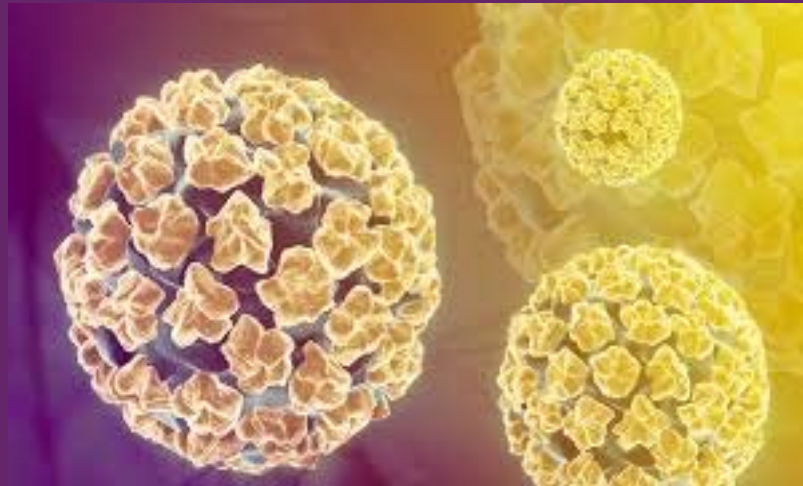




香港中文大學  
The Chinese University of Hong Kong

# Treatment with Human Papillomavirus Targeted Tumor-Infiltrating T Cells in Head and Neck Squamous Cell Carcinoma



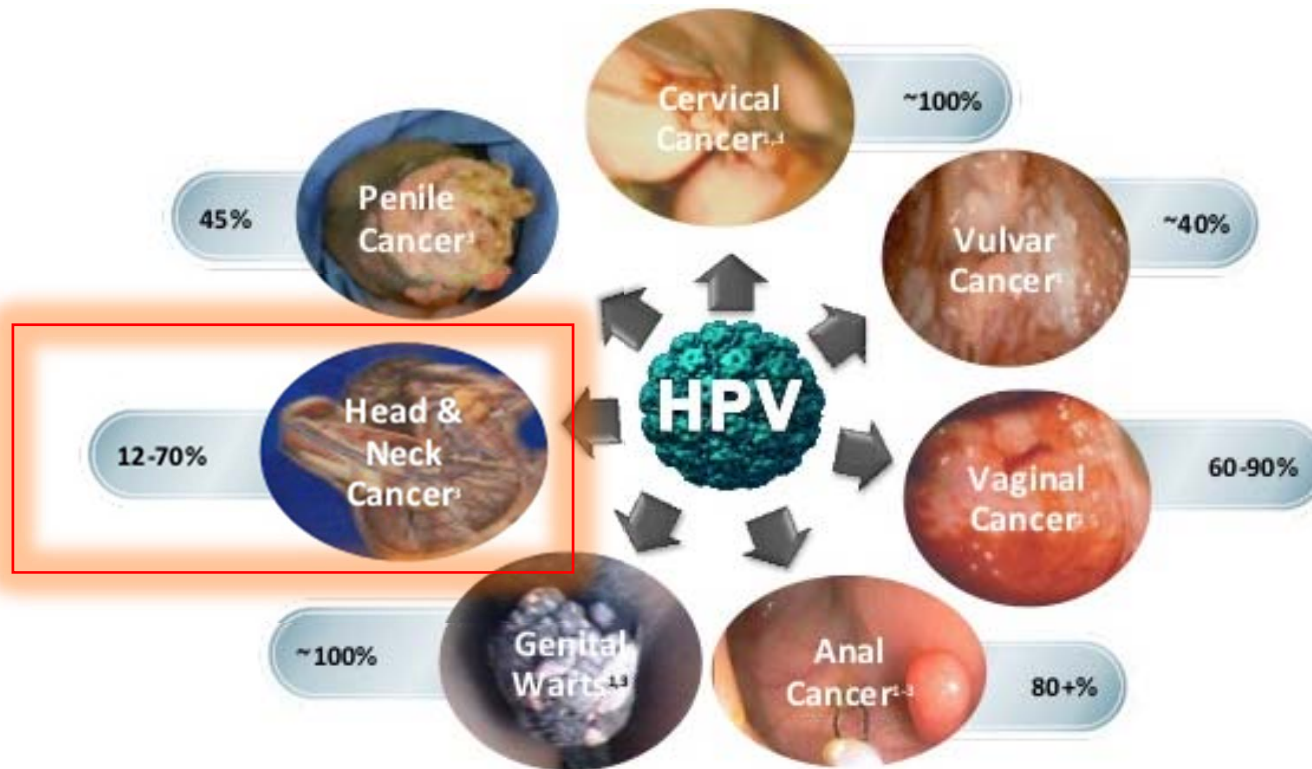
Jeffrey JIE XU

Supervisor: Professor Paul Chan

Department of Microbiology

1<sup>st</sup> Dec 2016

# HPV Causes More than Cervical Cancer



# Anatomic Sites of Head and Neck Cancer

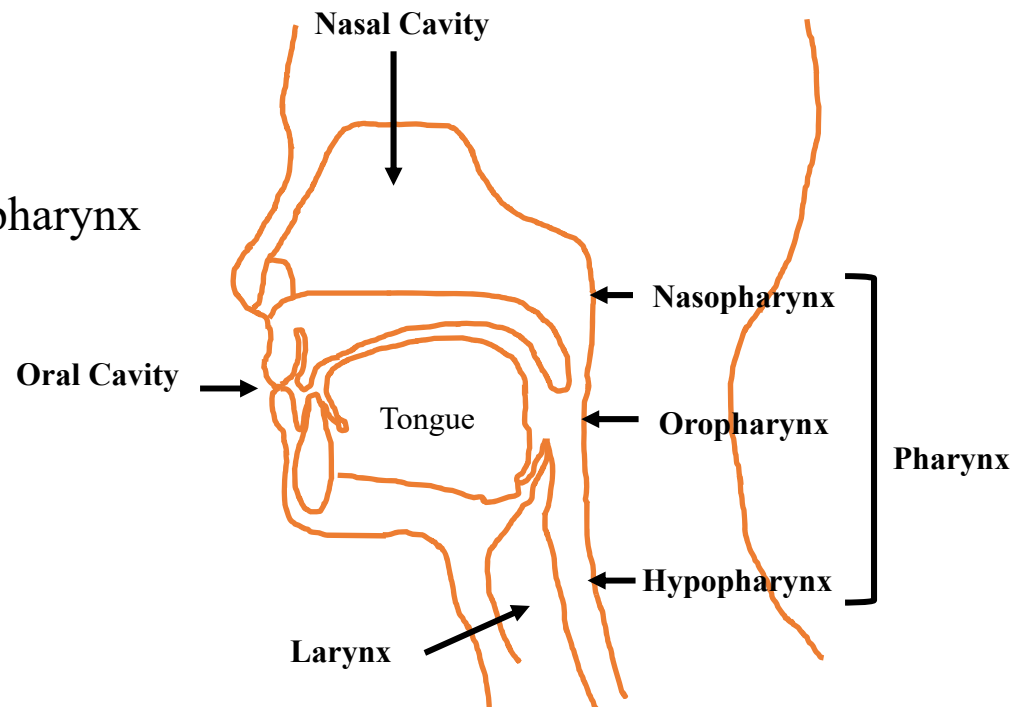
- Heterogeneous group of cancers; varying primary sites

- Anatomic sites

- Oral cavity
- Nasopharynx/oropharynx/hypopharynx
- Larynx

- Other anatomic sites

- Paranasal sinuses
- Lip
- Salivary glands



1. Adapted from: SEER training modules, head & neck cancer. National Institutes of Health, National Cancer Institute.

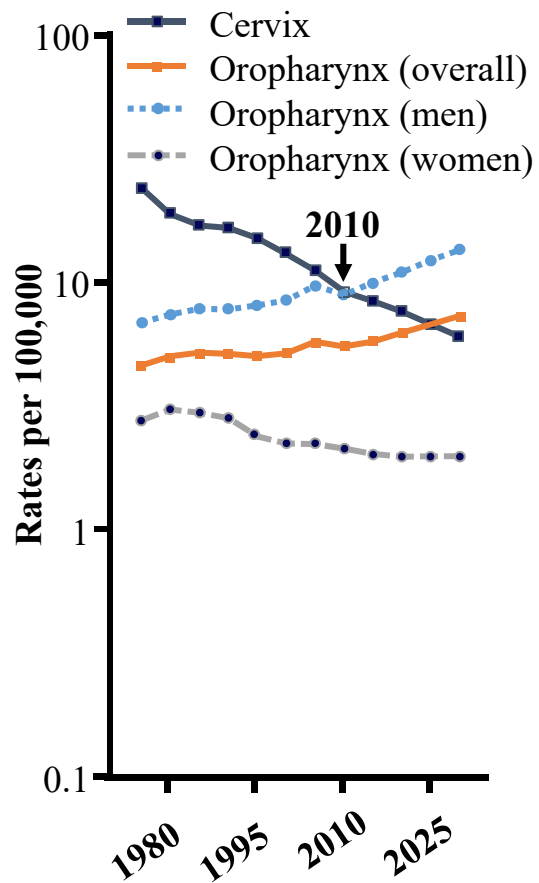
## HNSCC: Overview

- **6<sup>th</sup> most common cancer worldwide ( Globocan )**
  - 650,000 cases and 200,000 deaths/yr worldwide
  - One of most common cancers in central Asia
- **2 different etiologies and corresponding tumor types**

|                             | HPV-Positive HNSCC                     | HPV-Negative HNSCC                  |
|-----------------------------|--|-------------------------------------|
| Age <sup>[1]</sup>          | Younger; healthier                     | Older; higher rate of comorbidities |
| Risk factors <sup>[1]</sup> | Sexual behavior                        | Tobacco                             |
| Cofactors                   | Marijuana/immune suppression (eg, HIV) | Tobacco/alcohol                     |
| Incidence                   | Rising rapidly                         | Declining                           |

**Infection with high-risk HPV (HPV+) largely limited to oropharyngeal cancers**

# The HPV “Epidemic” in the United States

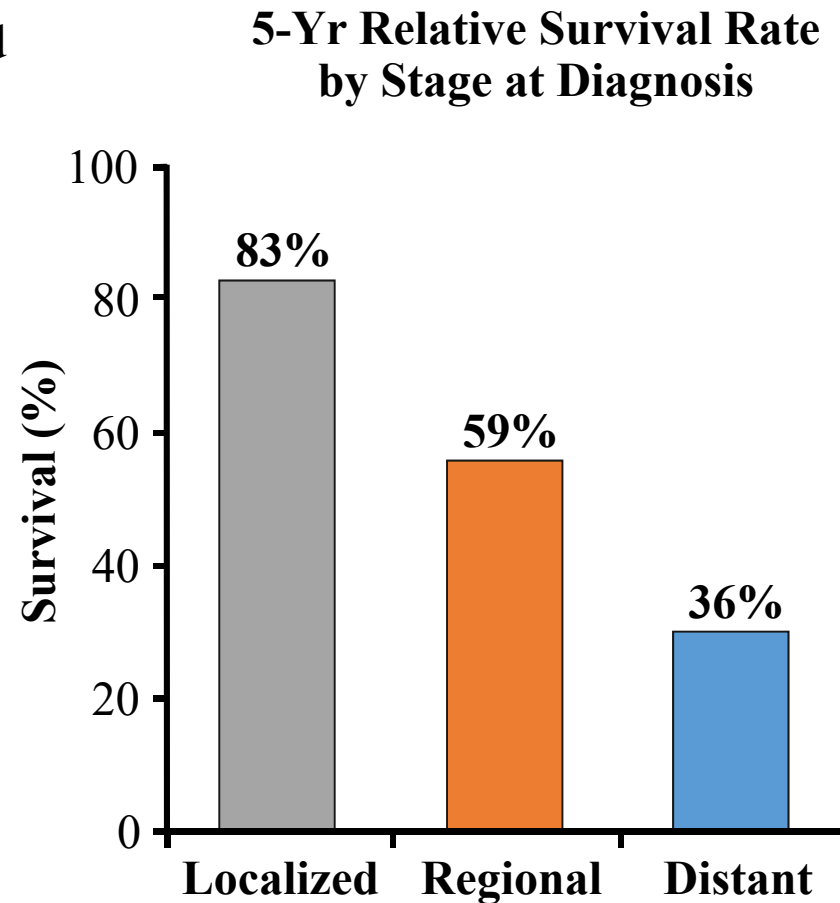


Chaturvedi AK, *et al.* J Clin Oncol. 2011;29:4294-4301.

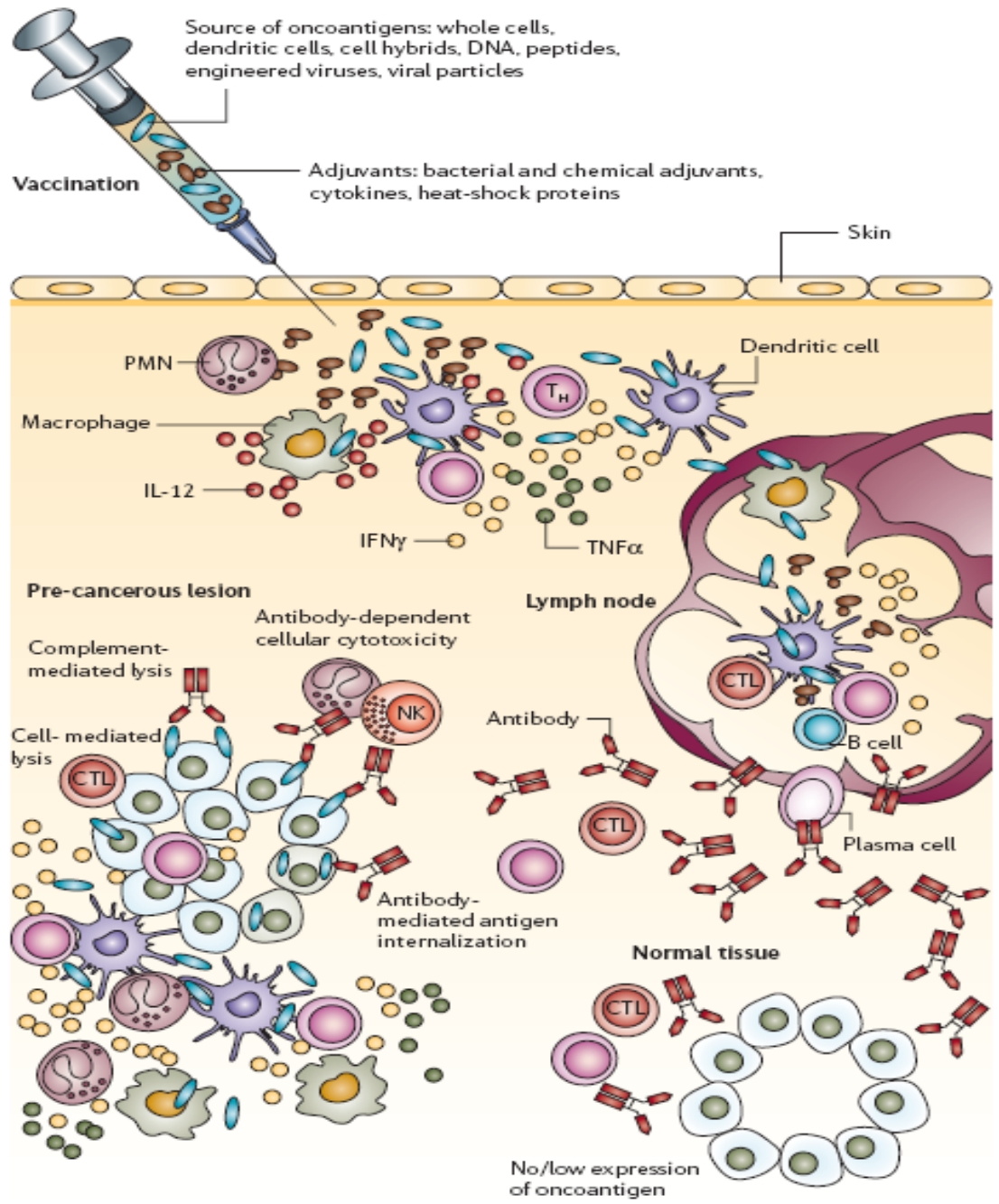
## HNSCC: Survival Rates by Stage of Disease

- High cures rates are achieved for localized and loco-regional disease using:
  - Surgery
  - Radiation
  - Chemo radiation
- Survival rates for recurrent/ metastatic disease remain very poor.
- HPV+ tumors are distinct entity with better prognosis and may require differential treatments

- Adoptive T cells therapy



SEER. Stat fact sheets: oral cavity and pharynx cancer. 2003-2009.



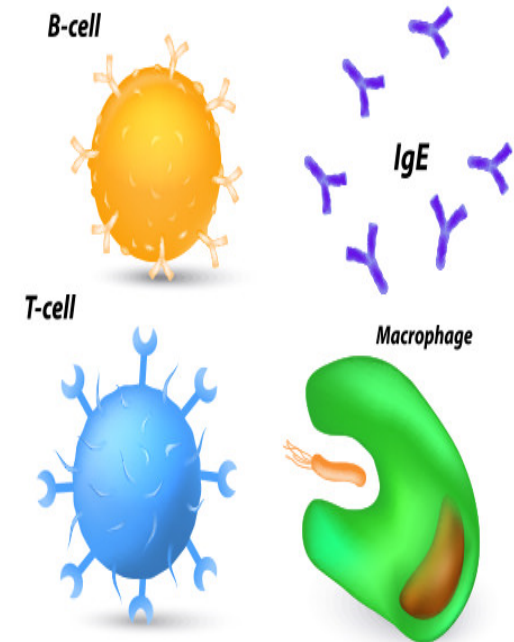
# Adoptive T cell Therapy

## Engineered T cells: Next-generation cancer immunotherapy

# General Immune Responses

## 1. Adaptive immune responses to tumors:

- a. CD8 CTLs are the key players on the killing effect of tumors.
- b. CD4 T helper cells => cytokines => CTLs
- c. Abs => activating complements or Ab-dep cell-med toxicity  
=> preventing oncogenic viruses



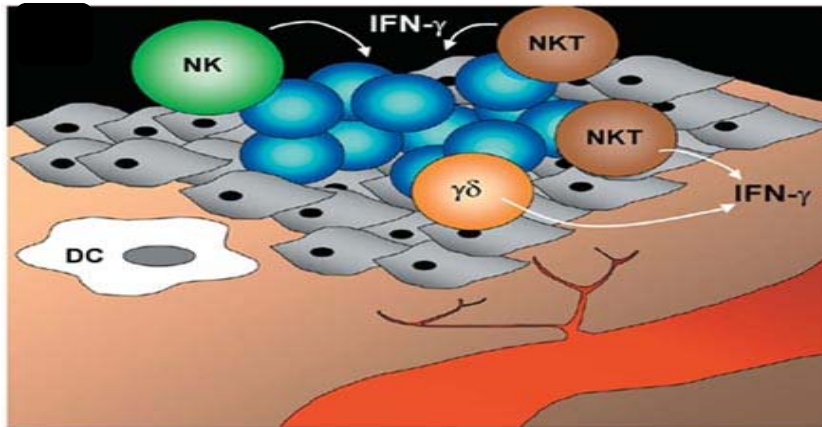
## 2. Innate immune responses to tumors:

- a. NK cells kill many types of tumor cells that have reduced class-I but express ligands for activating NK cells.
- b. Macrophages => Ab-med phagocytosis  
=> Cytokines (TNF-a), ROS, & NO

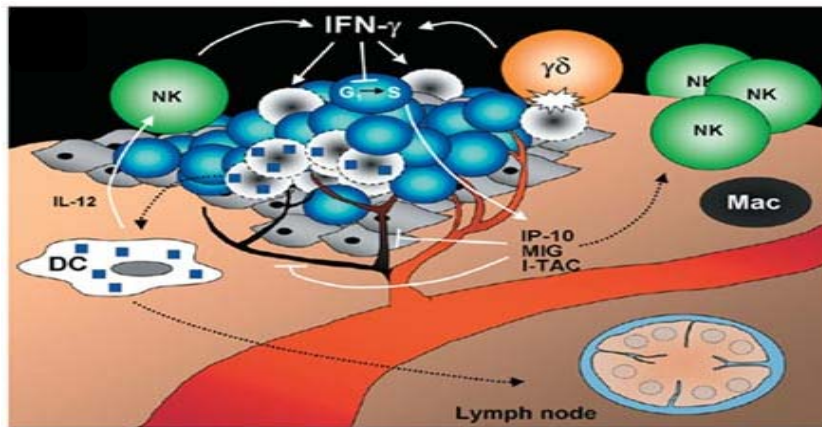


# Model of Innate Recognition and Initiation of the Adaptive Antitumor Immune Response

## Innate Recognition

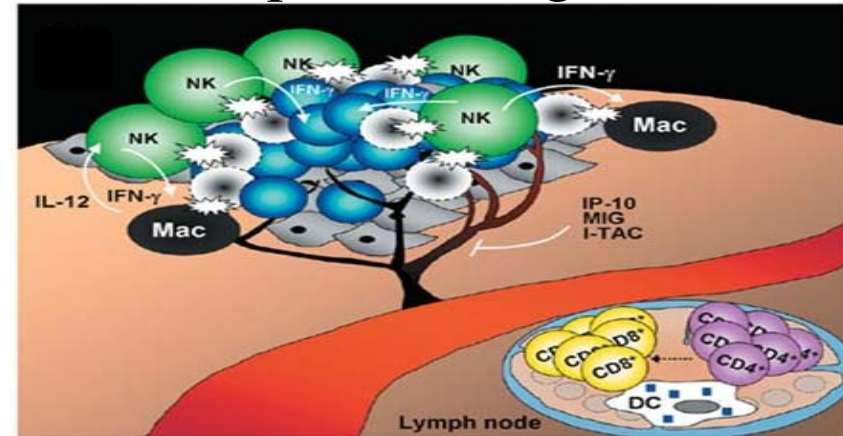


“danger”= invasion (inflam. response) + “stress” ligands of NKG2D

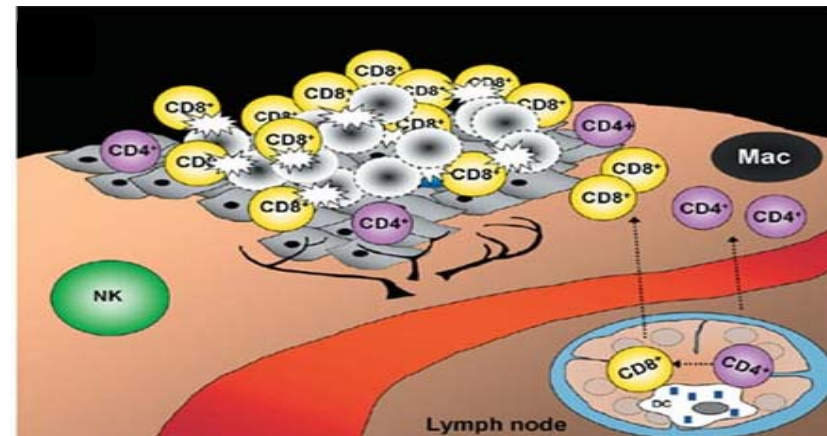


Apoptosis provides antigen delivery to DCs

## Adaptive Recognition



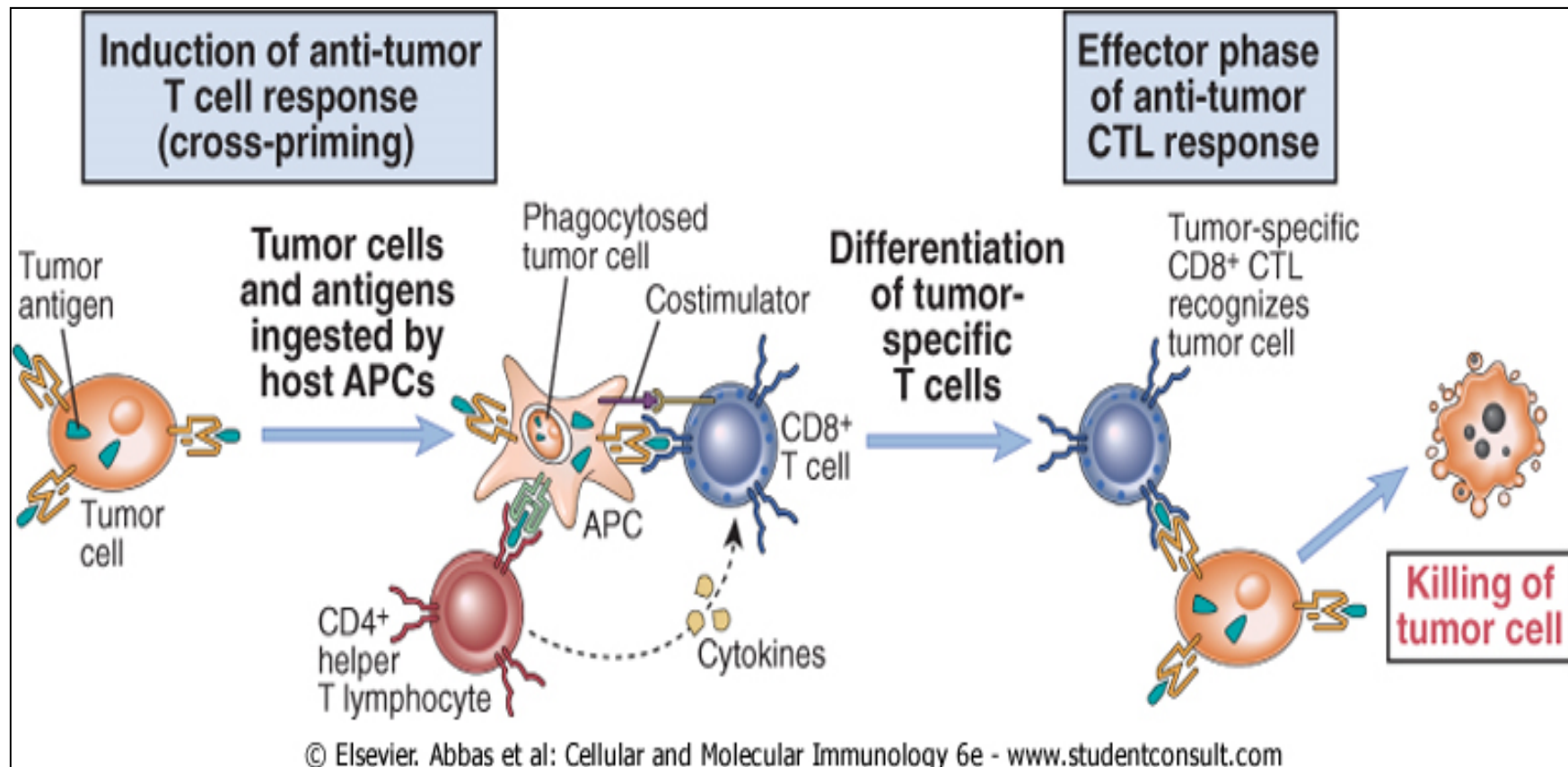
Amplification of innate and link to adaptive response



Elimination by adaptive response

# Induction of T cell responses to tumors

Cross-priming (cross-presentation) mediated by APCs, ex. DCs



# Immunosurveillance Theory /Tumor Antigens.

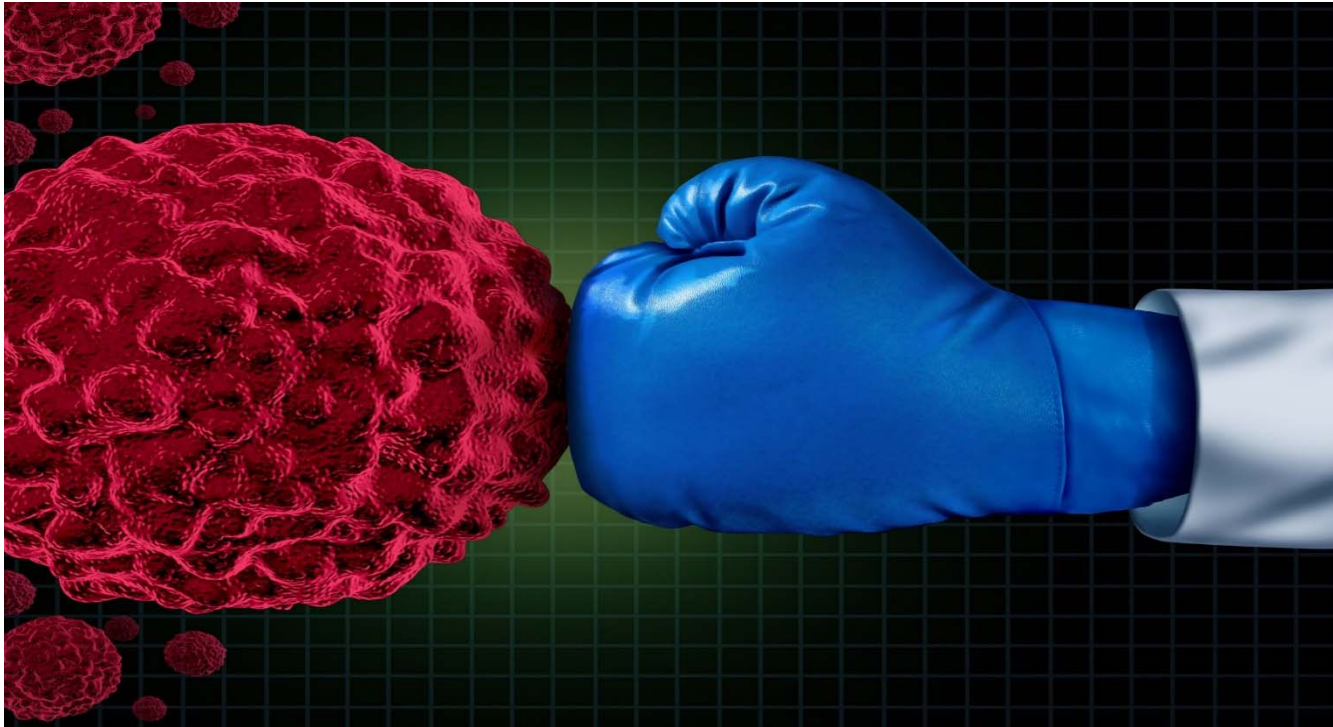
## **Tumor associated antigens (TAA)-present on Tumor cell + some normal cells**

- Alpha Fetoprotein (AFP)
- Prostate Specific Antigen (PSA)
- Carcinoembryonic Antigen (CEA)

## **Tumor specific antigens (TSA)-present on Tumor cell ,not on normal cells.**

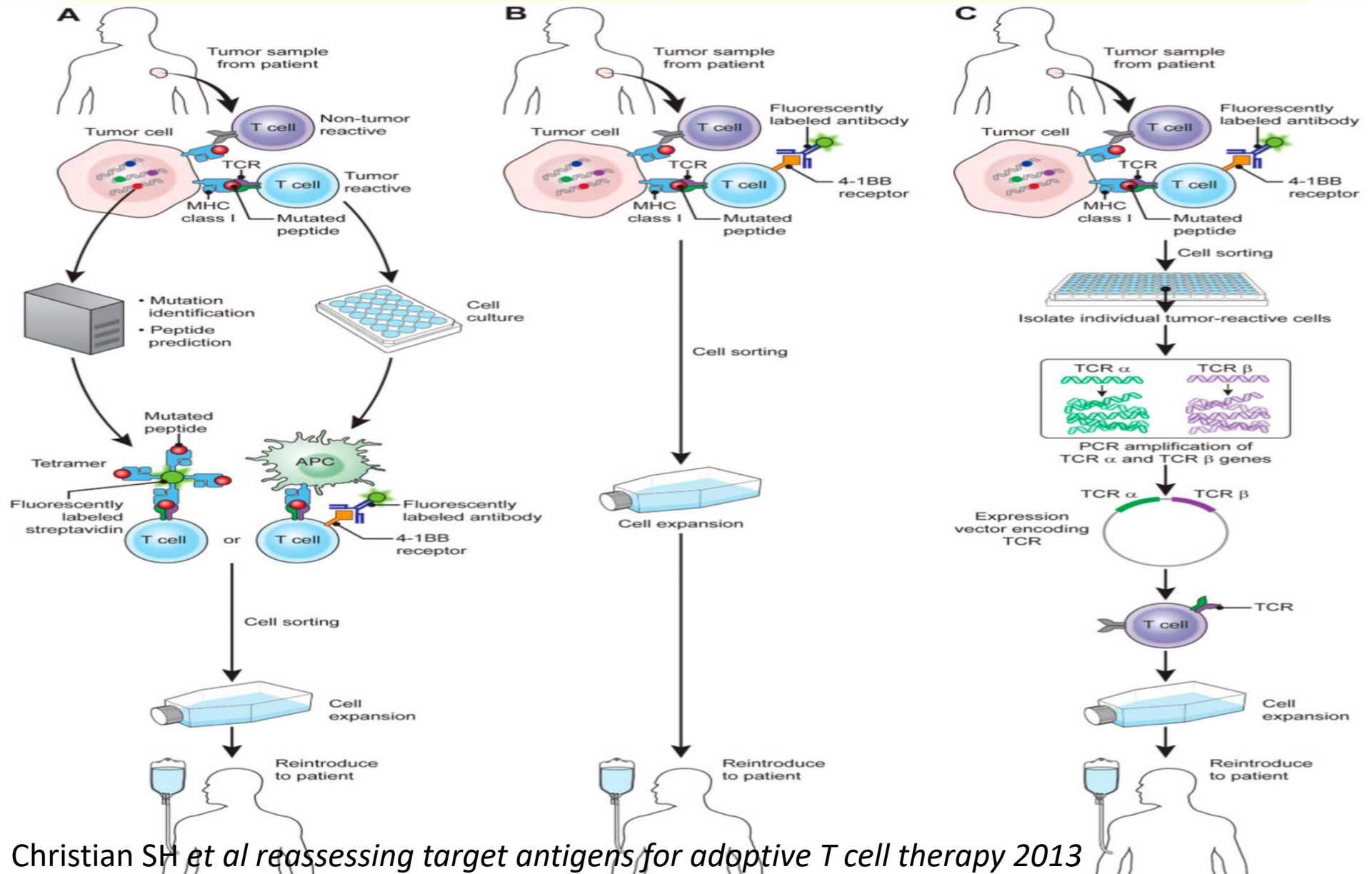
- Overexpressed proto-oncogenes: EGFR, HER2
- Point mutations: ras, b-catenin, CDC27, CDK4, Bcr/Abl
- Viral Antigens: **Human papillomavirus**, EBV

# Immunosurveillance Theory /Tumor Immunology



Can We Utilize Immunosurveillance Theory To Destroy The HNSCC ?

# How do we perform an Adoptive T cell Therapy



Christian SH *et al* reassessing target antigens for adoptive T cell therapy 2013

# Engineered T Cells in HNSCC Cell Lines

## Procedure for TCR Gene Therapy Protocols

**Obtain PBMC from patients' peripheral blood cells**



**Activate T cells using CD3 antibody for two days**



**Transduce T cells with MSGV1 Retroviral vectors containing E6 TCR( $\alpha$ - $\beta$ -chain)**



**Applied activated T cells in the SCC90 and SCC154 (HNSCC+) Cell lines, CaSki (HPV16+ cervical, HLA-A2 +) cell lines**

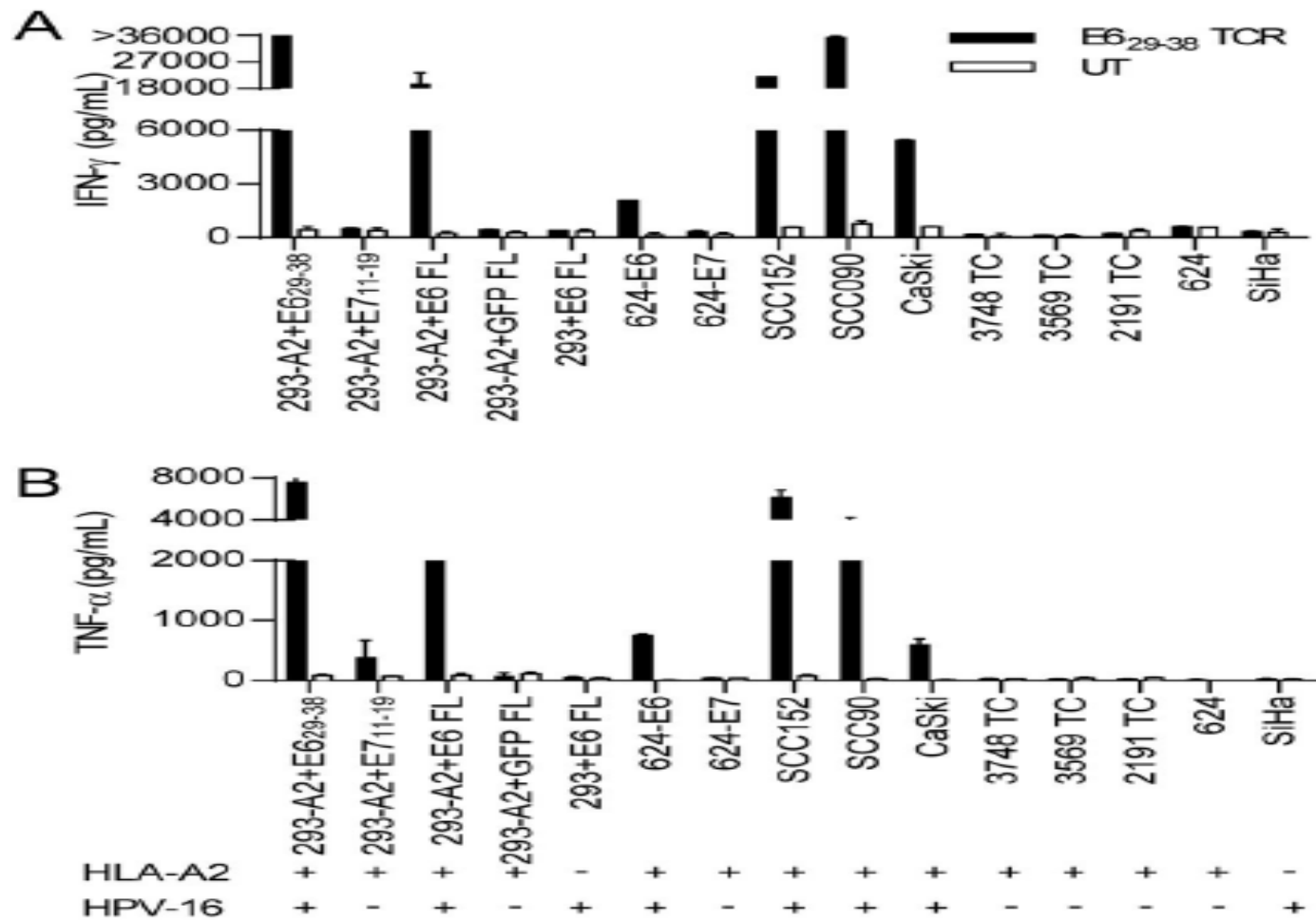


**Analysis**

**– Cytokine assay**

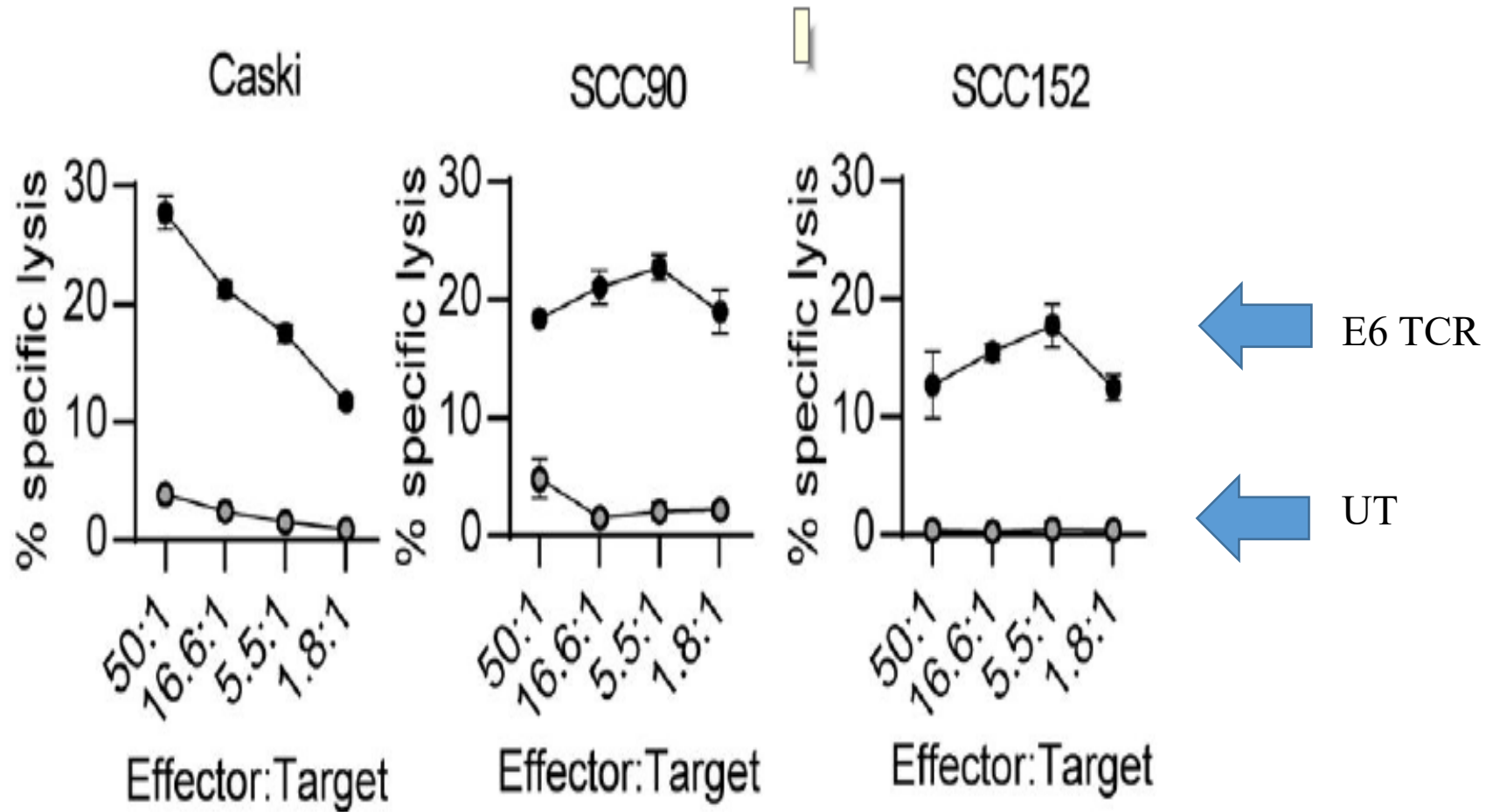
**- Cytolysis assay**

# IFN- $\gamma$ and TNF- $\alpha$ production by E6 TCR engineered T cells



Lindsey md *et al.* . Targeting of HPV-16+ epithelial cancer cells by TCR gene engineered T cells directed against E6 2015

# Specific cytolysis of tumor cells by E6 TCR gene engineered (E6 TCR) or untransduced (UT) T cells

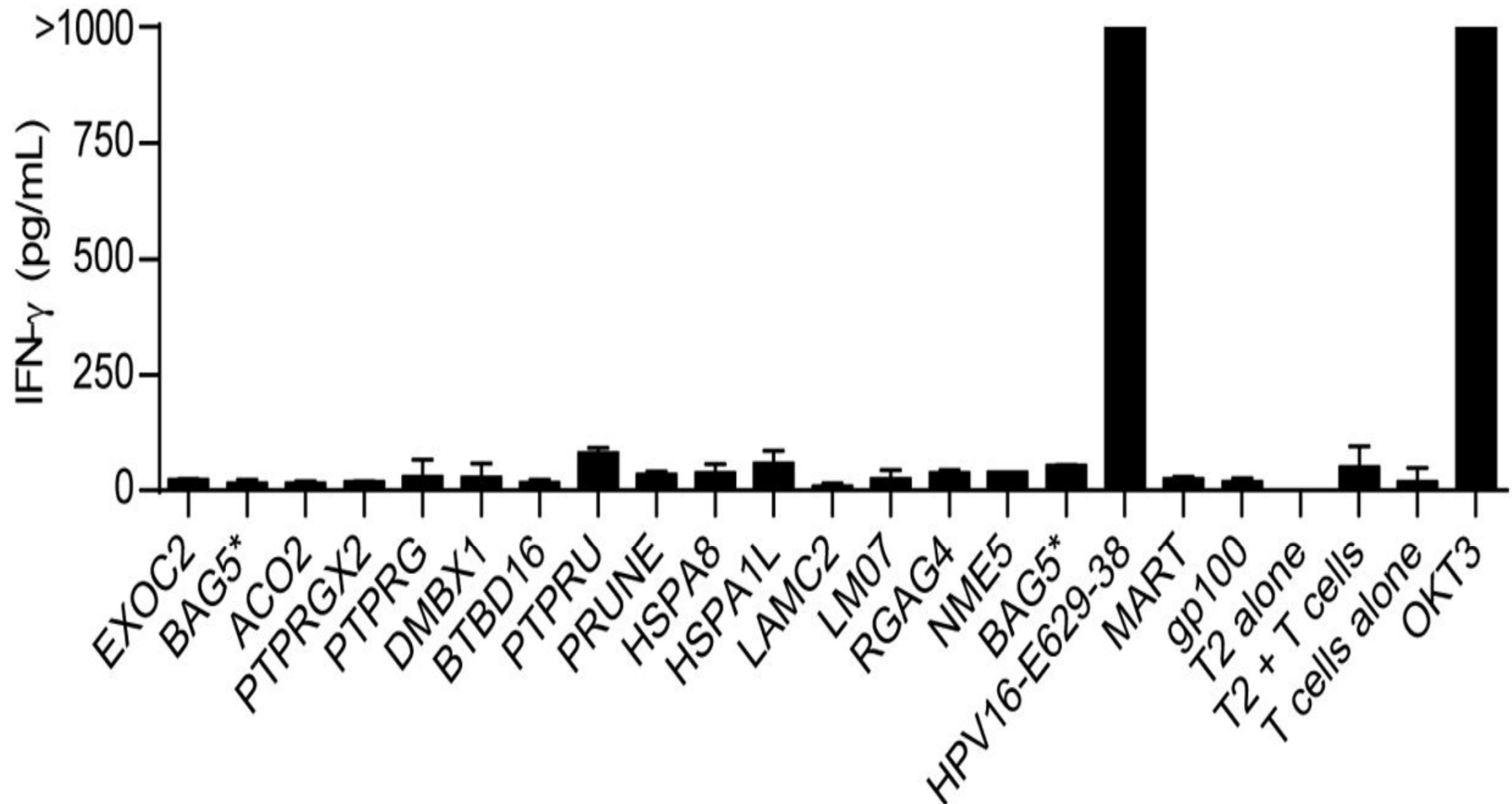


Lindsey md *et al.* Targeting of HPV-16+ epithelial cancer cells by

Effector: E6 engineered T  
Target : Caski ,SCC90 SCC152

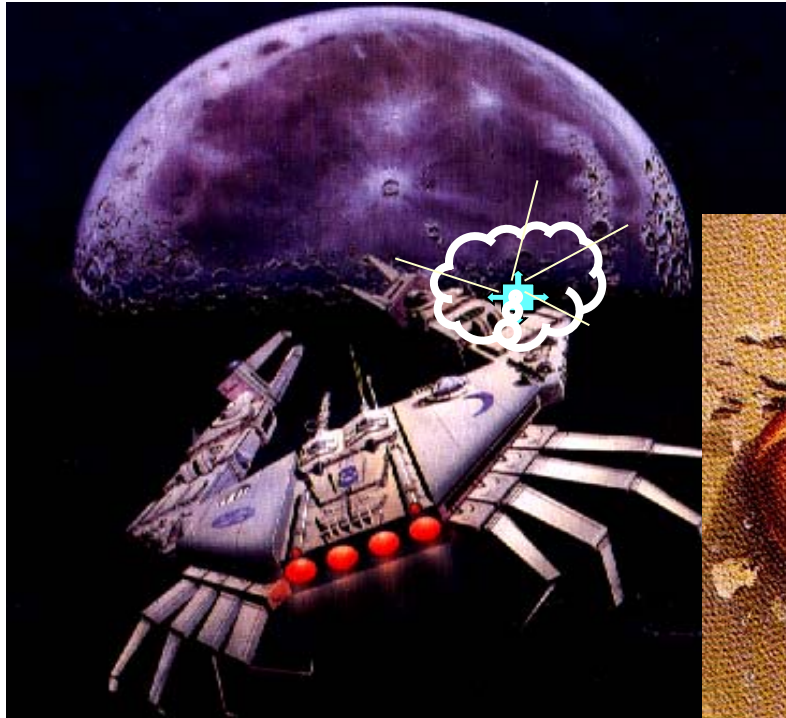


# E6 TCR gene engineered T cells did not display cross-reactivity against human peptides



Lindsey md *et al.* . Targeting of HPV-16+ epithelial cancer cells by TCR gene engineered T cells directed against E6 2015

## A fight between immune cells and cancer



**But, sometimes we lose**

# Tumor Escape

Mechanisms by which tumor escape immune defenses:

- 1) Reduced levels or absence of MHC molecule on tumor so that they can not be recognized by CTLs
- 2) Some tumors stop expressing the antigens  
These tumors are called “antigen negative variants”
- 3) Production of immunosuppressive factors by tumor e.g. transforming growth factor (TGF- $\beta$ )

# Summary

1. HNSCC is a common cancer worldwide
2. Infection with high-risk HPV (HPV+) HNSCC have better prognosis and may require differential treatments
3. Adoptive T cell therapy is based on host immune system
4. Advantages and Disadvantages of T cell therapy



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Thank you