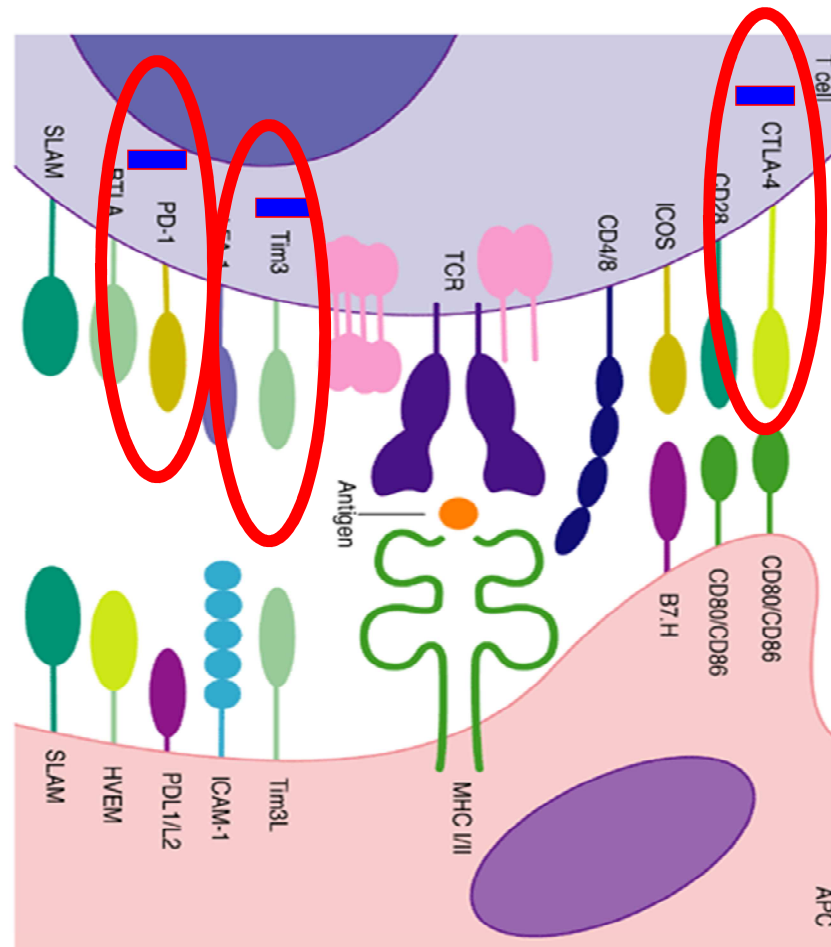




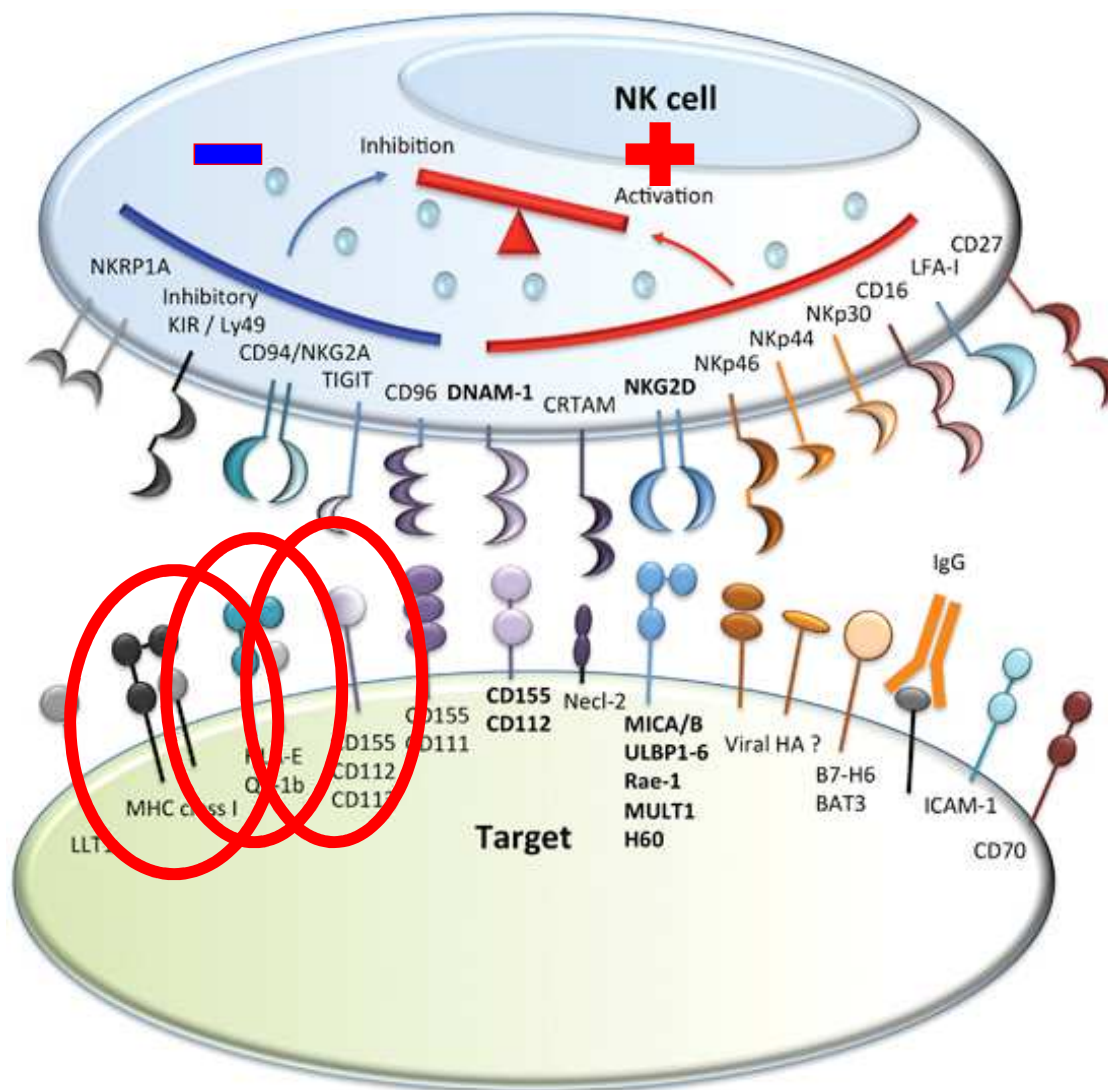
# Mechanisms of Immune Escape

- Antigen escape
  - Antigen loss or mutation
  - MHC loss

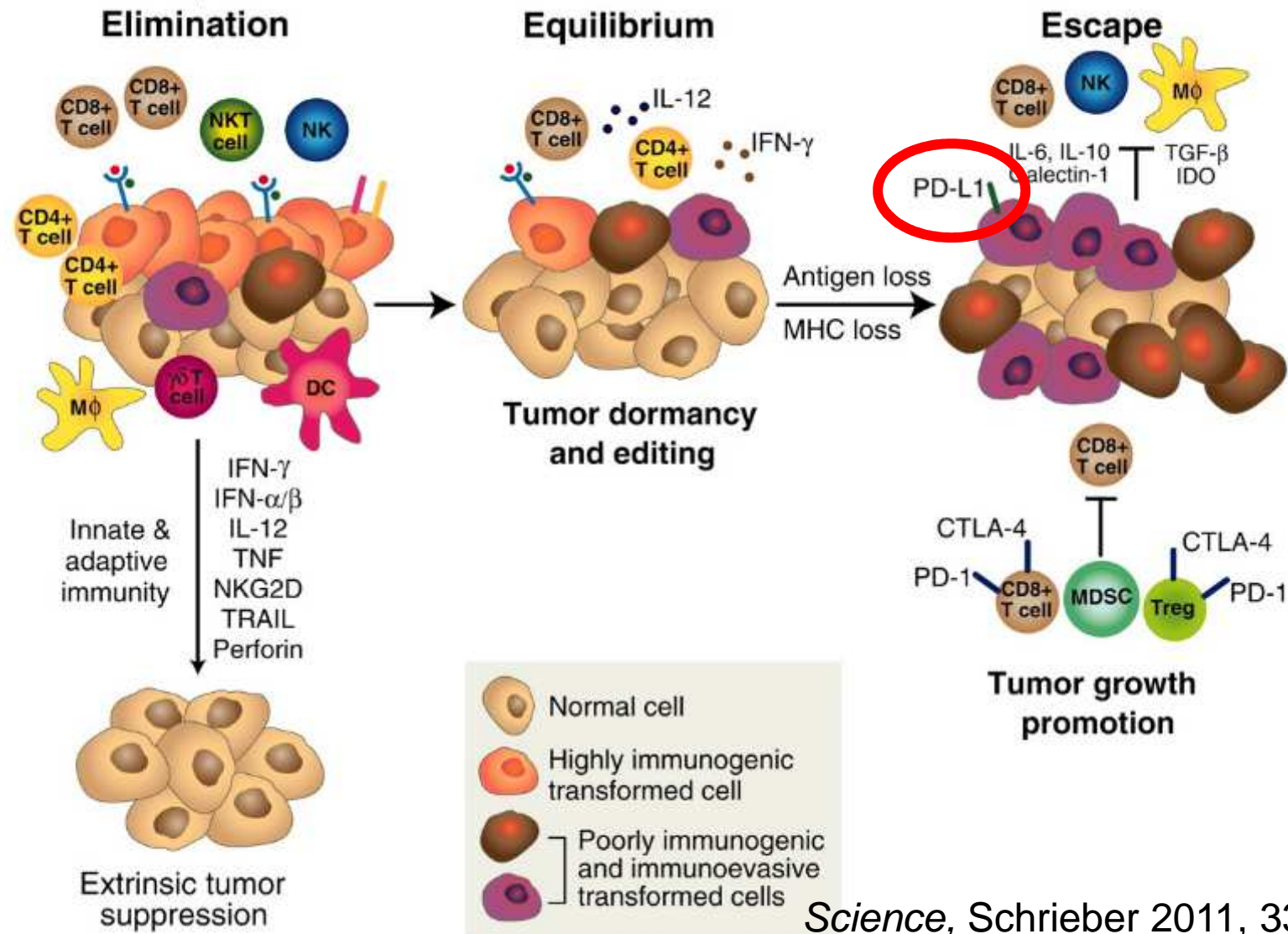
# T Cell Checkpoints



# NK Cell Checkpoints



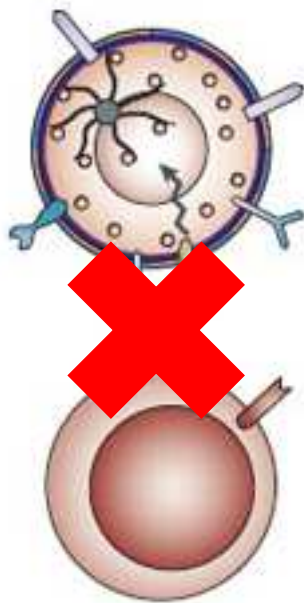
# Upregulation of Inhibitory Ligands



Science, Schreiber 2011, 331:1565

# Stages of Immune-Mediated Killing

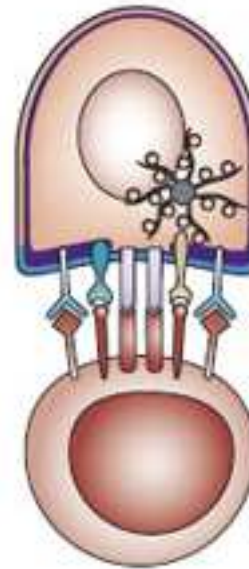
Activation  
signaling



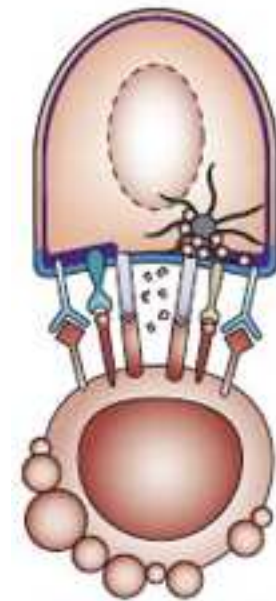
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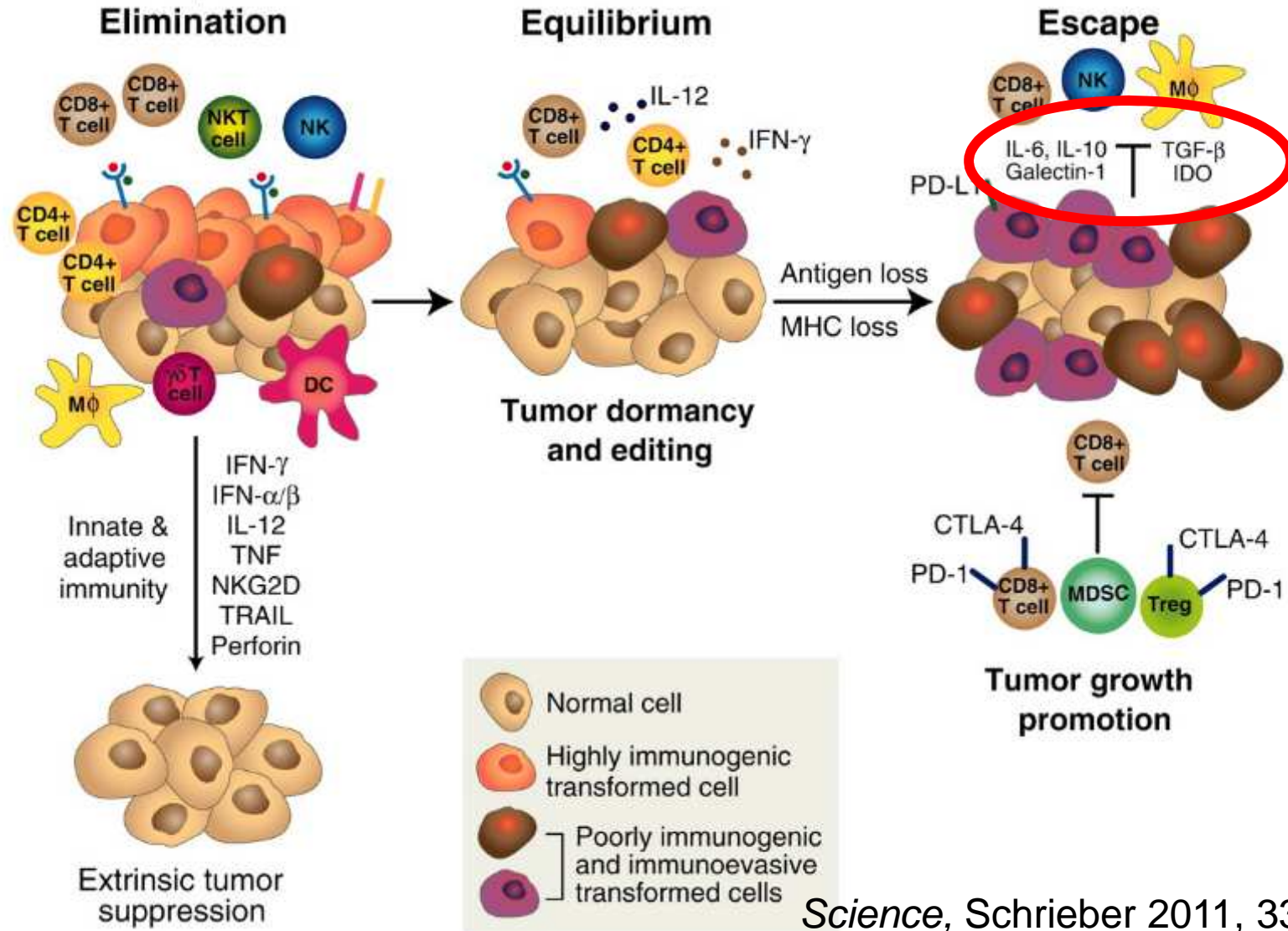




# Mechanisms of Immune Escape

- Antigen escape
  - Antigen loss or mutation
  - MHC loss
- Upregulation of inhibitory ligands

# Soluble Inhibitory Factors

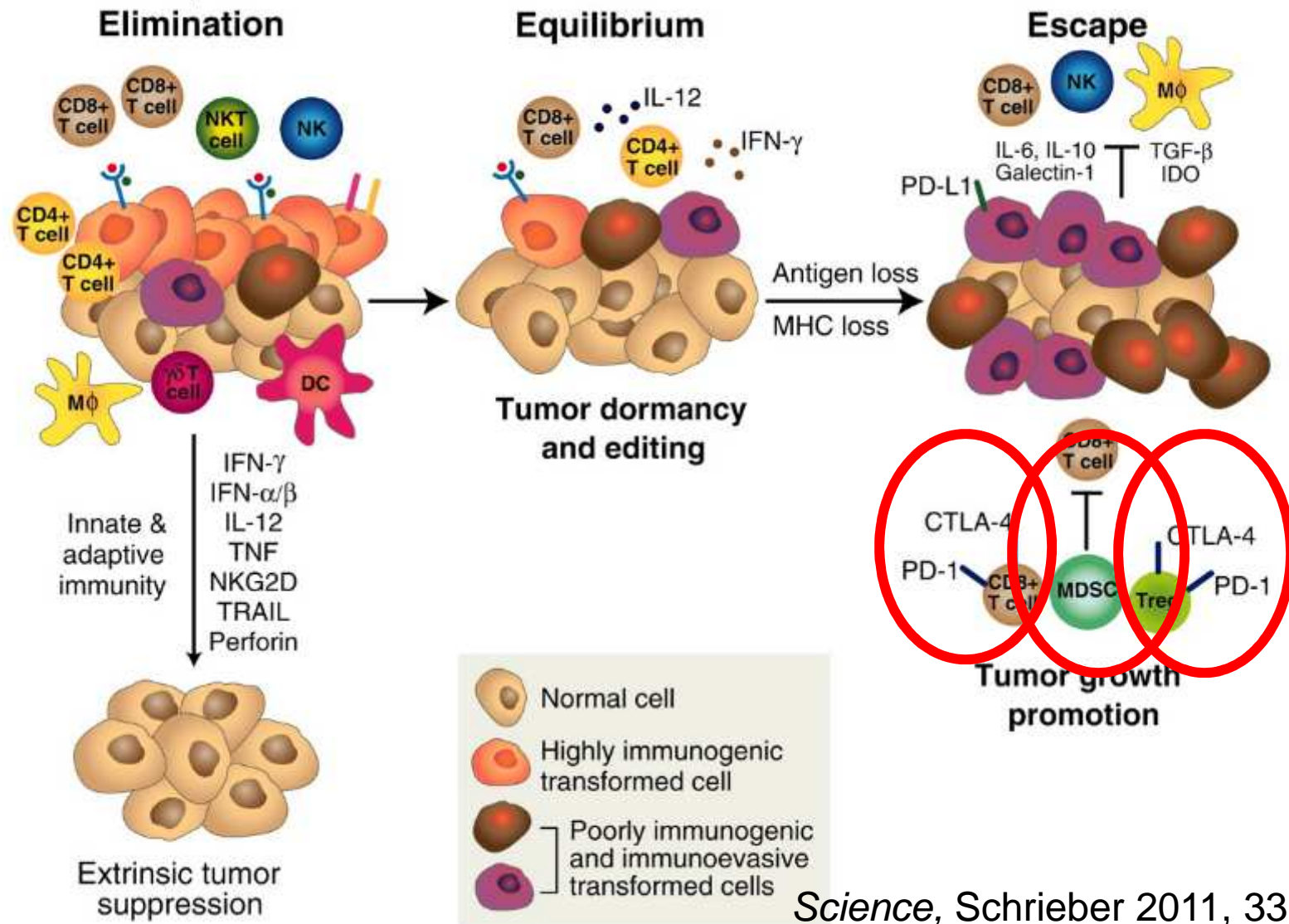


Science, Schrieber 2011, 331:1565

# Mechanisms of Immune Escape

- Antigen escape
  - Antigen loss or mutation
  - MHC loss
- Upregulation of inhibitory ligands
- Production of soluble inhibitory factors
  - TGF $\beta$ , Kynurenine, IL-10

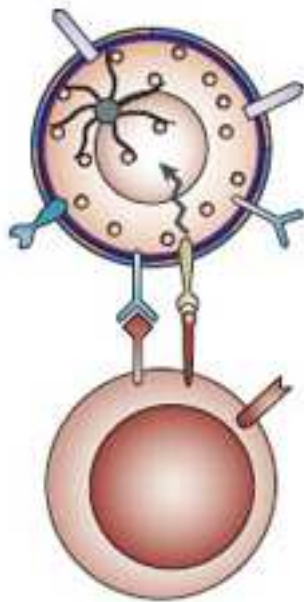
# Infiltration of Suppressive Cells



Science, Schreiber 2011, 331:1565

# Stages of Immune-Mediated Killing

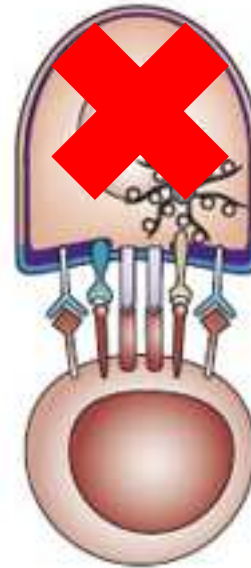
Activation  
signaling



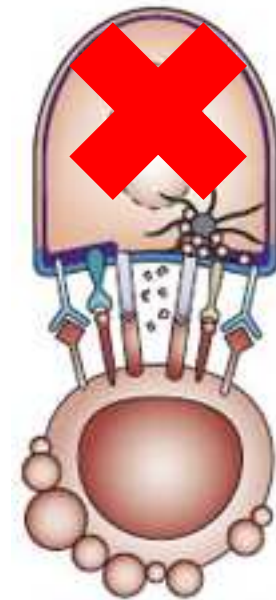
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release

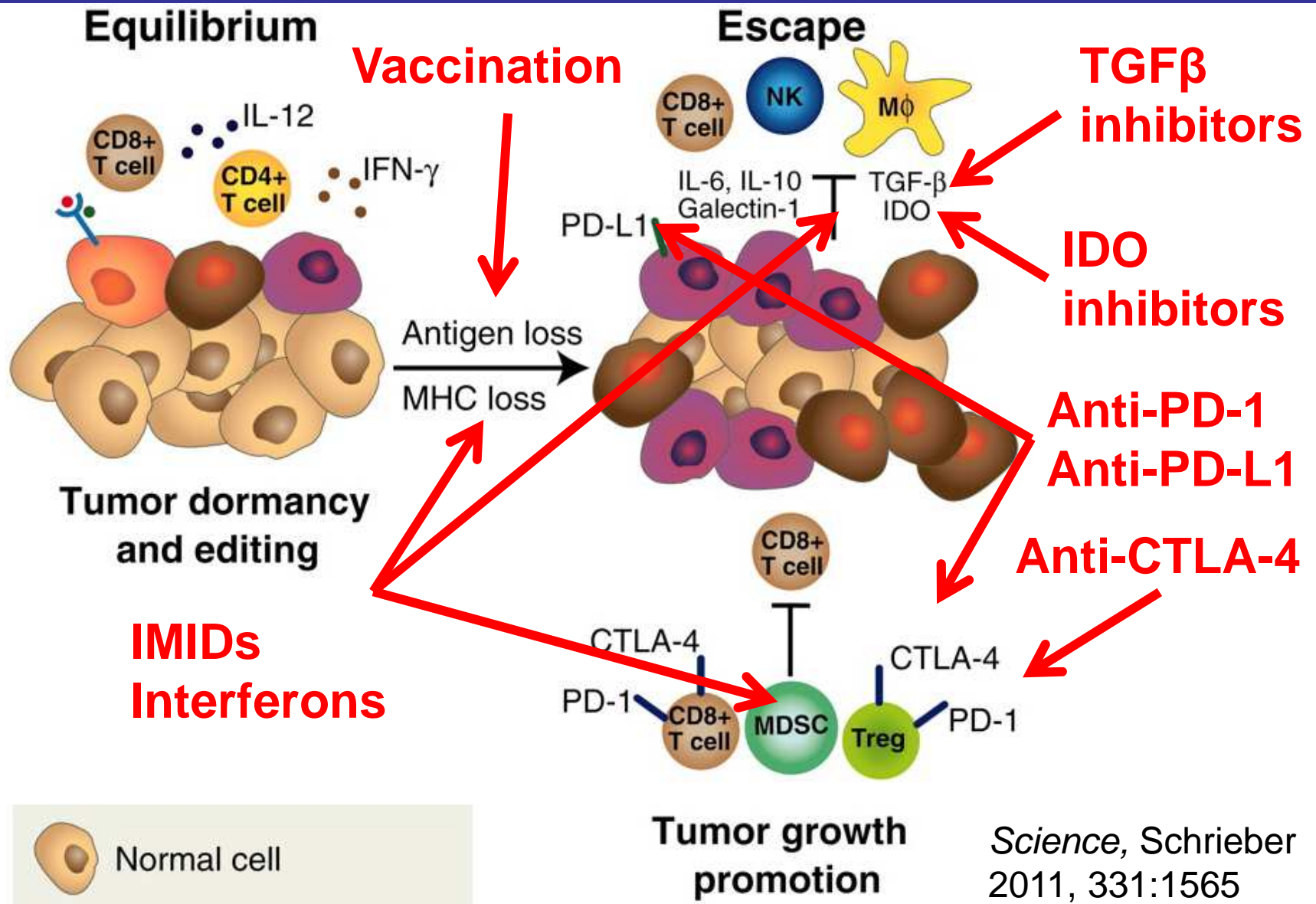




# Mechanisms of Immune Escape

- Antigen escape
  - Antigen loss/mutation
  - MHC loss
- Upregulation of inhibitory ligands
- Production of soluble inhibitory factors
  - TGF $\beta$ , Kynurenine, IL-10
- Infiltration of suppressive cells

# Clinical Targeting of Immune Escape



# Lessons and Take Home Messages

- Key Points

- Understanding and overcoming resistance is a long-valued concept in cancer biology which has unique but parallel applications in cancer immunology

- Potential impact on the field

- Understanding immune escape mechanisms allows targeted intervention in restoring anti-tumor immunity

- Lessons learned

- Immunotherapists must remember the lessons of early chemotherapists and microbiologists: Applying multiple therapies with non-overlapping mechanisms of resistance will reduce the frequency of treatment failure.



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