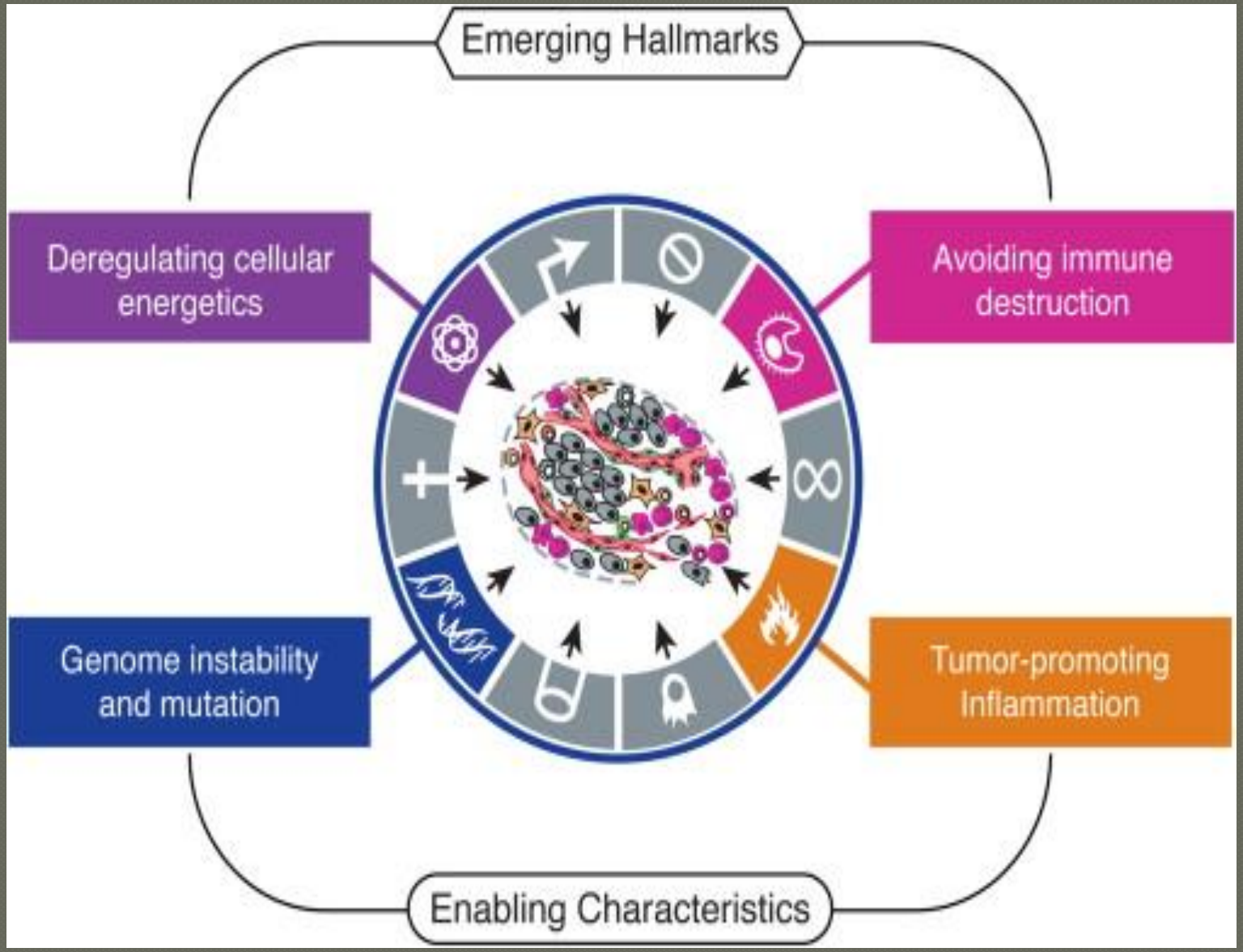
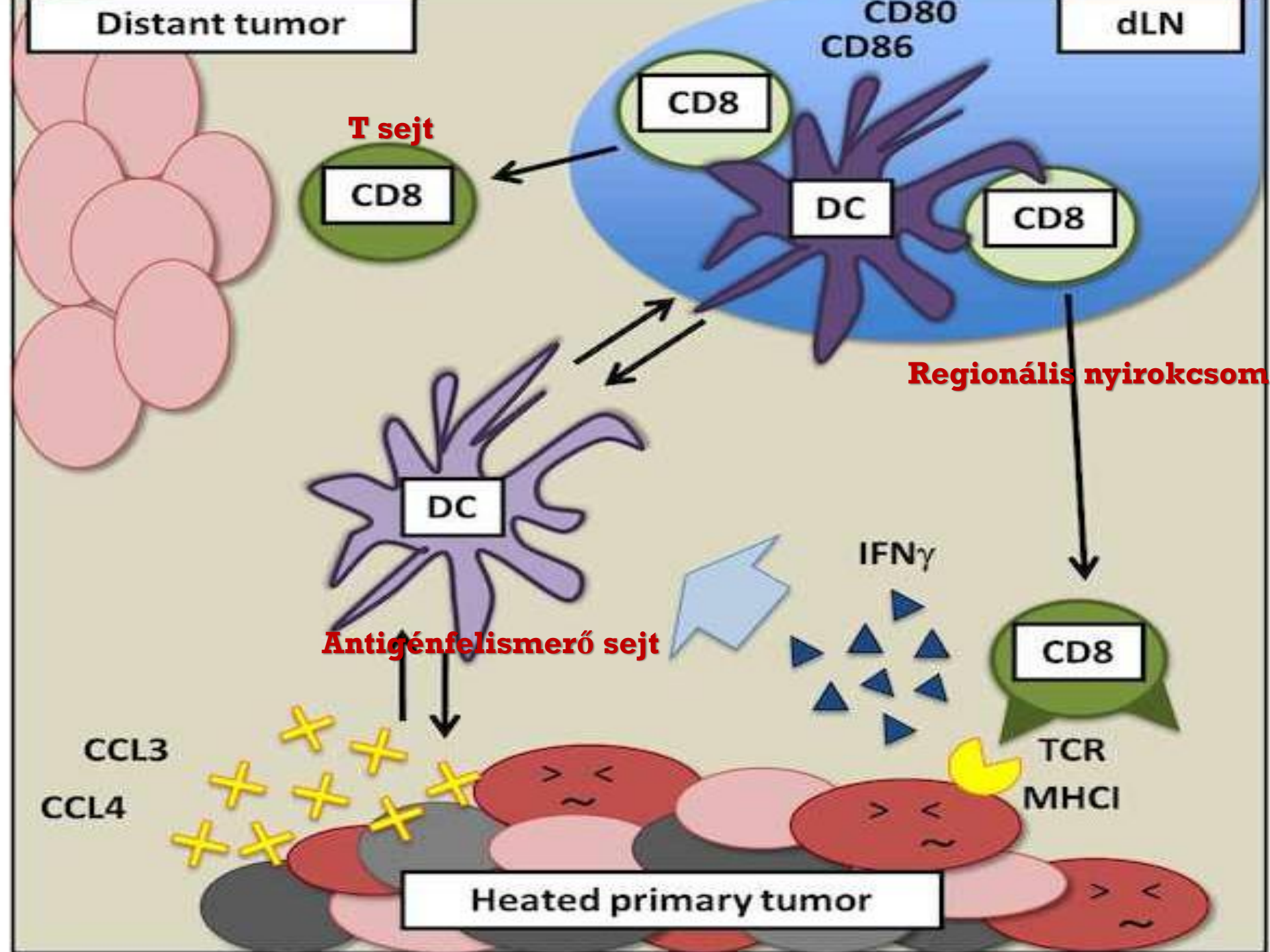
„Az ellenségem ellensége a barátom”
Orvosi Nobel díj 2018:
Az immunonkológiai alapjai

Tímár József
Semmelweis Egyetem
2.sz. Patológiai Intézet



Figure?3 Emerging Hallmarks and Enabling Characteristics An increasing body of research suggests that two additional hallmarks of cancer are involved in the pathogenesis of some and perhaps all cancers. One involves the capability to modify, or ...


Distant tumor
CD80
CD86
dLN
CD8
T sejt
CD8
DC
CD8
Regionális nyirokcsom
DC
IFNγ
Antigénfelismerő sejt
CD8
CCL3
CCL4
TCR
MHCI
Heated primary tumor

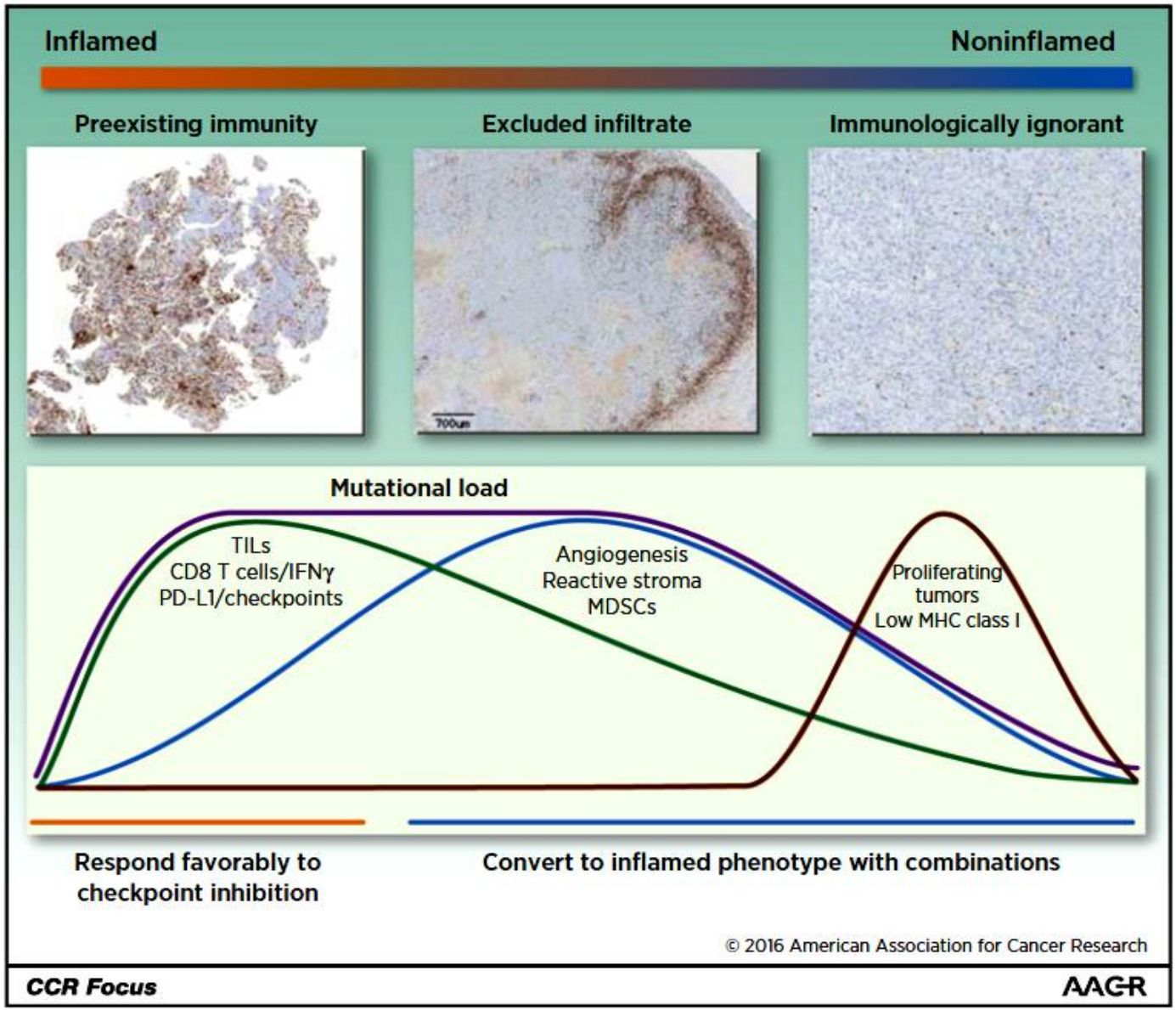
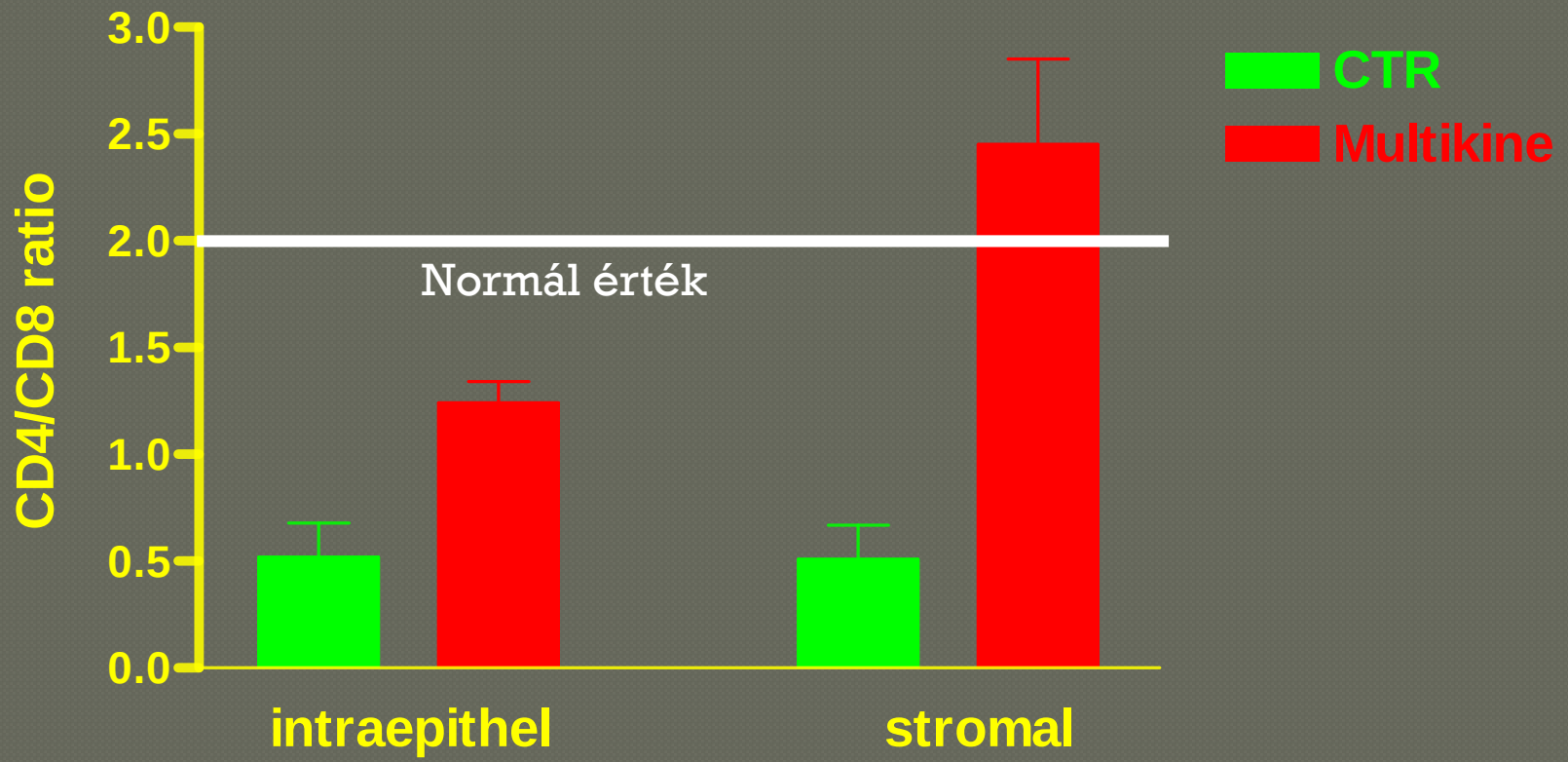


Figure 1.
The tumor immunity continuum. Representative images of tumor CD8 IHC show three patterns of T cells associated with tumor cells. Tumors with preexisting immunity are represented by abundance of TILs, dense functional $CD8^+$ T-cell infiltration reflected by increased IFNγ signaling, expression of checkpoint markers, including PD-L1, and high mutational burden. These characteristics reflect highly inflamed tumors. Despite high mutational burden, tumors with the excluded infiltrate or stromal T-cell phenotype are represented by increased influence of immunosuppressive reactive stroma, myeloid-derived suppressor cells (MDSC), and angiogenesis, all of which prevent infiltration of T cells into the tumors or suppress activation of T cells in the tumor milieu. Finally, immunologically ignorant tumors that contain very low infiltration of T cells are genomically stable with highly proliferating tumor cells. These are representative of noninflamed tumors.

Hegde PS et al, CCR 22:1865,2016

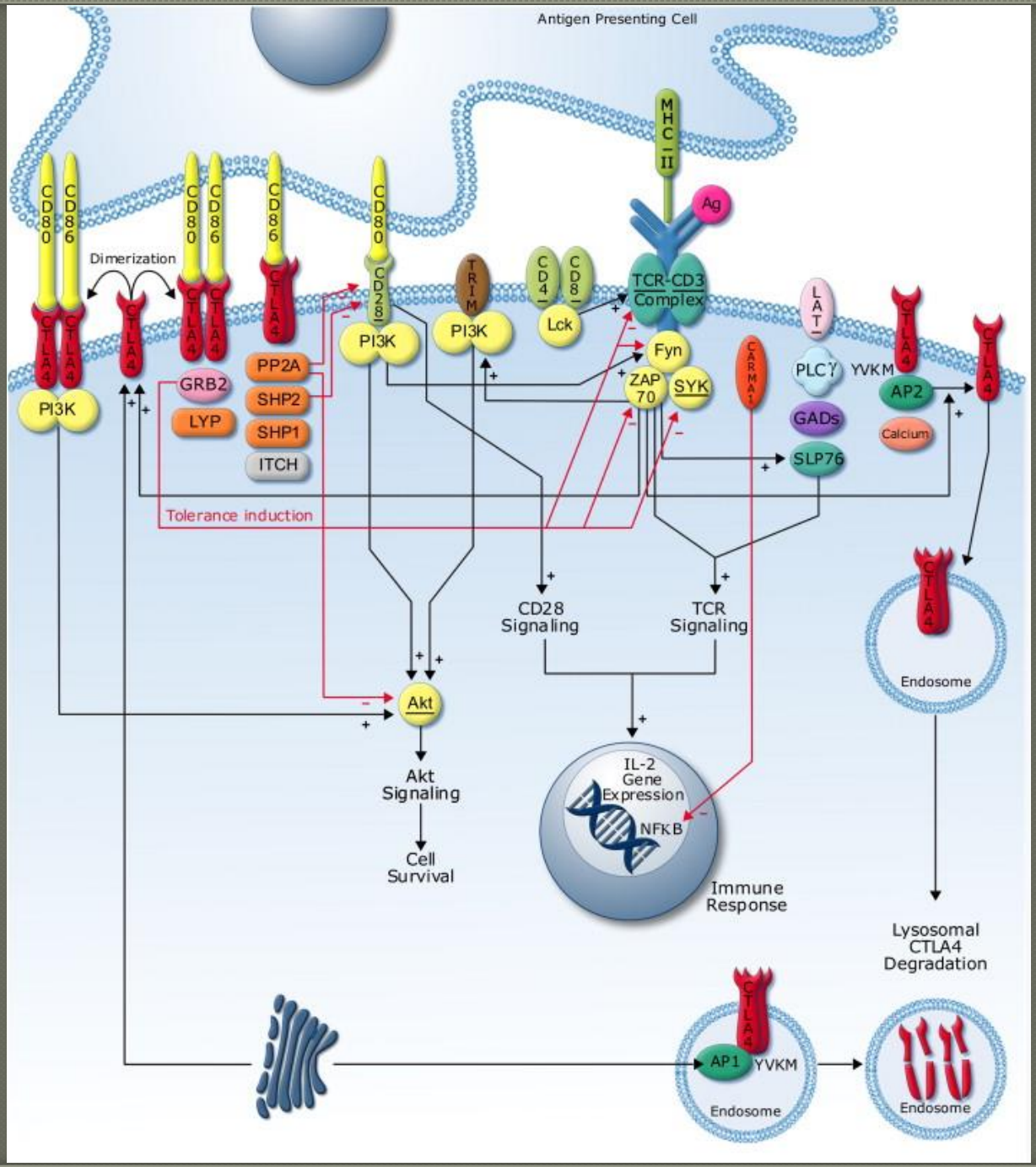
CD4/CD8 arány: fejnyaki laphámrák immunterápiájakor

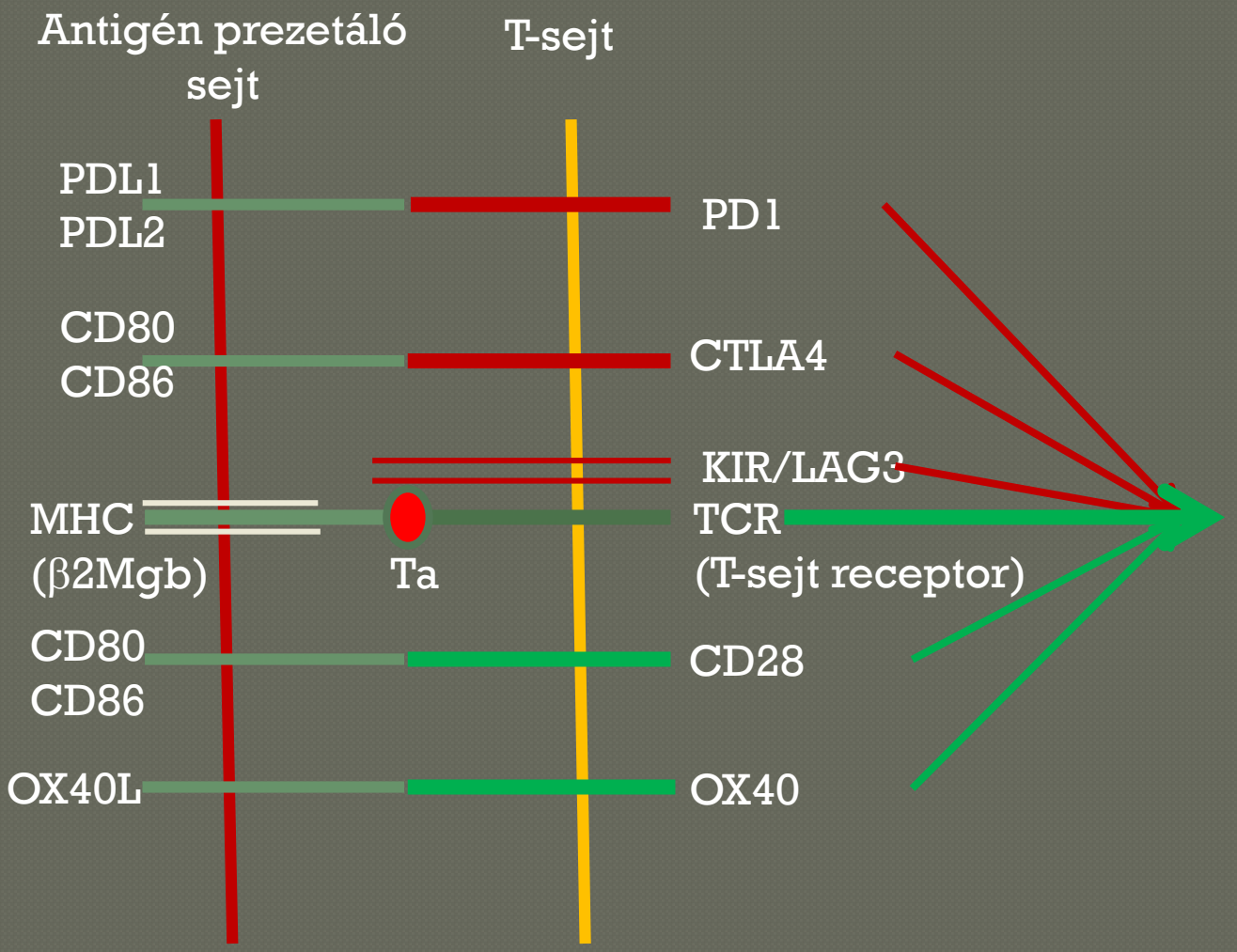


Tímár et al. J Clin Oncol23:3421, 2005

Nem működik az immunitás

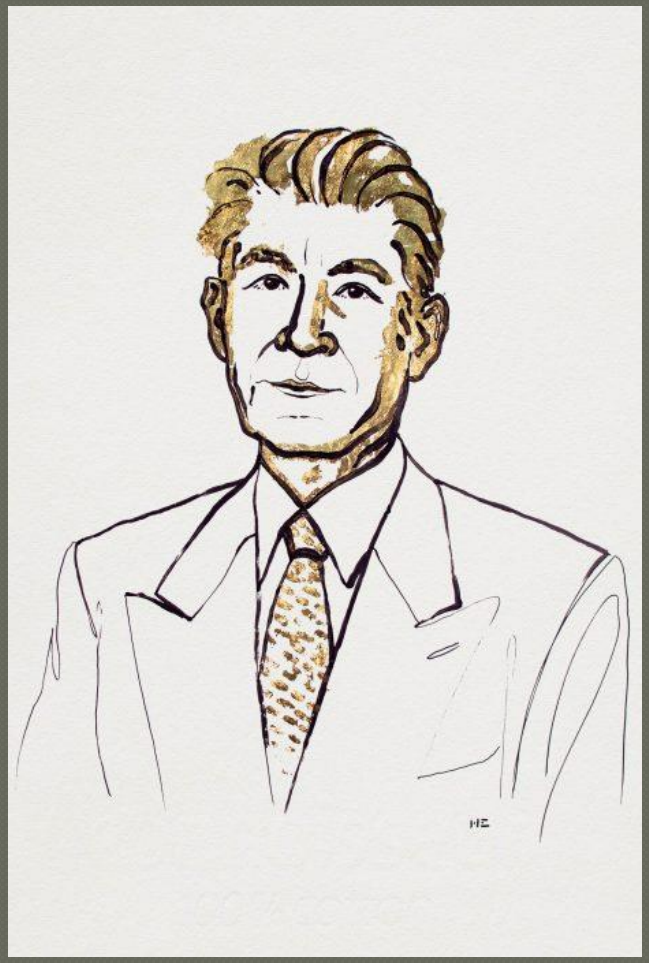
- Tumor antigén probléma
- Antigén prezentáló sejt probléma (DC)
- Antigén specifikus T sejt probléma
- Tumor mikrokörnyezeti probléma:
- VEGF termelés gyakori ok /hipoxia
- PDL1 expresszió a tumoron
- PDL1 expresszió a TIL sejteken a tumorsejt miatt (PDL1- tumorban)
- CTLA4 aktivitás a tumor miatt (PDL1 független…)

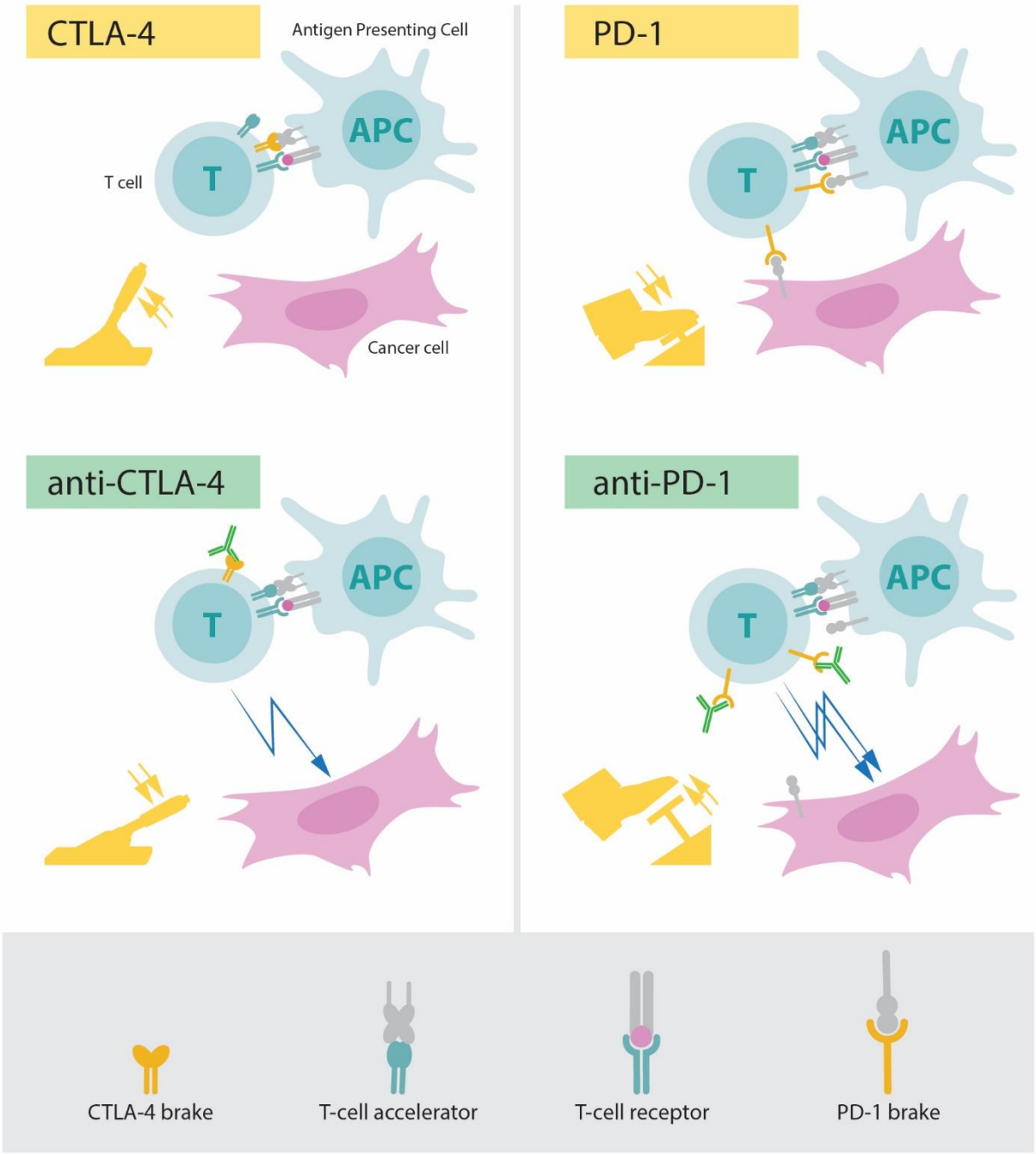

Antigen Presenting Cell
MHC-II
Ag
TCR-CD3 Complex
CD4
CD8
Lck
Fyn
ZAP 70
SYK
LAT
PLCγ
YVKM
GADs
SLP76
CARMA1
AP2
Calcium
CD80
CD86
CTLA4
Dimerization
PI3K
GRB2
LYP
PP2A
SHP2
SHP1
ITCH
CD28
TRIM
Tolerance induction
CD28 Signaling
TCR Signaling
Endosome
Akt
Akt Signaling
Cell Survival
IL-2 Gene Expression
NFKB
Immune Response
Lysosomal CTLA4 Degradation
AP1


Antigén prezetáló sejt
T-sejt
PDL1
PDL2
PD1
CD80
CD86
CTLA4
KIR/LAG3
MHC
(β2Mgb)
Ta
TCR
(T-sejt receptor)
CD80
CD86
CD28
OX40L
OX40

1. ábra

JP Allison és T Honjo




CTLA-4
Antigen Presenting Cell
APC
T
T cell
Cancer cell
PD-1
APC
T
anti-CTLA-4
APC
T
anti-PD-1
APC
T
CTLA-4 brake
T-cell accelerator
T-cell receptor
PD-1 brake

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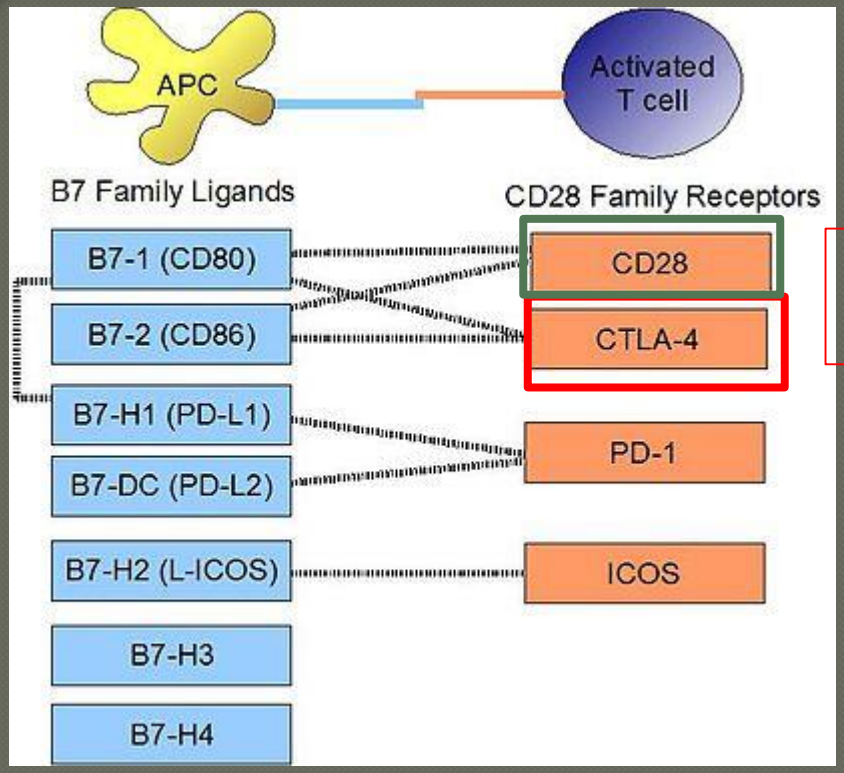
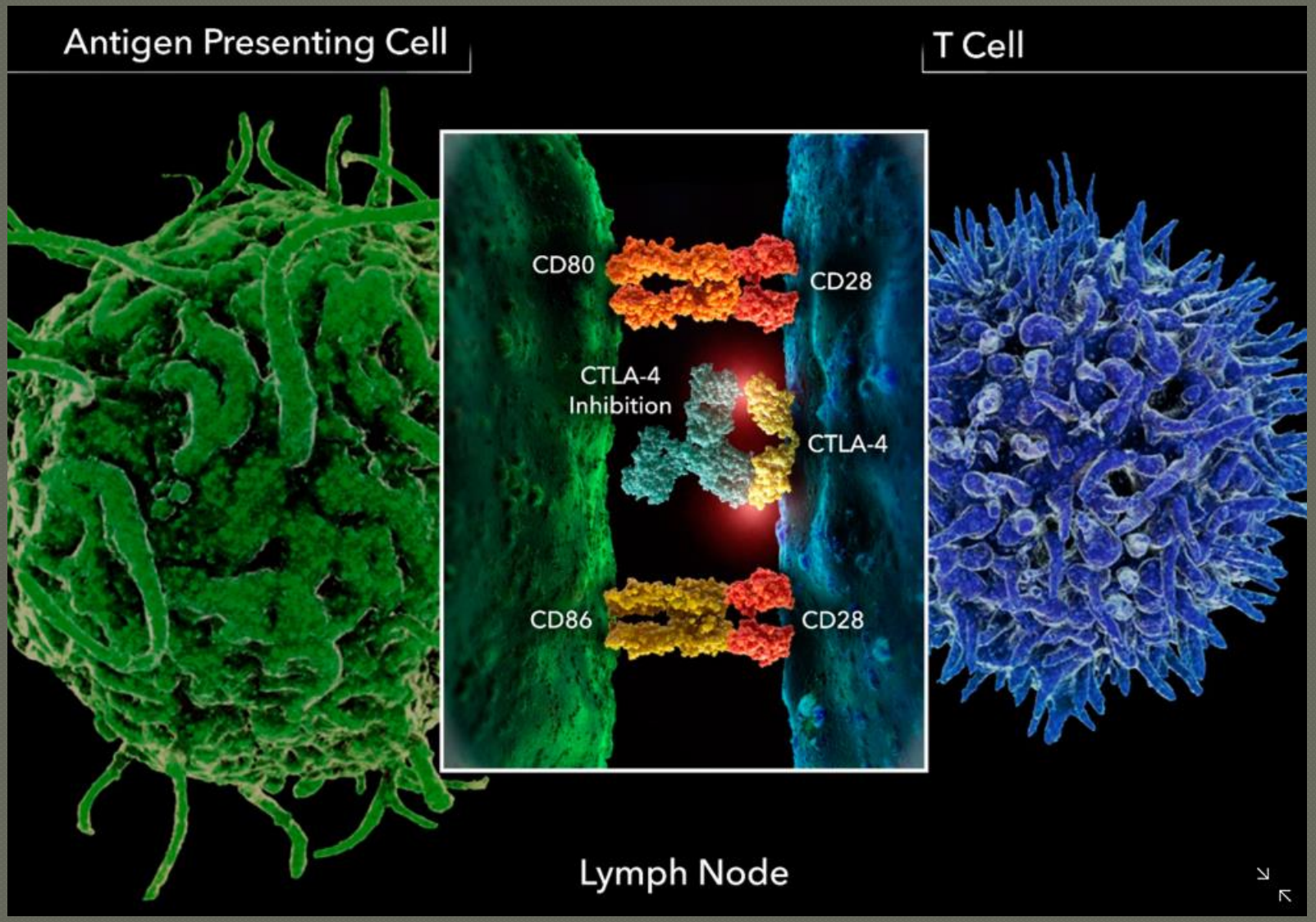


ICSt
ICG

CTLA-4/CD152

T-sejt receptor
TM/Ig superfam
Chr2q33
Autoimm/mutáció

PP2A
SHP2/3 kötő
ZAP-70 inhibitor
ADC-blokkoló


Antigen Presenting Cell
T Cell
CD80
CD28
CTLA-4
Inhibition
CTLA-4
CD86
CD28
Lymph Node

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- VEGF termelés gyakori ok
- PDL1 expresszió a tumoron
- PDL1 expresszió a TIL sejteken a tumorsejt miatt (PDL1- tumorban)
- PD1 aktivitás a TIL-en
- **T effektor blokkolás**
- CTLA4 aktivitás a tumor miatt (PDL1 független…)

PD1/CD279

Chr 2 (mint a CTLA-4)

Ig superfam

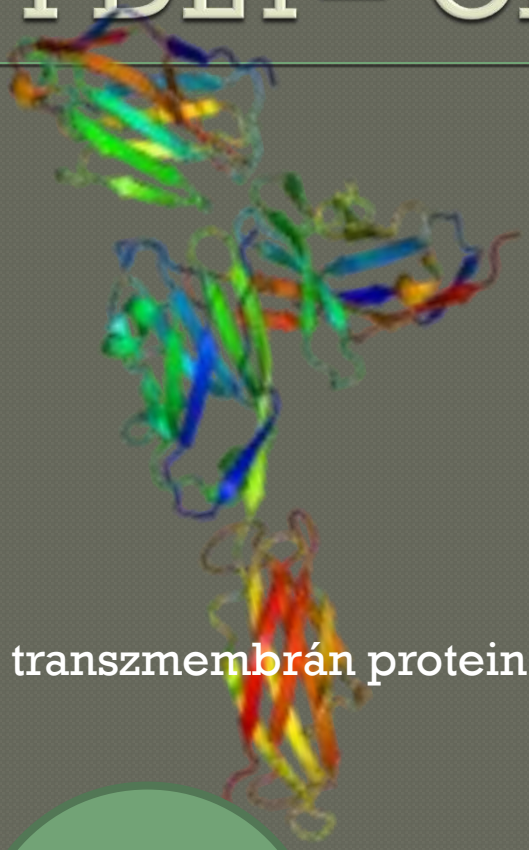
T-sejt receptor

SHP-kötő

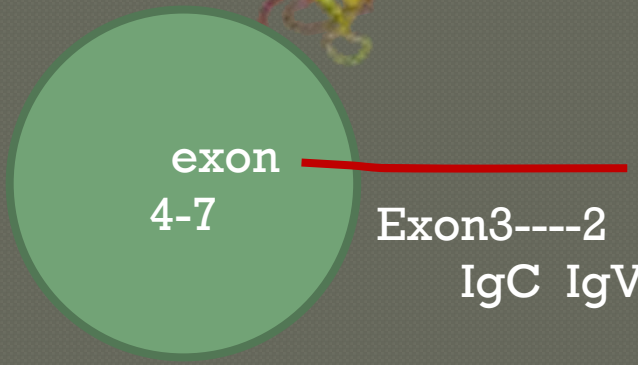
PKC teta inhibitor

ZAP-70 jelpálya blokkoló

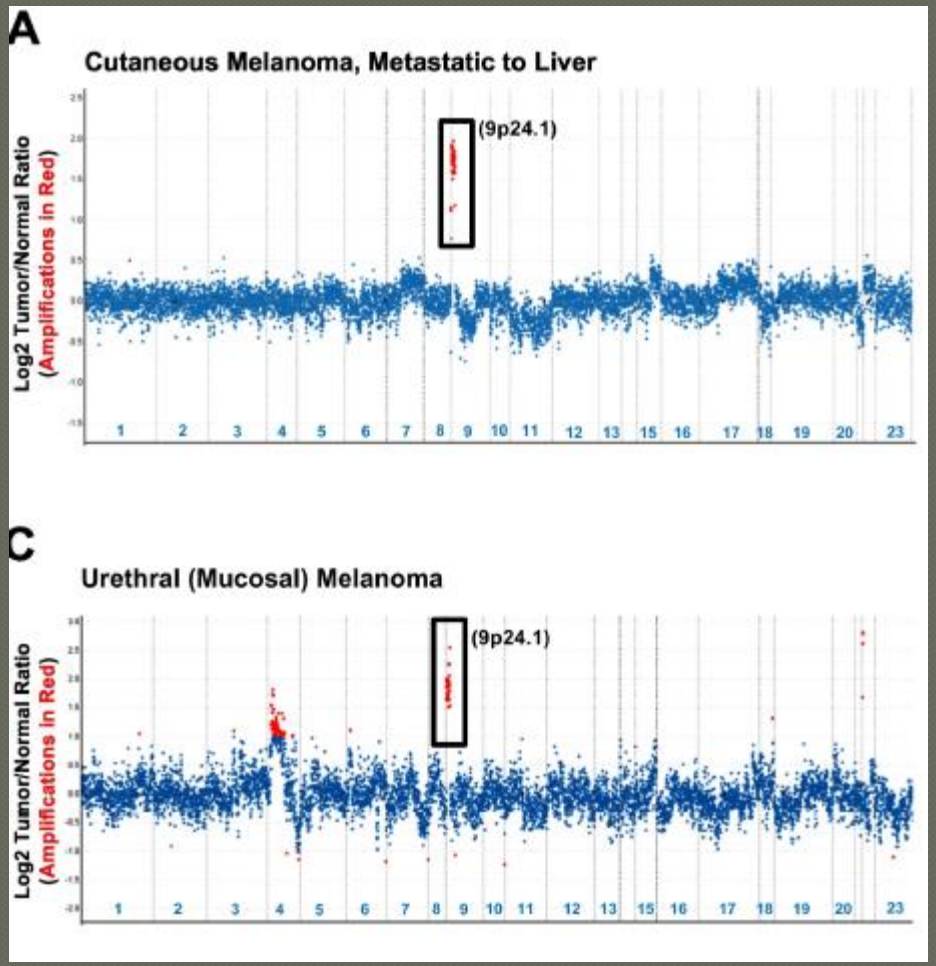
PDL1= CD274/B7H1



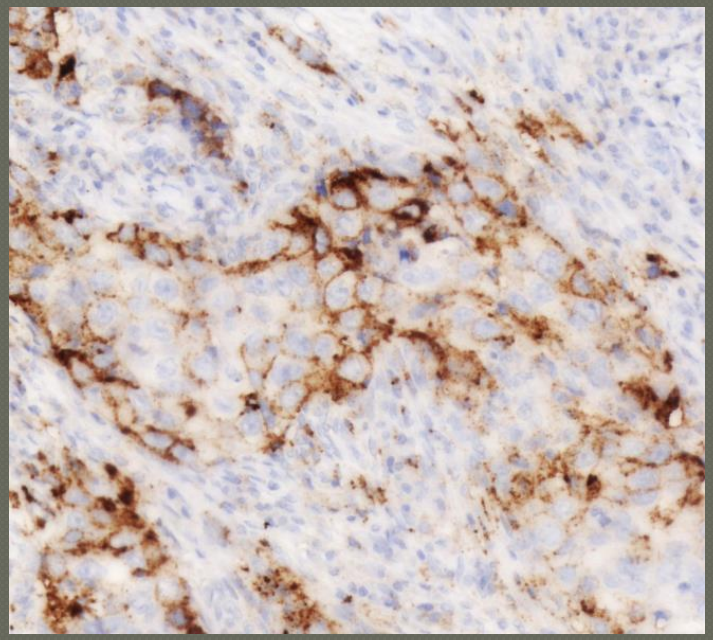
PDL1: 290 AS hosszú transzmembrán protein (9kr.)



PDL1 fehérje expresszió a daganatban



PDL1 gén amplifikáció (1-10%)



IHC

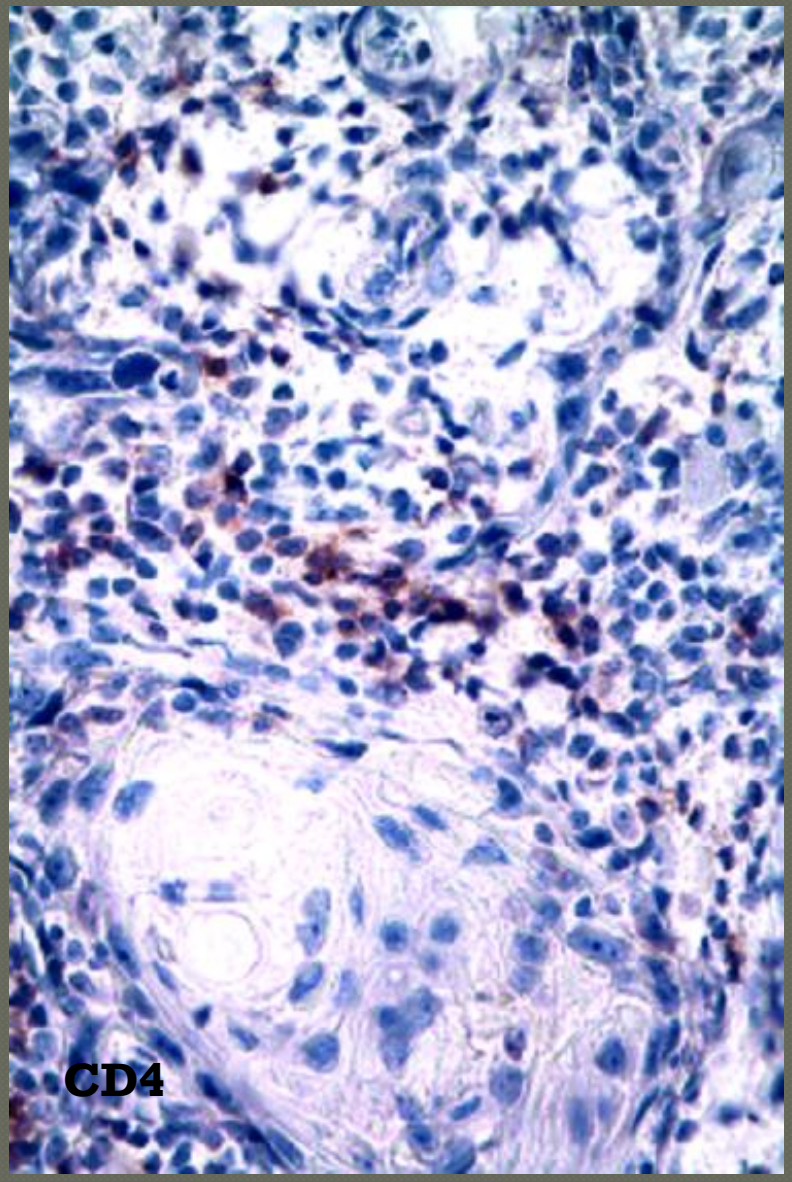
Prediktív Biomarkerek

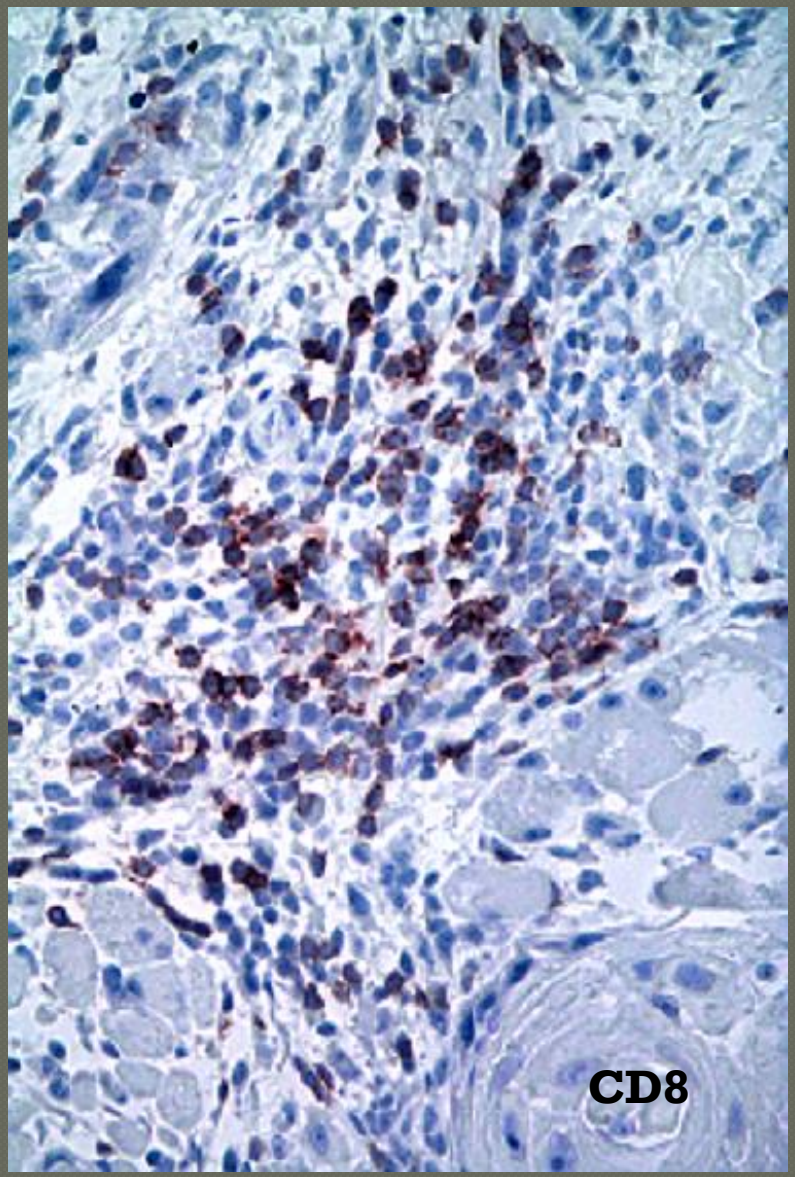
- Anti-CTLA4 terápia esetében nincsen beválogatási biomarker

- Anti-PD1/PDL1 terápia esetében:
- Egyes törzskönyvezett gyógyszerek esetében a daganat és/vagy a TIL PDL1 pozitivitása
- >1%, >50% határértékekkel…….

- Mindkét terápia esetében a **„Teljes Mutációs Terhelés”** független pozitív prediktív tényező

T-sejt vagy CD8 cytoxikus T sejt?





Melanoma kezelés kombinációban

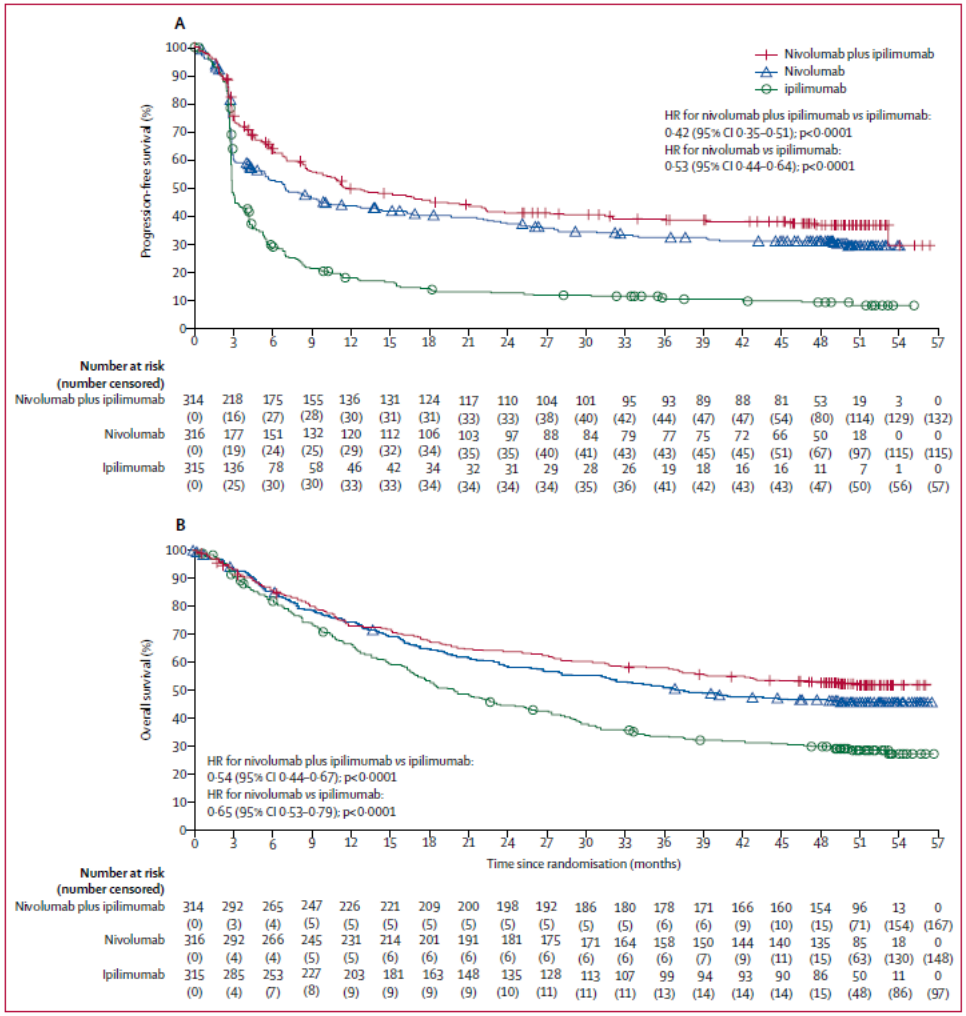


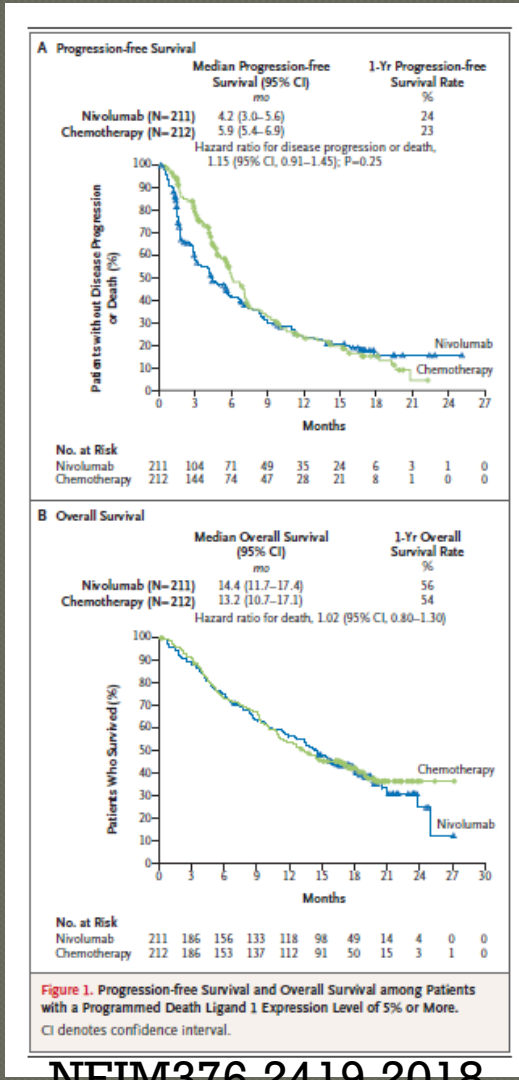
Figure 2: **Kaplan-Meier estimates of (A) progression-free survival and (B) overall survival**
HR=hazard ratio.

www.thelancet.com/oncology **Published online October 22, 2018 http://dx.doi.org/10.1016/S1470-2045(18)30700-9**

Anti-CTLA-4+anti-PD1

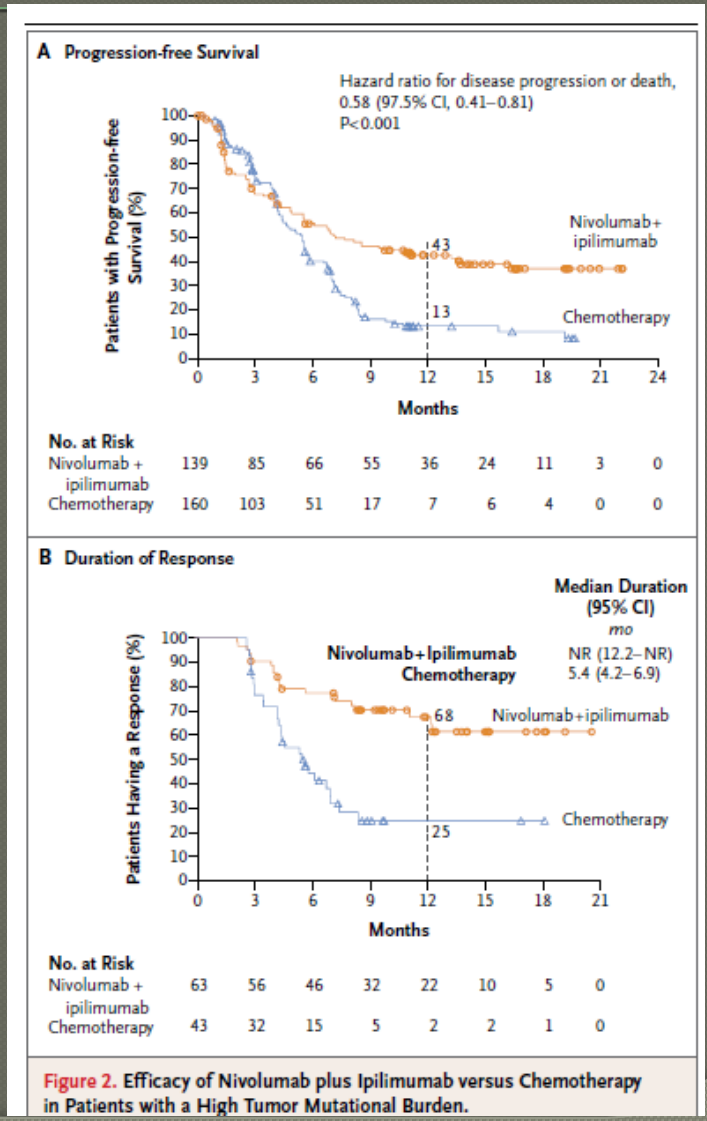
Lancet 2018 epub

Ipilimumab+Nivo tüdőrákban



NEJM376,2419,2018

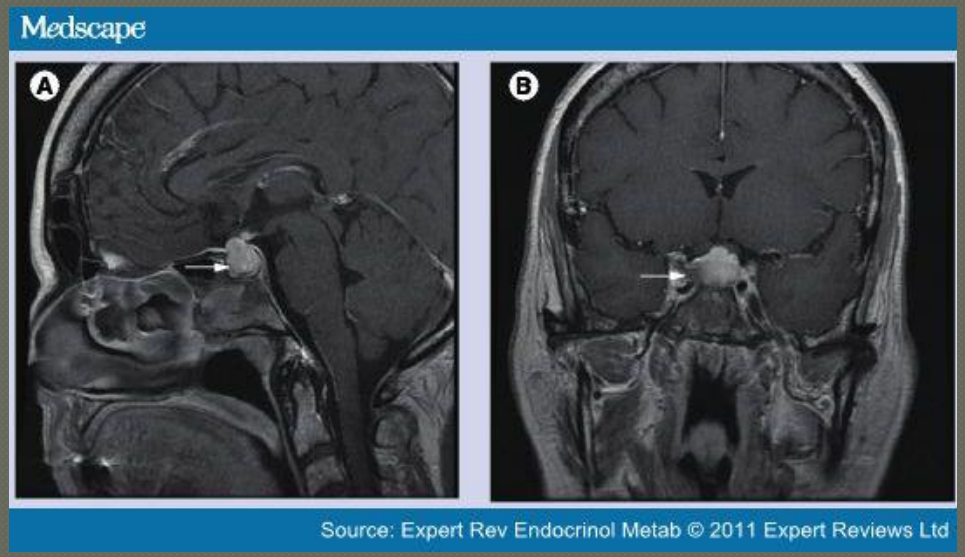
NEJM378:2093,2018



anti-CTLA4, anti-PD1 és anti-PDL1 antitest immunterápiák immunológiai mellékhatásai:

autoimmun gyulladások

oka: főleg az első generációs IgG2 típusú antitestek okozzák (ADCC)



- **Hypophysitis**
- **Hepatitis**
- **Colitis**
- **Pneumonitis**

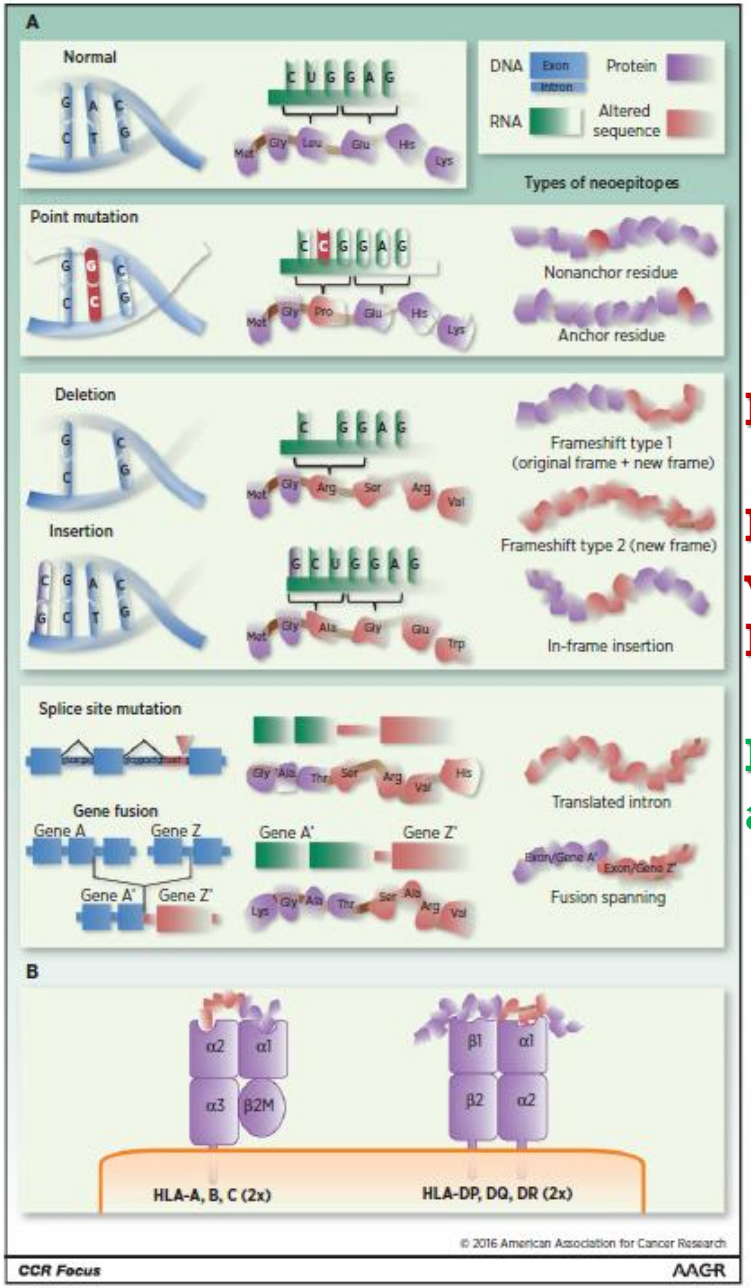


Figure 1.
Types of genomic mutations and T-cell neoepitopes resulting from them. A, nonsynonymous point mutations in the coding sequence of a gene alter a single amino acid. By creating an anchor residue or changing the TCR-binding properties (nonanchor residue), a neoepitope may be formed. Insertion of three or a multiple of 3 nucleotides in frame introduces novel amino acids into the protein sequence, potentially generating a T-cell response. Insertion or deletions of exonic nucleotides, mutations in intronic regions that affect RNA splicing, or gene fusions (altered genes after fusion marked with an apostrophe) can cause inclusion of introns into mRNA and a shift of the open reading frame. Resulting T-cell epitopes may be in part (type 1) or fully (type 2) comprised of an altered amino acid sequence. In addition, T cells may target neoepitopes formed by translated introns or fusion of distant exons and genes as a result of splice site mutations and gene fusion. B, human cells express up to 6 different MHC class I (2 alleles of HLA-A, -B, and -C) and class II molecules (2 alleles of HLA-DP, -DQ, and -DR), thereby presenting neoepitopes to T cells.

Problémák:

MHC-I génvesztés vagy B2mikroglobulin m

Nincsen antigénfelismerés

Türeci Ö et al. CCR 22:1885,2016

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Tumor mutációs terheltség (TMB)

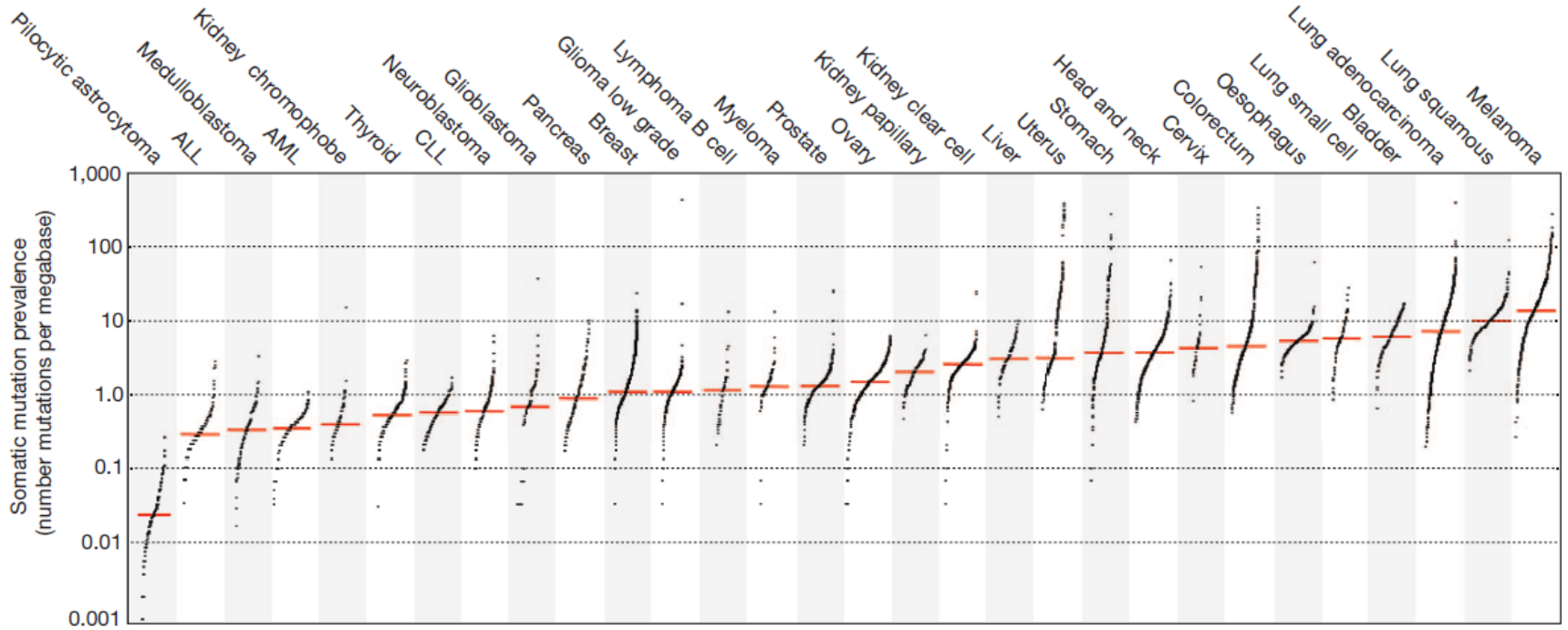


Figure 1 | The prevalence of somatic mutations across human cancer types. Every dot represents a sample whereas the red horizontal lines are the median numbers of mutations in the respective cancer types. The vertical axis (log scaled) shows the number of mutations per megabase whereas the different cancer types are ordered on the horizontal axis based on their median numbers of somatic mutations. We thank G. Getz and colleagues for the design of this figure[26]. ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; CLL, chronic lymphocytic leukaemia.

DDR gene defects in Lung Cancer

Repair type	DDR genes	Lung Cancer
Homologue repair	BRCA1/2	-
	RAD50	?
	PALB2	?
	FRANCA	?
	ATM	?
	ATR	?
MMR	MLH1	-
	MSH2	-
	MSH6	-
	PMS2	-
Excision repair	**ERCC1/2**	**+**
	POLE	**+**

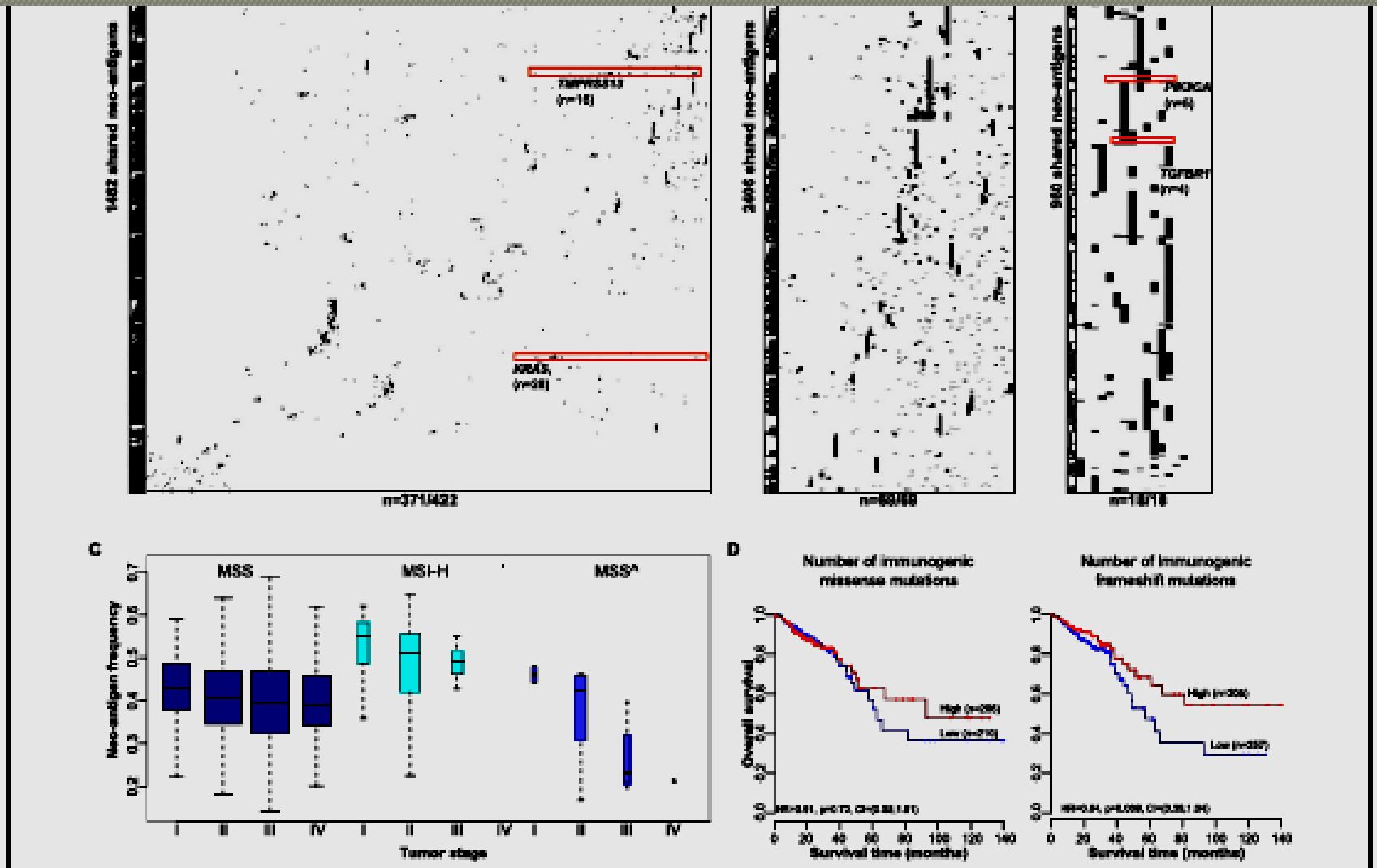


Figure 2 (See legend on next page.)

(See figure on previous page)

Figure 2 CRC antigenome comprising two antigen classes: cancer-germline antigens and neo-antigens. (A) Two-dimensional hierarchical clustering of the expression of cancer-germline antigens calculated from the RNA sequencing data for the three molecular phenotypes (MSS, MSI-H and MSS^). All displayed matrix elements met the threshold as described in Methods. Genes marked in bold were significantly higher expressed in a specific patient group. **(B)** Two-dimensional hierarchical clustering of neo-antigens, that is, identical peptides shared in more than

Mlecnik B et al. Immunity 44:698,2016

MAGE
NYESO
Gp100

.....

neoantigének

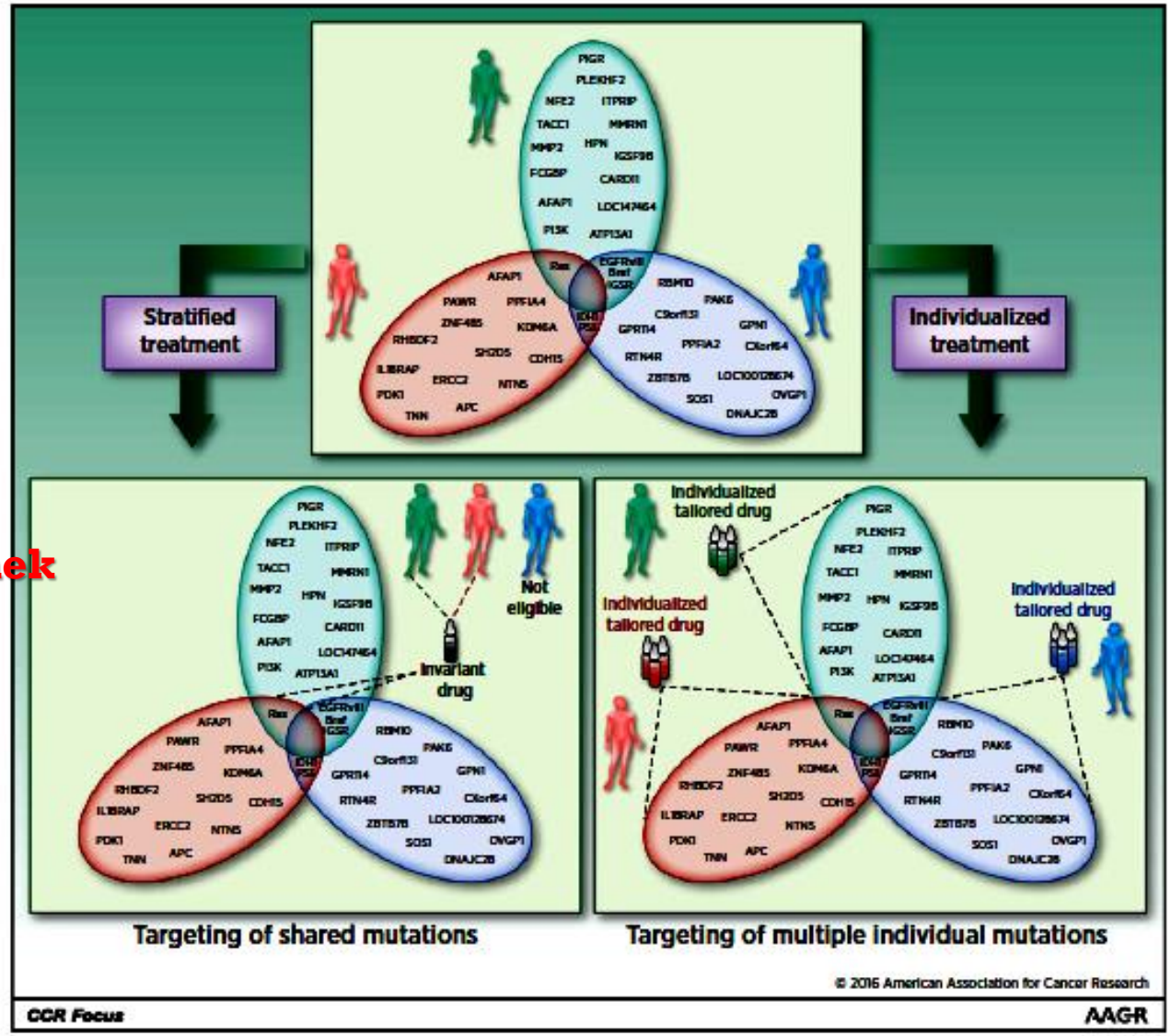
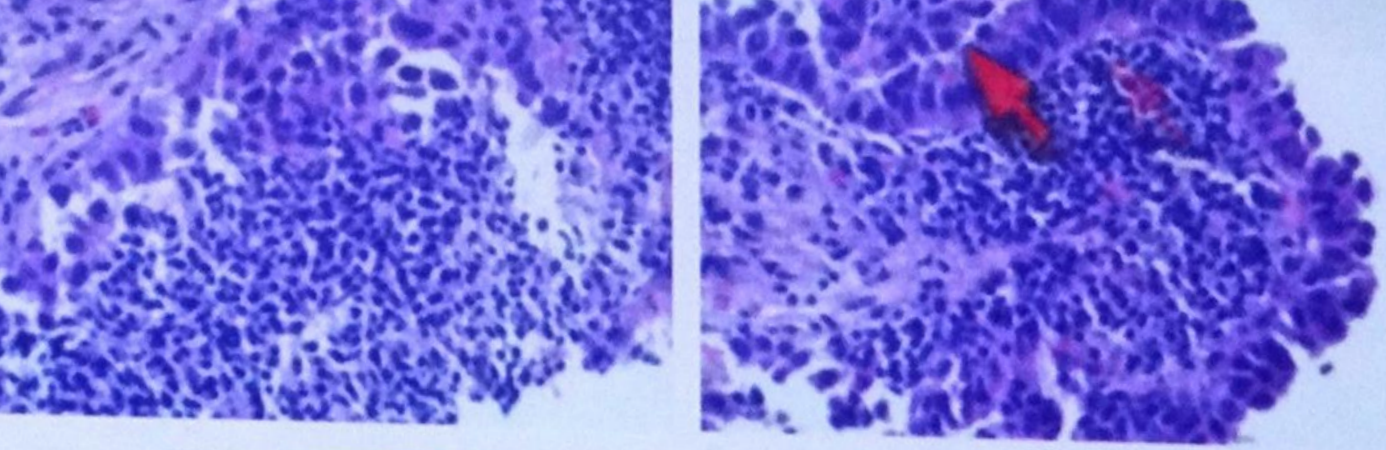
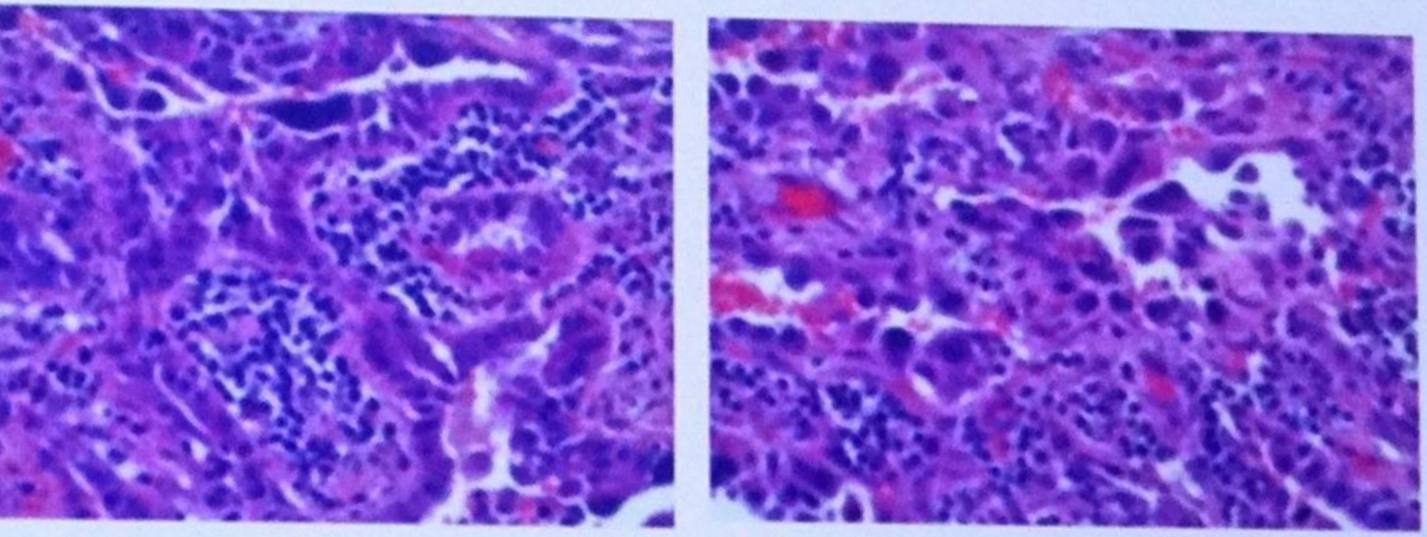


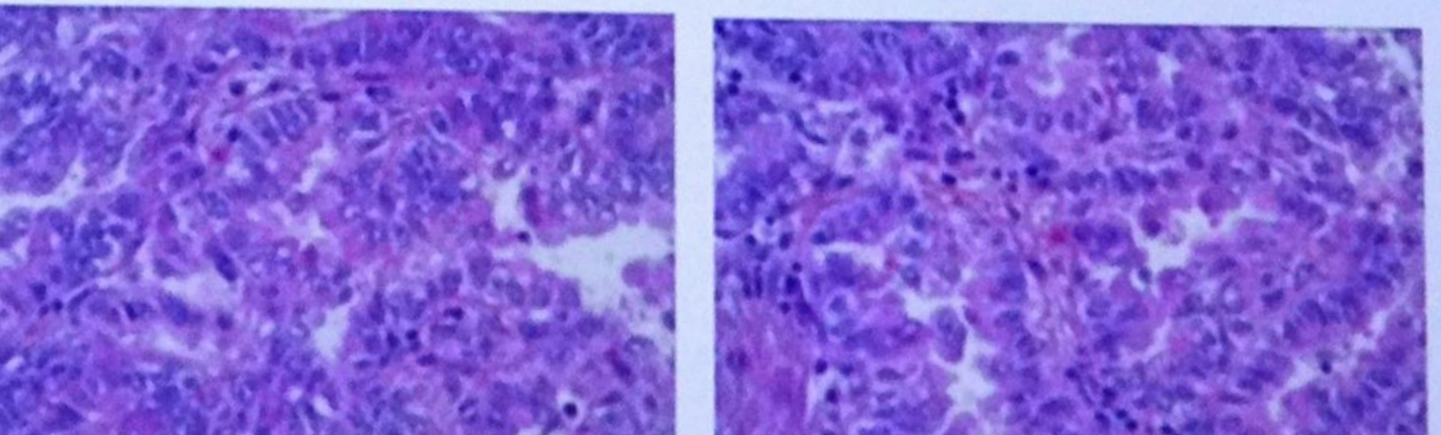
Figure 2.
Stratified versus individualized mutation–based vaccine approaches. As the vast majority of cancer-associated mutations is unique to the individual patient, the common denominator of mutations shared by different patients is small. Stratified approaches are based on one or more vaccine targets shared by a considerable number of patients. Patients are screened for presence of the mutation, and only those individuals carrying the respective mutation are treated with the invariant "off-the-shelf" drug. For an individualized treatment, in contrast, neoepitopes were selected out of the patient's mutanome based on rational criteria deemed to correlate with the induction of strong immune responses. Each and every patient receives an "on-demand" manufactured vaccine.



High TIL



Moderate TI



Low TIL

Dendritikus sejt vaccináció

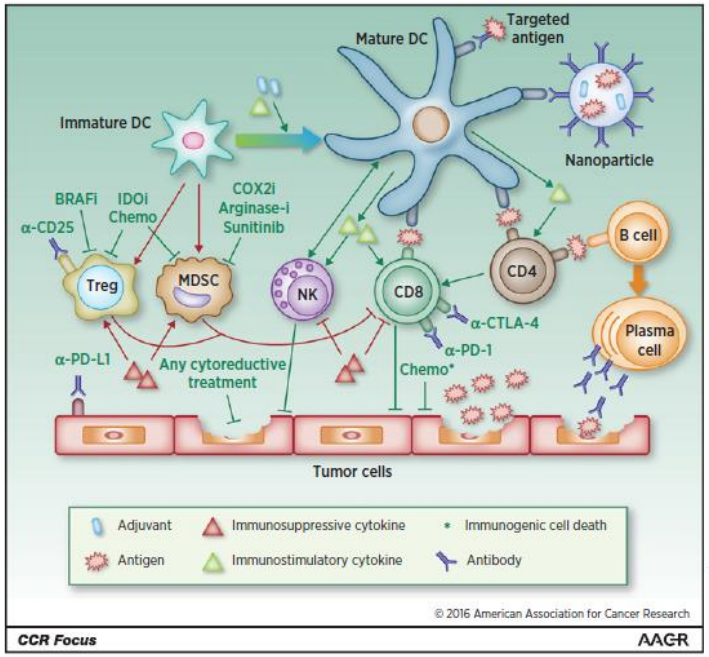


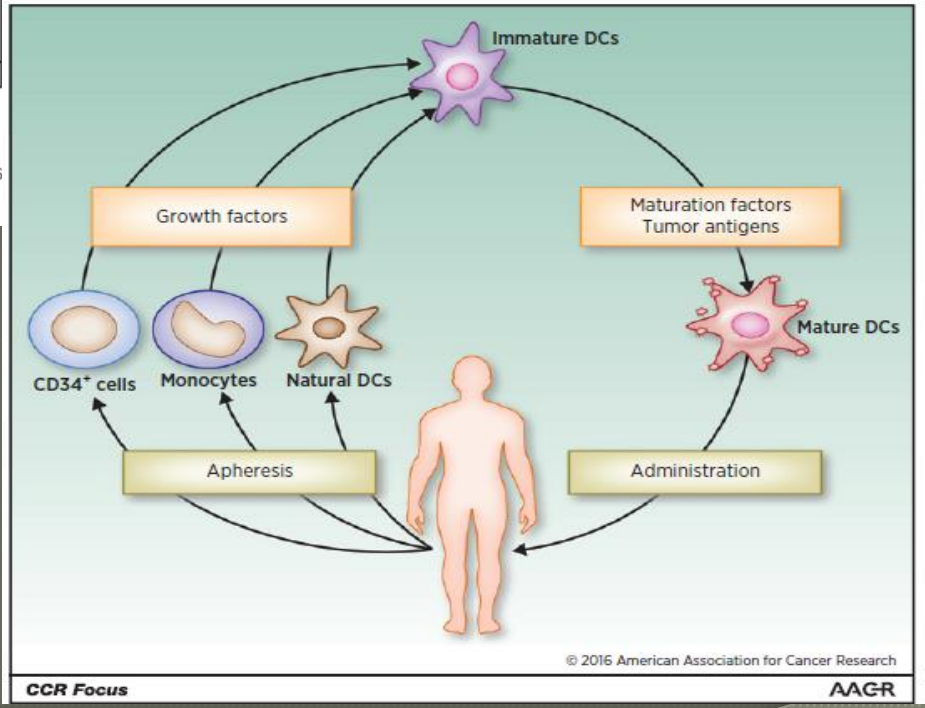
Figure 2.
Interplay between dendritic cells, other immune cells, tumor cells, and therapies. Arrows indicate a stimulatory effect on cell function or a process, and blockers indicate an inhibitory effect on cell function or a process. The arrows/blockers shown in red indicate interactions that favor tumor growth. Arrows/blockers shown in green indicate interactions that favor tumor killing, for example, sunitinib inhibits (blocker) MDSCs and by blocking MDSCs this favors tumor killing (green). To promote clarity, not all known interactions are depicted in this figure. αCD25, anti-CD25 antibody; αCTLA-4, anti-CTLA-4 antibody; αPD-1, anti-PD-1 antibody; αPD-L1, anti-PD-L1 antibody; Arginase-i, arginase inhibitor; BRAFi, BRAF inihibitor; CD4, $CD4^+$ T-helper cell; CD8, cytotoxic $CD8^+$ T cell; Chemo, chemotherapy; IDOi, indoleamine 2,3-dioxygenase inhibitor; MDSC, myeloid-derived suppressor cell; Treg, regulatory T cell.

www.aacrjournals.org Clin Cancer Res; 22(8) April 15, 2016

Bol KF et al. CCR 22:1897,2016

<u>Sipuleucel (Dendreon): PRCA</u>

Dendritikus sejt izolálás
PAP protein aktiválás (+GMCSF)
Re-infusion



Adaptív T sejt terápia vagy génmódosított T sejt terápia

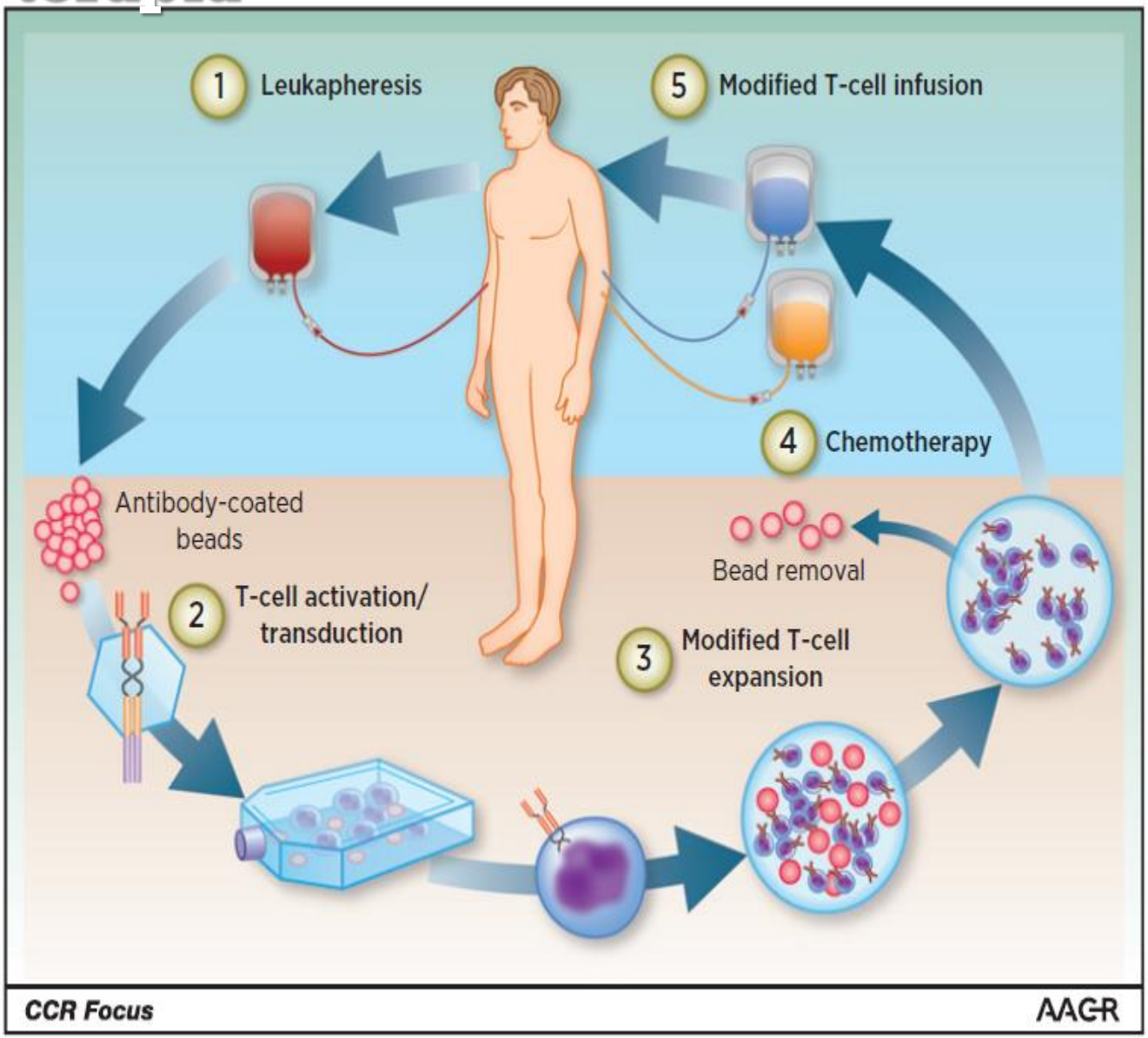


Figure 1.
Overview of CAR T-cell therapy in the clinic. A patient's T cells are harvested through leukapheresis, followed by T-cell activation on antibody-coated beads serving as artificial dendritic cells. The activated T cells are then genetically reprogrammed *ex vivo* by transduction with a construct encoding the CAR, and the CAR T cells are further expanded *ex vivo*. When the CAR T-cell product has been prepared and has passed all quality control testing, the patient receives lymphodepleting chemotherapy and CAR T-cell infusion. © Novartis Pharmaceuticals.