The Blockade of PD-1/PD-L1 signal pathway combined with therapeutic vaccination of HPV-associated head and neck squamous cell carcinoma

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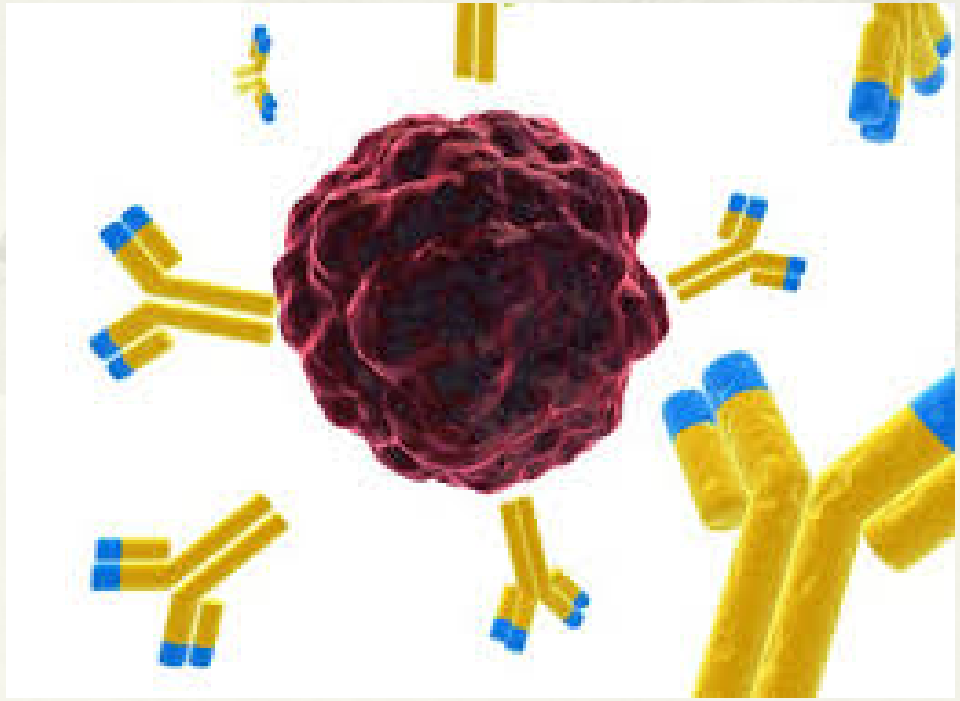
Breakthrough of the Year 2013

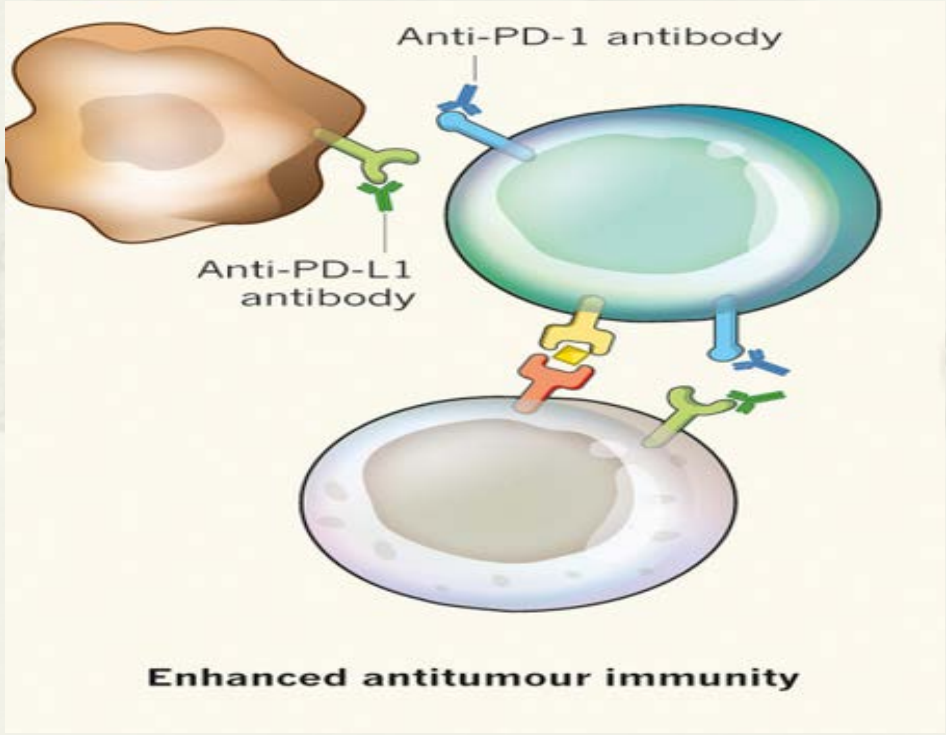
Cancer immunotherapy attacks tumors by harnessing a person's immune system. researchers saw promising results from multiple clinical trials such as PD-1 immune checkpoint blockade in non-small cell lung cancer , melanoma and colon-rectal cancer. But there are still a lot to learn how this therapy works .

Change of Treatment Concept

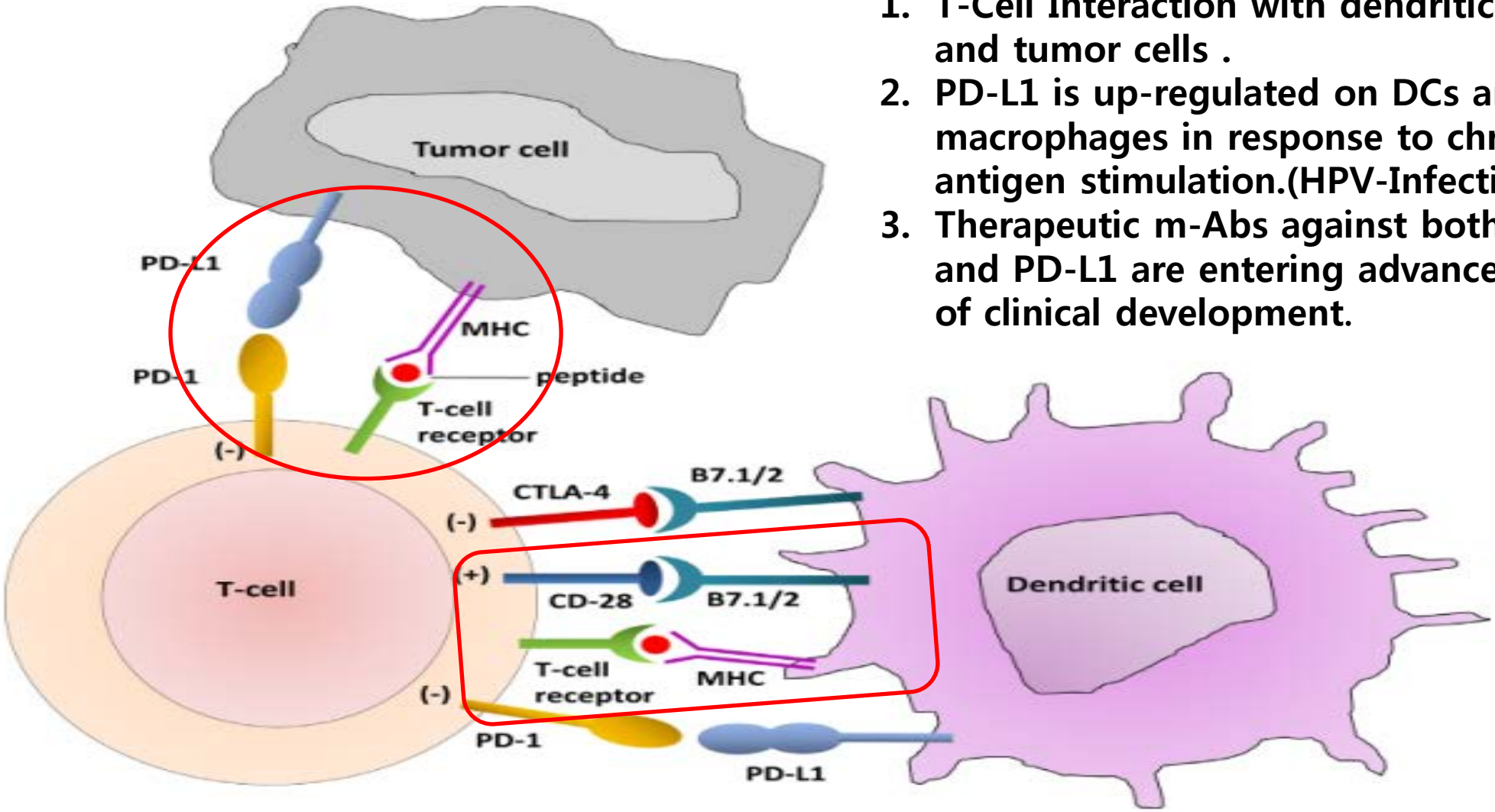
Historical Paradigm:
Targeting Tumor Cells
Chemical Therapy , Radiation

New Paradigm: Targeting
Immune Cells



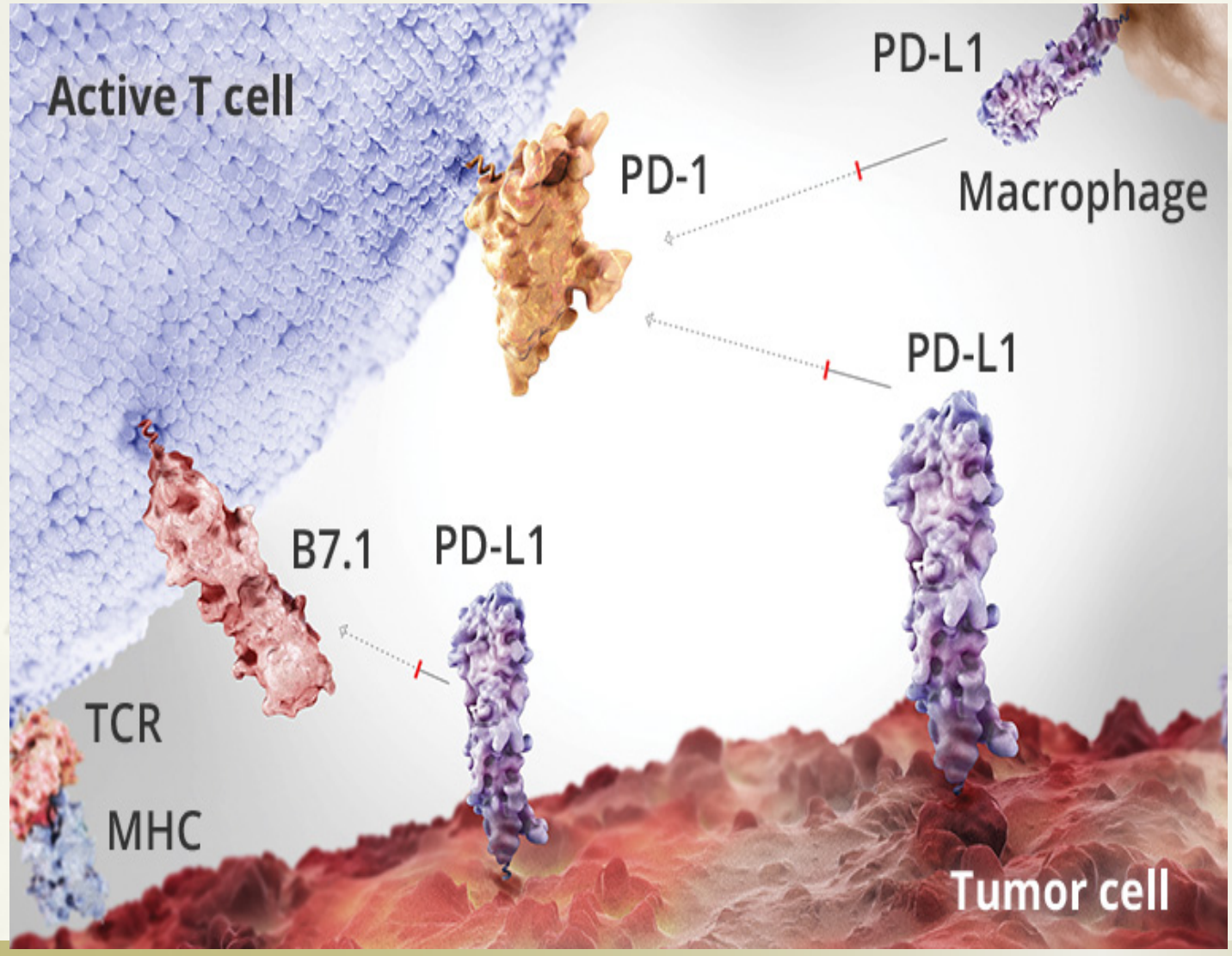


The Tumor Microenvironment

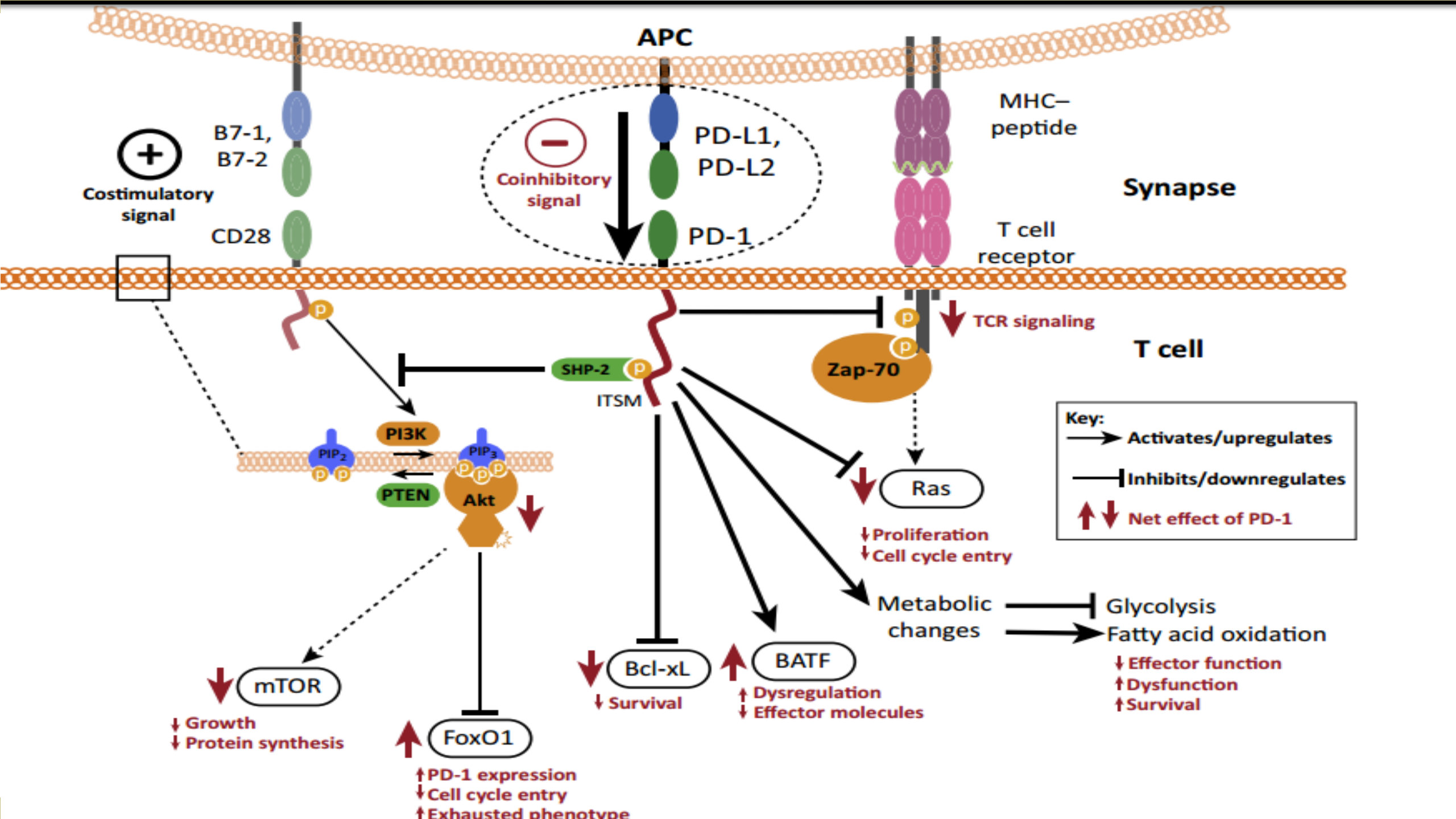


1. T-Cell Interaction with dendritic cells and tumor cells .
2. PD-L1 is up-regulated on DCs and macrophages in response to chronic antigen stimulation.(HPV-Infection)
3. Therapeutic m-Abs against both PD-1 and PD-L1 are entering advanced stages of clinical development.

The PD-1/PD-L1 Immune Check Point



1. PD-1 (CD279) . A member of CD28 family .
2. PD-1 is expressed on various immune cells T,B,DC,Mo,MØ
3. PD-L1 (B7-H1, CD274) and PD-L2 (B7-DC, CD273)
4. PD-L1 can be seen on tumor cell.Monocytes, Macrophages, DCs, peripheral tissues.


APC
B7-1,
B7-2
Costimulatory
signal
CD28
Coinhibitory
signal
PD-L1,
PD-L2
PD-1
MHC–
peptide
Synapse
T cell
receptor
T cell
TCR signaling
Zap-70
SHP-2
ITSM
PI3K
PIP2
PIP3
PTEN
Akt
Ras
Proliferation
Cell cycle entry
Key:
Activates/upregulates
Inhibits/downregulates
Net effect of PD-1
Metabolic
changes
Glycolysis
Fatty acid oxidation
Effector function
Dysfunction
Survival
mTOR
Growth
Protein synthesis
FoxO1
PD-1 expression
Cell cycle entry
Exhausted phenotype
Bcl-xL
Survival
BATF
Dysregulation
Effector molecules

Some Facts about HNSCC

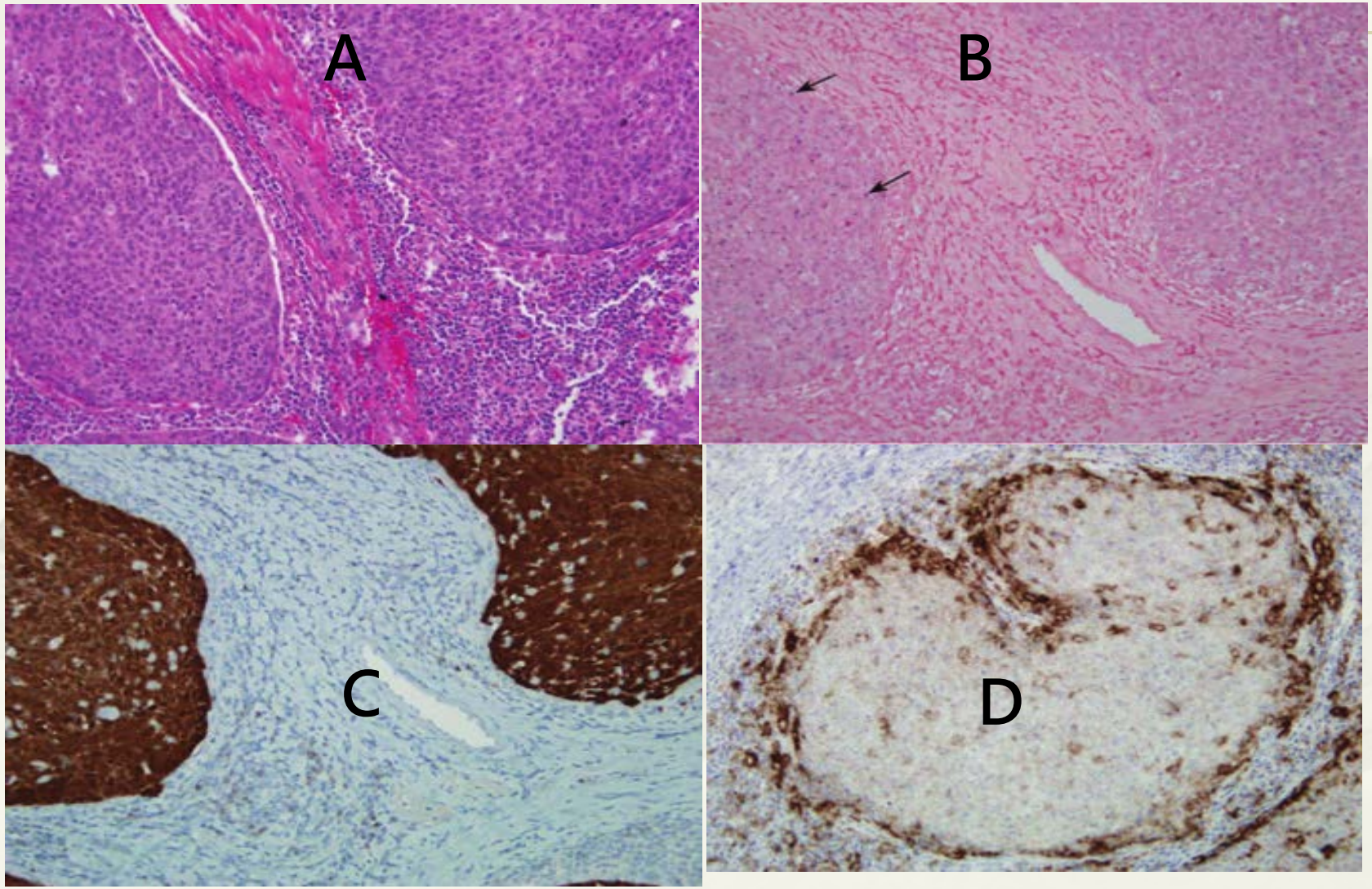
- HNSCC is a common cancer and represents about 3.5% of all malignant tumors in the western societies .
- High-risk HPVs (HPV-16) is also the most frequently detected HPV type in HNSCC found in up to 90% of HPV-positive cases, and also account for the development in some individuals who do not have the classical risk factors (tobacco and/or alcohol abuse) .
- Several studies suggest that oral-HPV infection is sexually acquired through oral–genital contact and direct mouth-to-mouth contact.

PD-L1 Expression in head and neck cancers

Table 1. PD-L1 Expression in head and neck cancers

	HPV+ (*N* = 20)		HPV− (*N* = 7)	
	Positive	**Negative**	**Positive**	**Negative**
PD-L1 expression	14/20 (70%)	6/20 (30%)	2/7 (29%)	5/7 (71%)
Membranous staining	14/14 (100%)	—	2/2 (100%)	—
Tumor periphery	13/14 (93%)	—	2/2 (100%)	—
Diffuse within tumor	1/14 (7%)	—	—	—
Presence of TILs	14/14 (100%)	3/6 (50%)	2/2 (100%)	2/5 (40%)

High levels of PD-L1 Expression Present In the Tumor Microenvironment of HPV-HNSCC



A:H E stain of HPV-HNS CC shows tumor nests

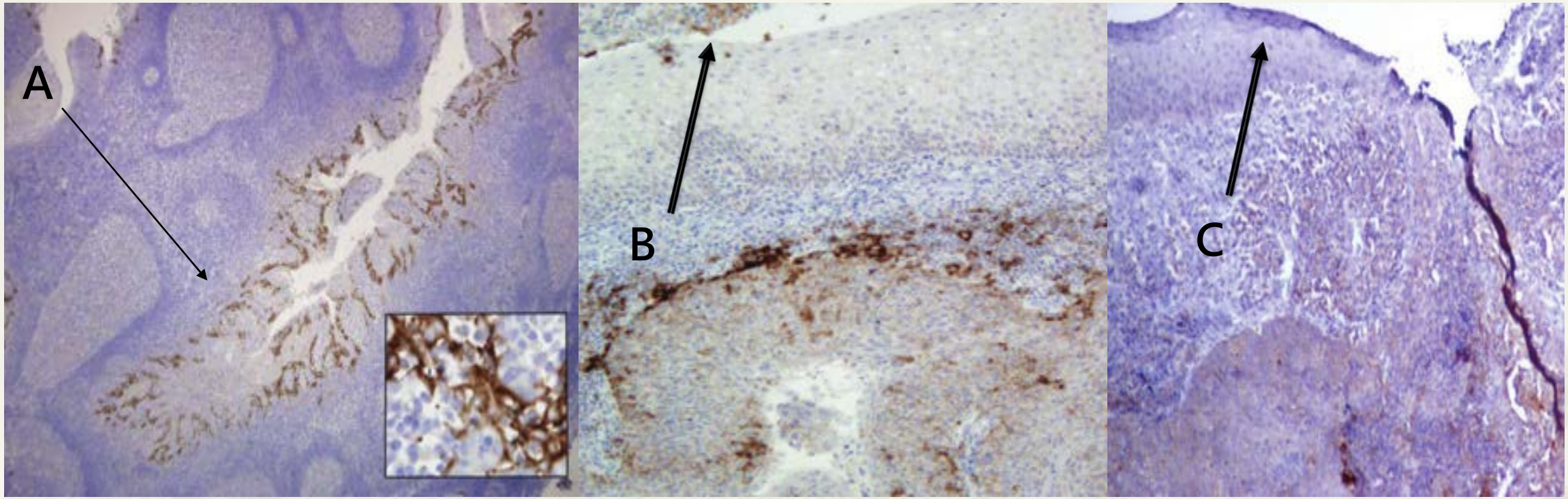
B:HPV ISH intranuclear Staining(blue color)

C: p16 Pr IHC ;
D: PD-L1 IHC

Magnification:400

The figures presented above are from Prof. William H research work in Johns Hopkins University School of Medicine

PD-L1 is seen overexpressed on cancers as a mechanism the cancerous cells to avoid immune surveillance.



HPV-Naïve pediatric patients of tonsil tissue shows localized PD-L1 expression within the reticulated epithelium of tonsillar crypts(long arrow). MagnificationX40.The inset(magnification400)shows cell surface staining of the crypt epithelial cells. In contrast, the surface epithelium of the tonsils was negative for PD-L1 expression (short arrows; B and C). Magnificationx40.

Why Therapeutic Cancer Vaccines

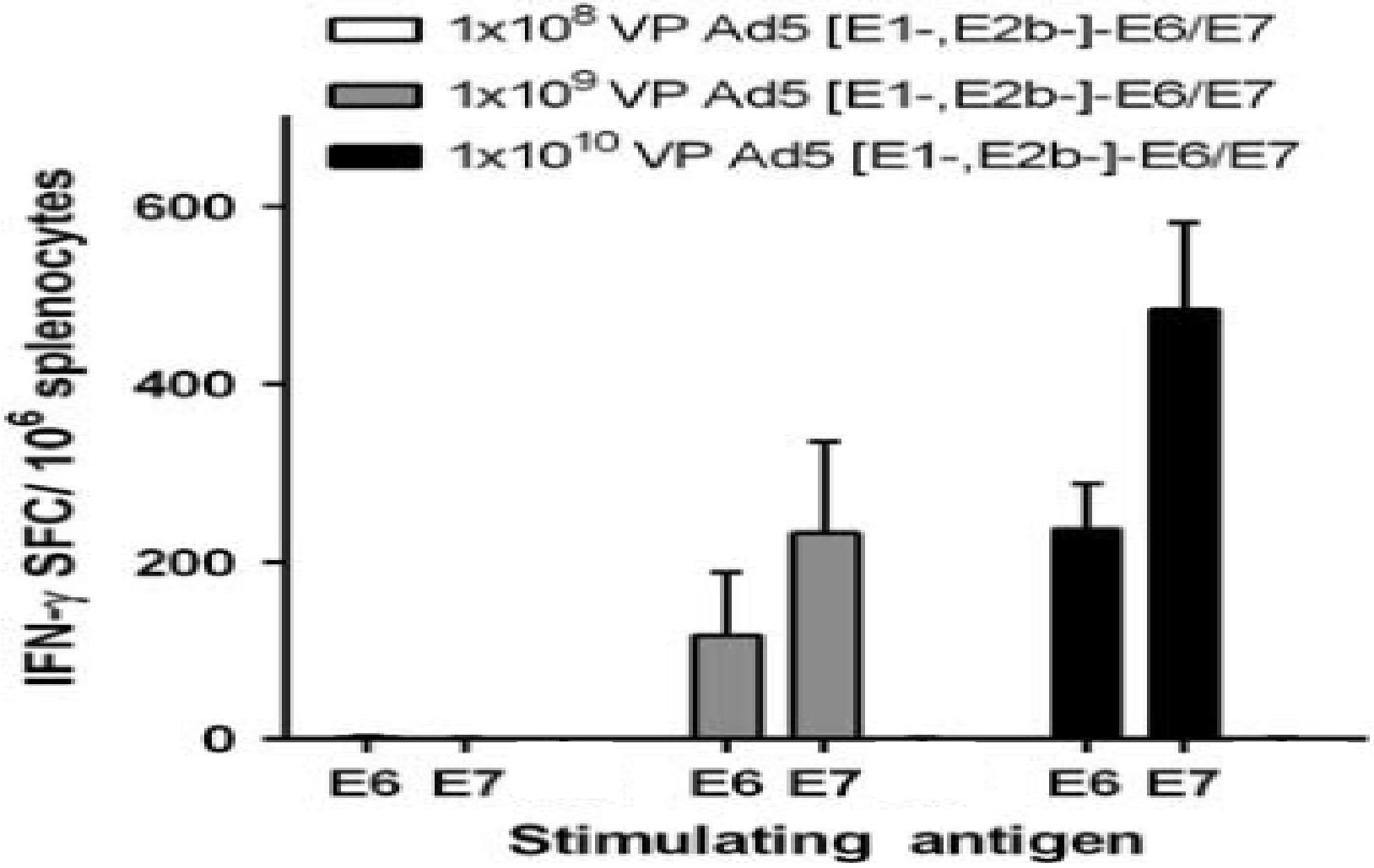
- The HPV early 6 (E6)and early 7 (E7) genes are expressed at high levels in HPV-induced cancers and are involved in the immortalization of primary human epidermal cells .
- HPV viral antigens are "non-self" and thus do not have the potential to induce autoimmunity.

HPV vaccines

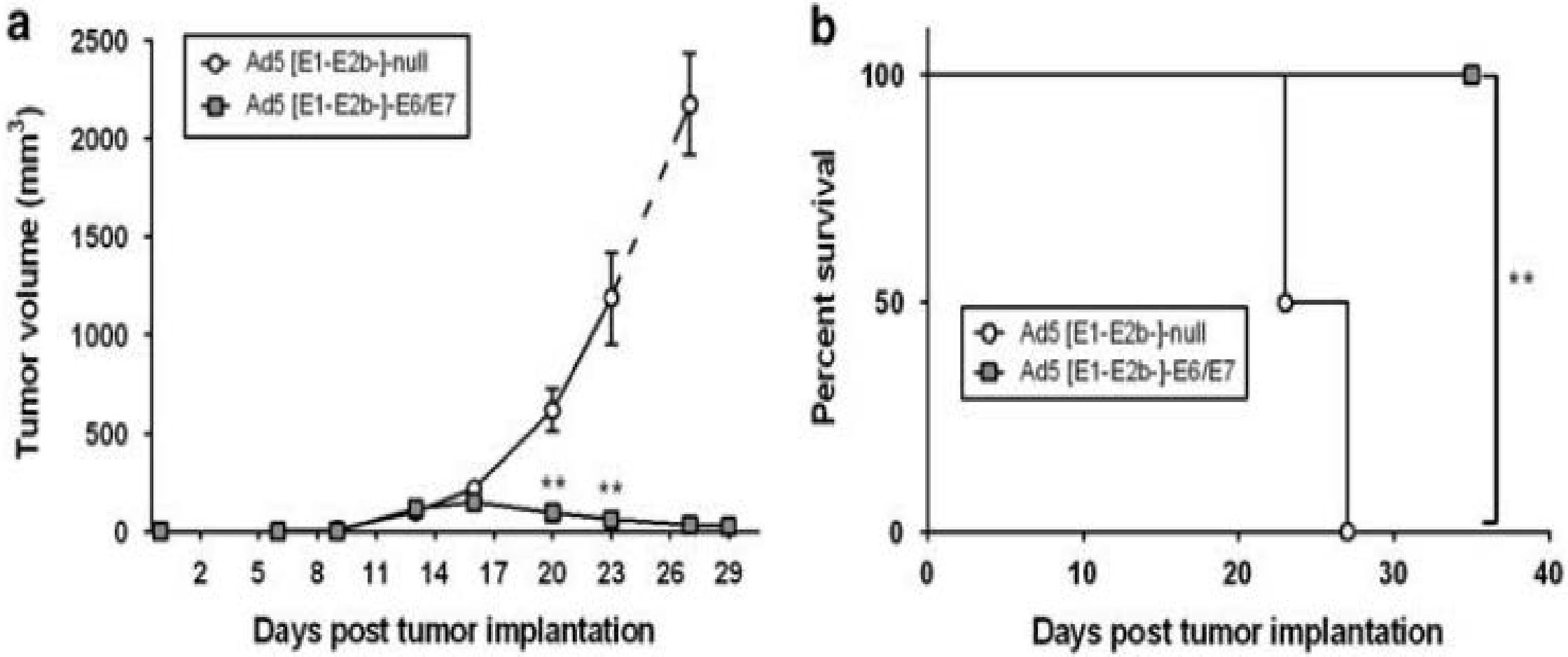
Prophylactic vaccine (HPV-capsid protein :L1)

Therapeutic vaccine (HPV-16 E6/E7

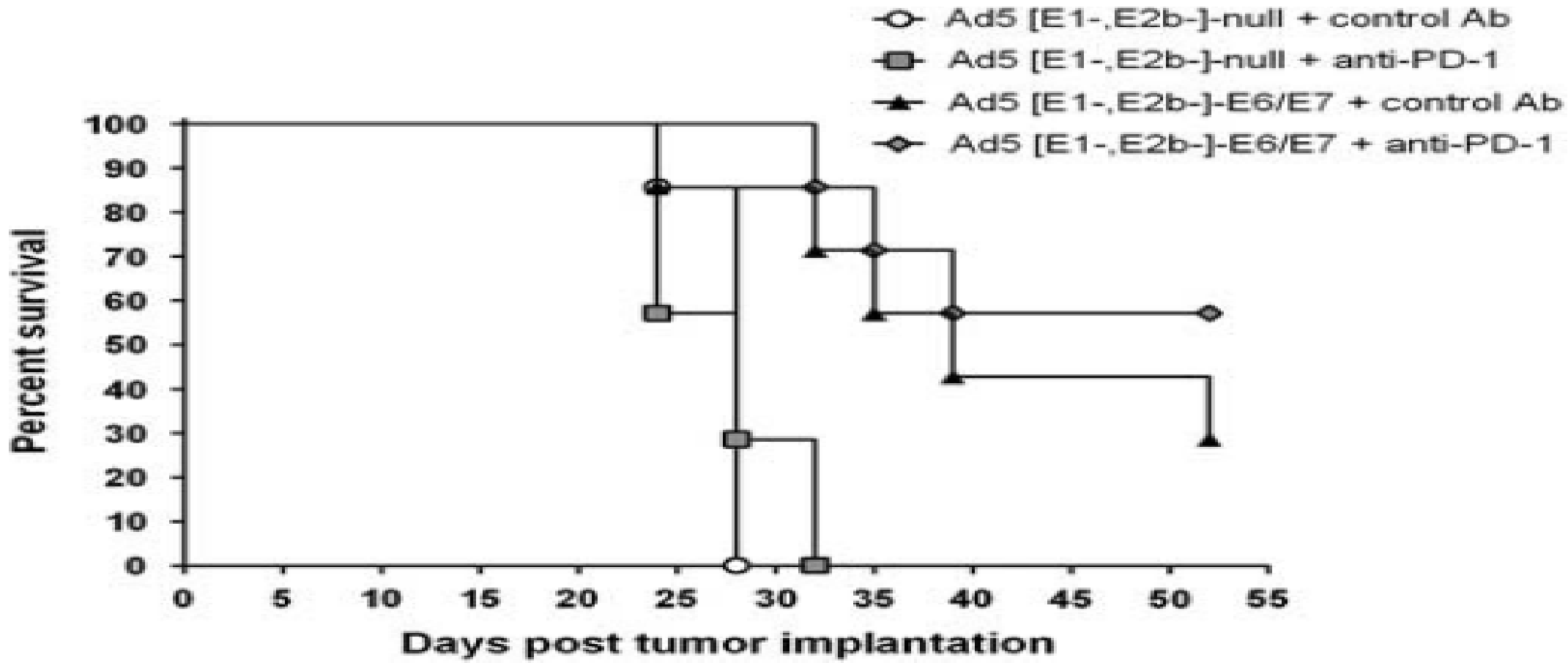
CMI dose response of Ad5 [E1-, E2b-]-E6/E7. C57BL/6 mice



Lab results of HPV-vaccination plus PD-1 blockade on C57BL/6 MICE



Percentage of survival in different groups



SUMMARY

- PD-1 is an inhibitory receptor on T cells and is responsible for dysfunction in infectious diseases and cancers.
- The observation that combined treatment was associated with reductions in large tumor mass indicates that immunotherapy with Ad5 [E1-, E2b-]-E6/E7 combined with anti-PD-1 antibody might increase clinical effectiveness during the immunotherapy of patients with HPV-associated HNSCC
- Immunotherapy seems to offer great promise as a new


Thank
You!