IMUNOLOGIA TUMORAL E IMUNOTERAPIAS

Introdução, com perspectiva histórica

Inflamação como mecanismo de carcinogênese

Antígenos tumorais e respostas imunes contra tumores

Imunoedição

Mecanismos de escape

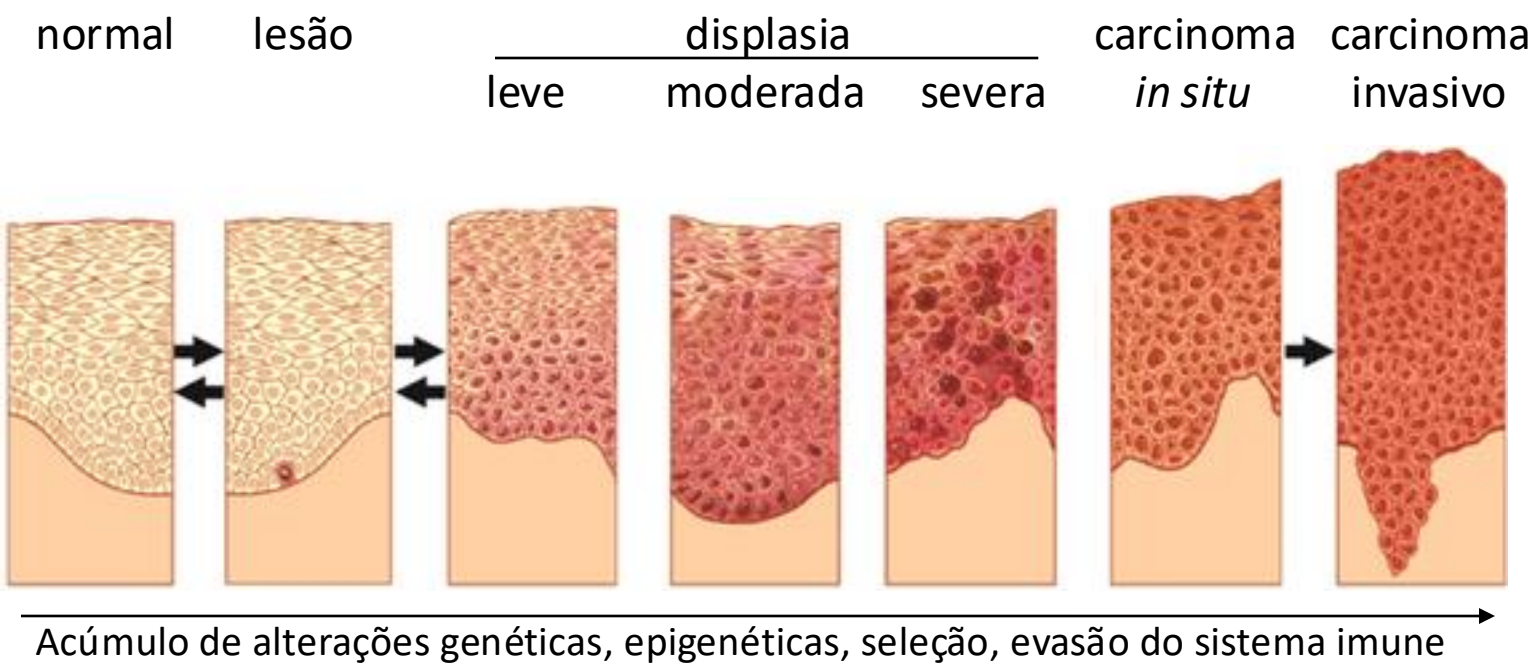
Efeito de respostas crônicas

Imunoterapias

Introdução, com perspectiva histórica

CÂNCER

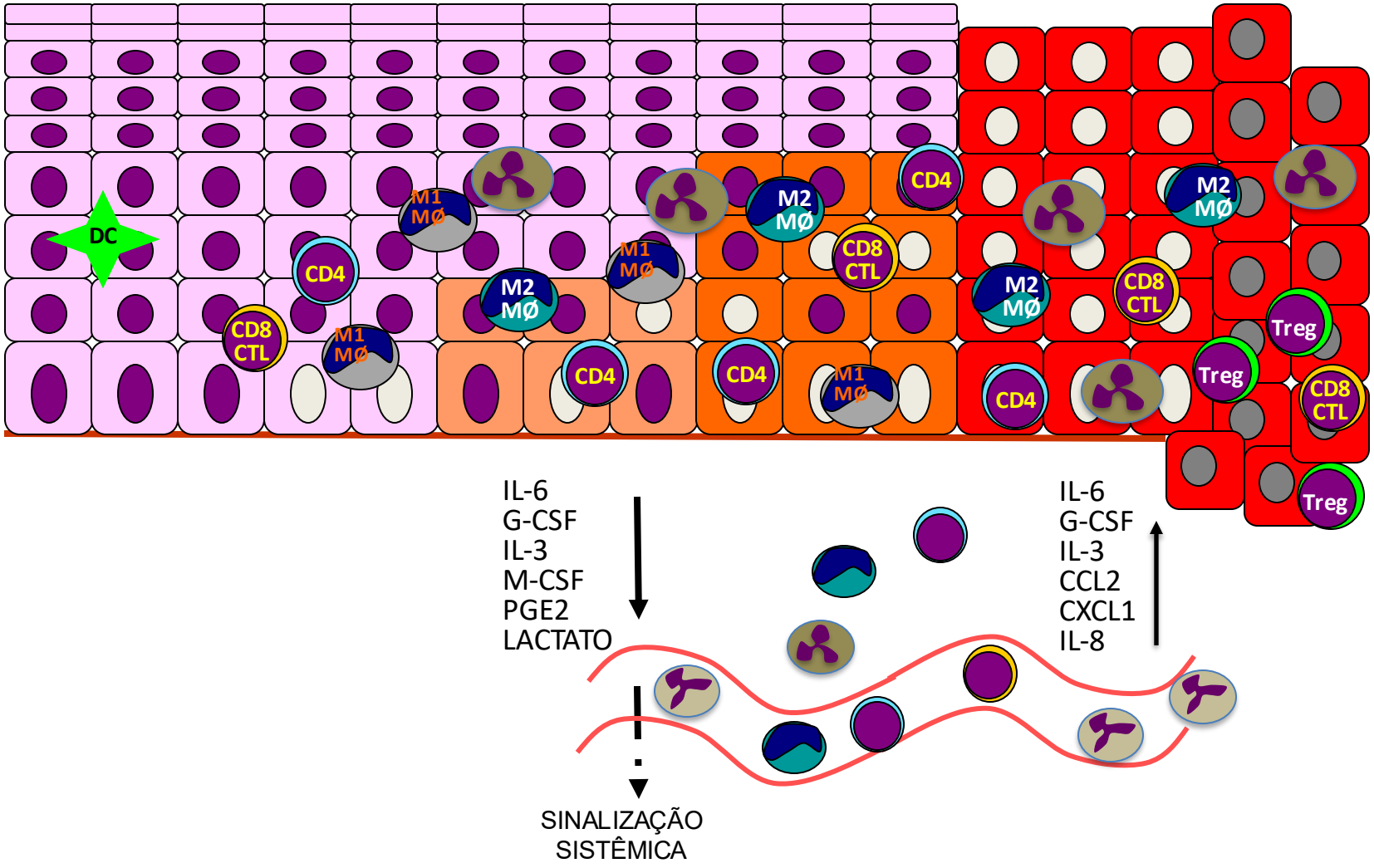
Câncer é uma coleção de doenças que podem acontecer em praticamente qualquer tecido humano, onde células ganham a capacidade de proliferação descontrolada e capacidade de invasão de outros tecidos. (NCI)



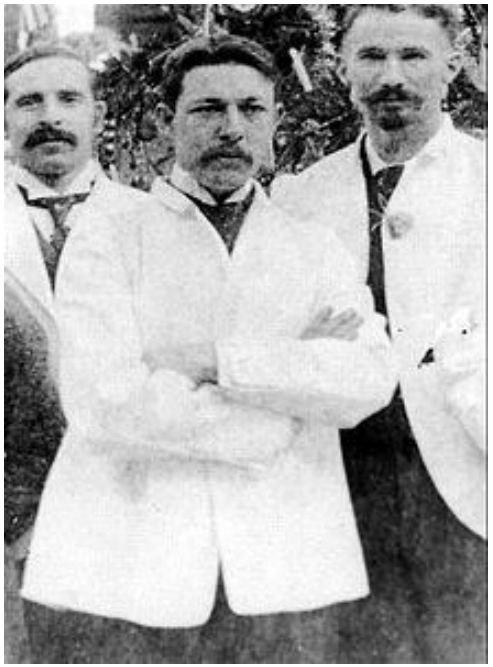
"Tumors destroy man in a unique and appalling way, as flesh of his own flesh which has somehow been rendered proliferative, rampant, predatory and ungovernable. They are the most concrete and formidable of human maladies, yet despite more than 70 years of experimental study they remain the least understood."

Francis Peyton Rous, Nobel lecture 1966.

MICROAMBIENTE TUMORAL

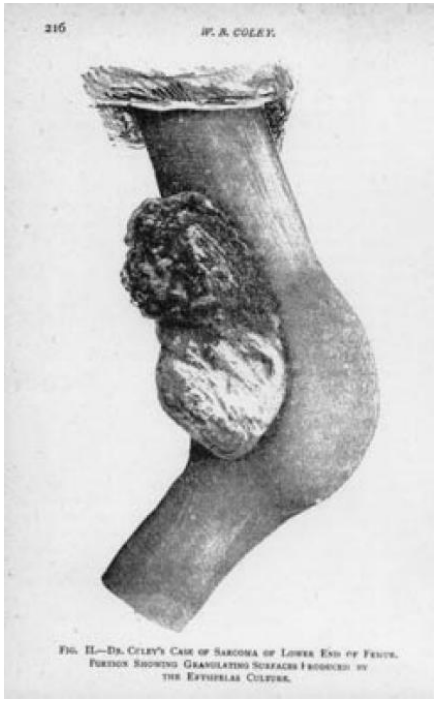


PERSPECTIVA HISTÓRICA



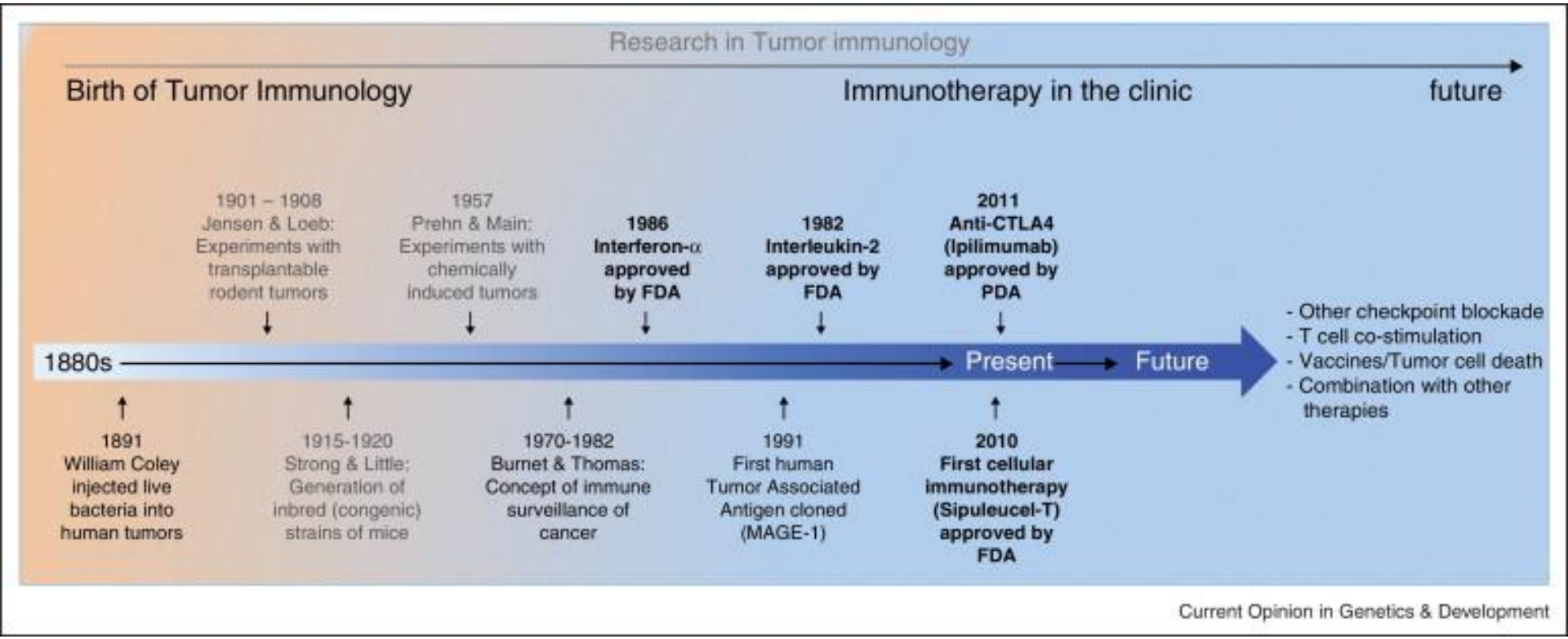
William Coley
MSKCC – NY

Descoberta de caso de paciente com sarcoma de "round cells", com caso grave de erisipela, que eliminou o tumor

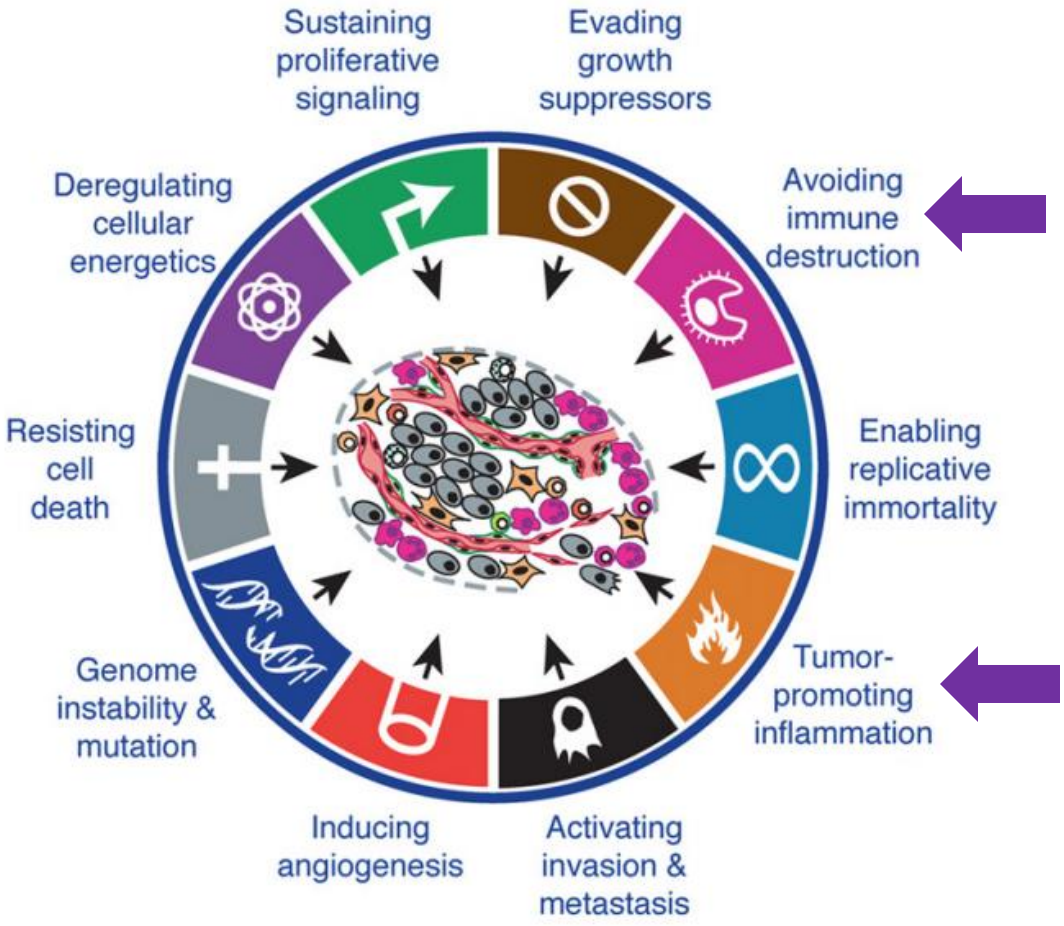


1891 – tratamento de pacientes com Sarcoma, com inoculação de *Streptococcus pyogenes* (Culturas cedidas por Kock) nos tumores

PERSPECTIVA HISTÓRICA



THE HALLMARKS OF CANCER



Hanahan & Weinberg, 2011

MECANISMOS DE CARCINOGÊNESE

DIRETOS

Mutação pontual

ganho ou perda de função do produto

alteração da atividade da região promotora

Deleção

perda de fragmentos de genes supressores de tumor, de regiões reguladoras;

Inserção

região promotora forte a montante de proto-oncogene

Translocação

geração de novo produto com atividade alterada, ex. Brc/Abl

Alterações epigenéticas

INDIRETOS

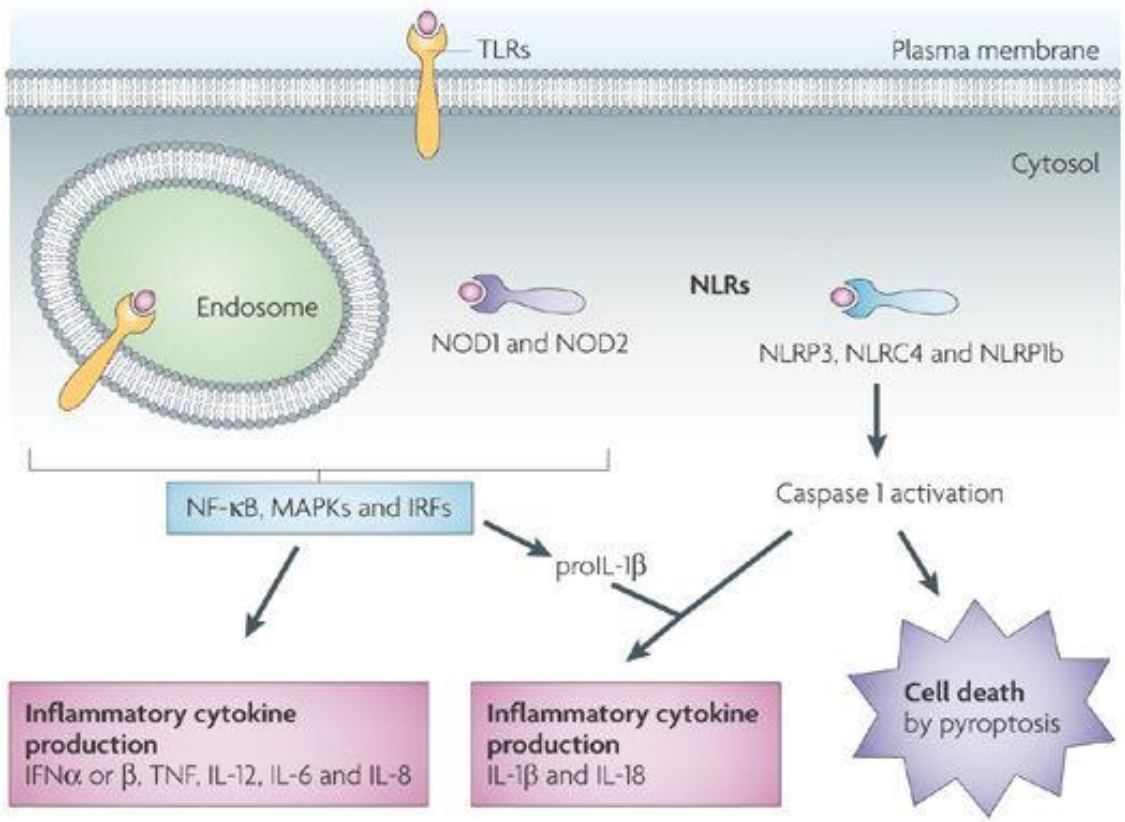
Inflamação causando estresse oxidativo – mutação

Inflamação levando à produção de citocinas e fatores de crescimento

Angiogênese mediada por células inflamatórias

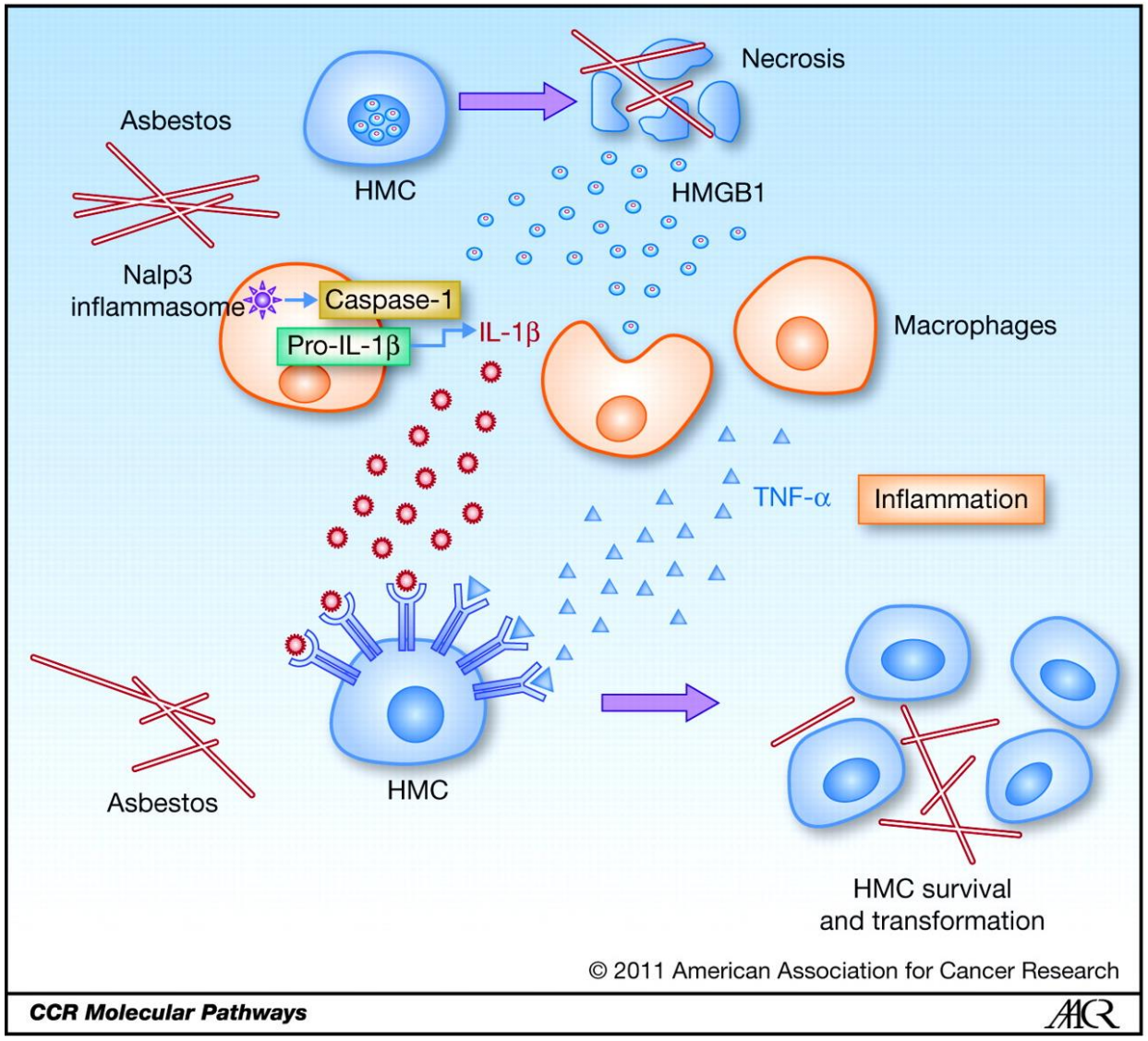
INFLAMAÇÃO COMO INICIADOR OU PROMOTOR DE CARCINOGÊNSE

PIROPTOSE E INFLAMASSOMO

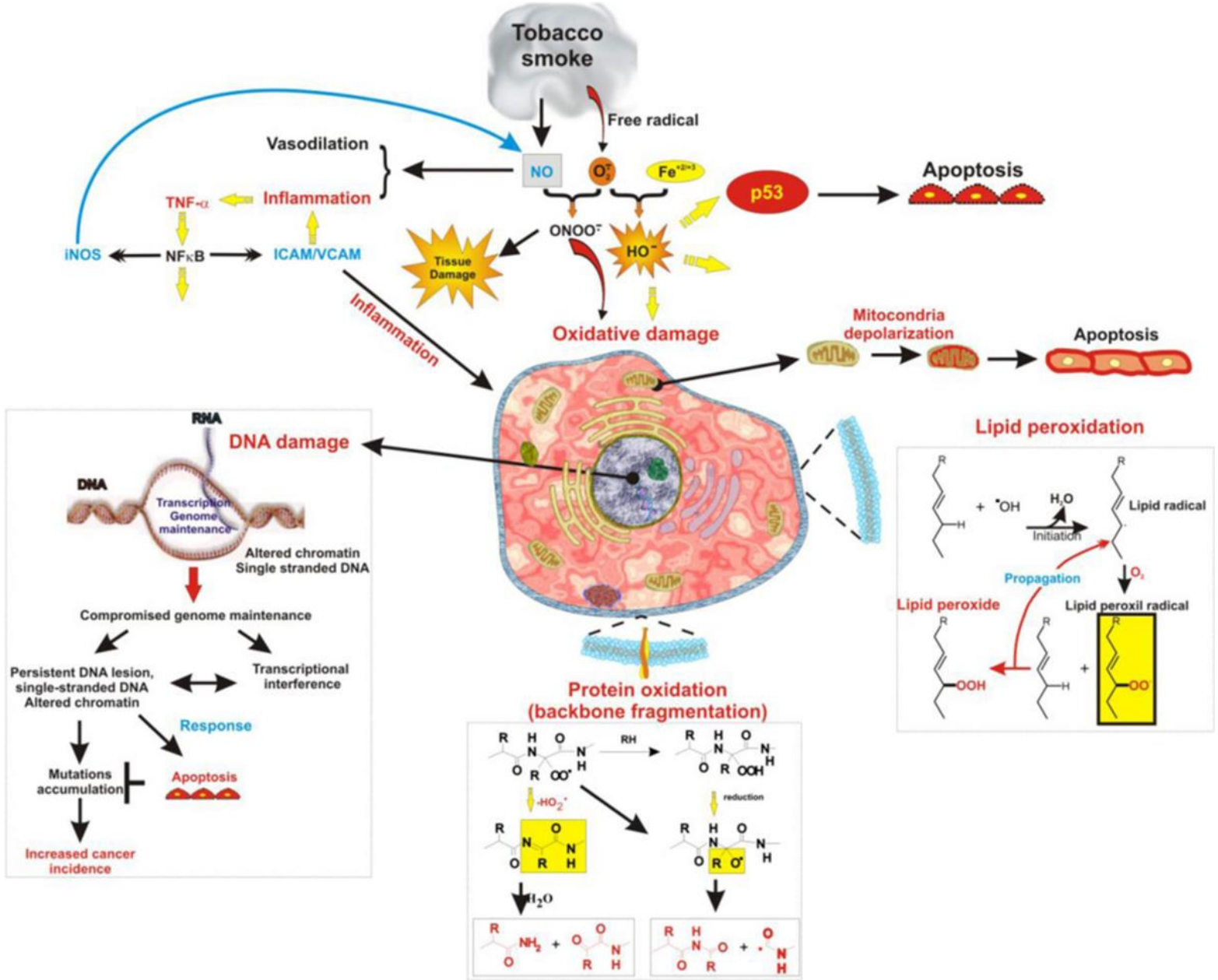


Pyroptosis: host cell death and inflammation
Tessa Bergsbaken, Susan L. Fink & Brad T. Cookson
Nature Reviews Microbiology 7, 99-109 (February 2009)

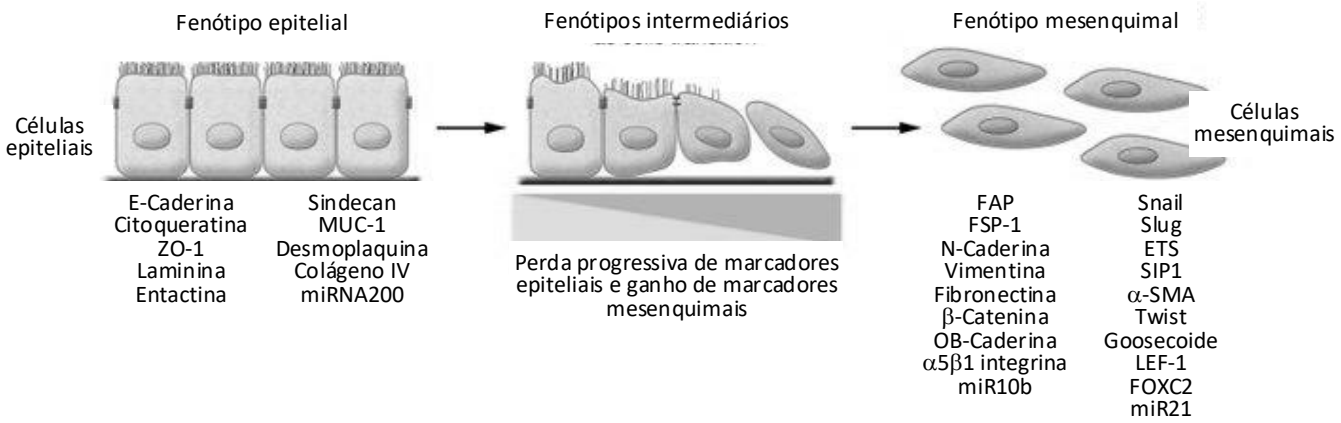
ASBESTOS E MESOTELIOMA

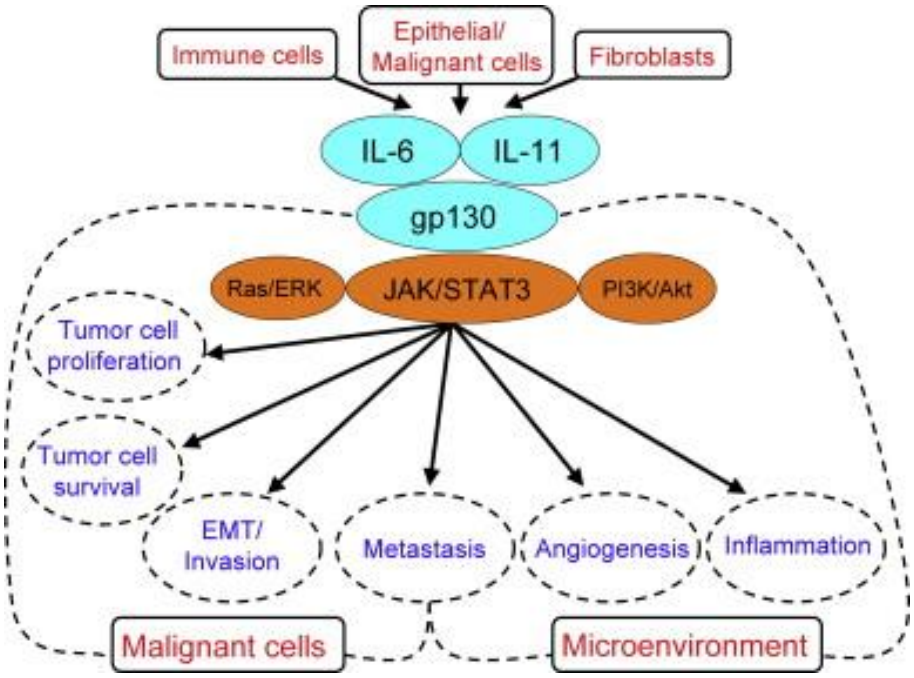


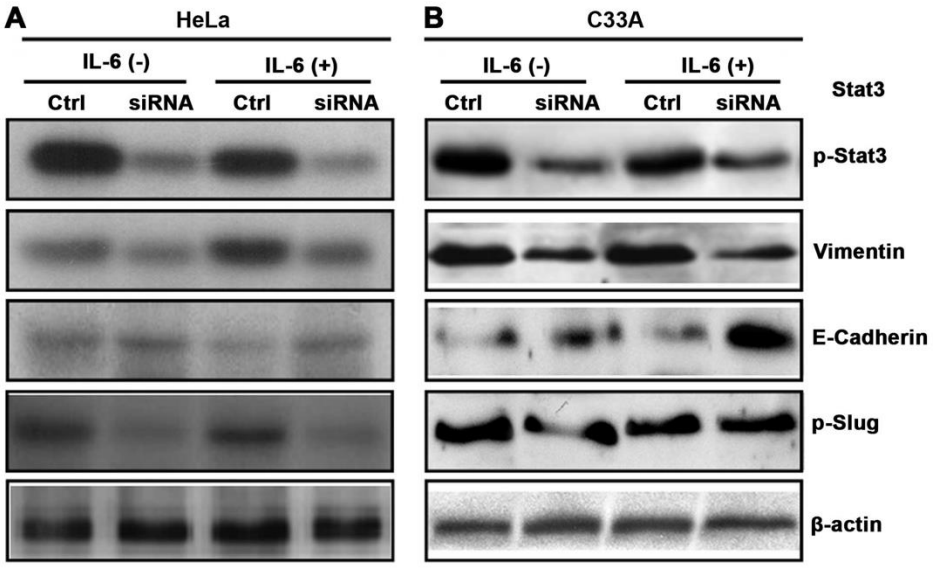
ESTRESSE OXIDATIVO E INFLAMAÇÃO



IL-6/STAT3, INFLAMAÇÃO E TEM (transição epitélio-mesênquima)

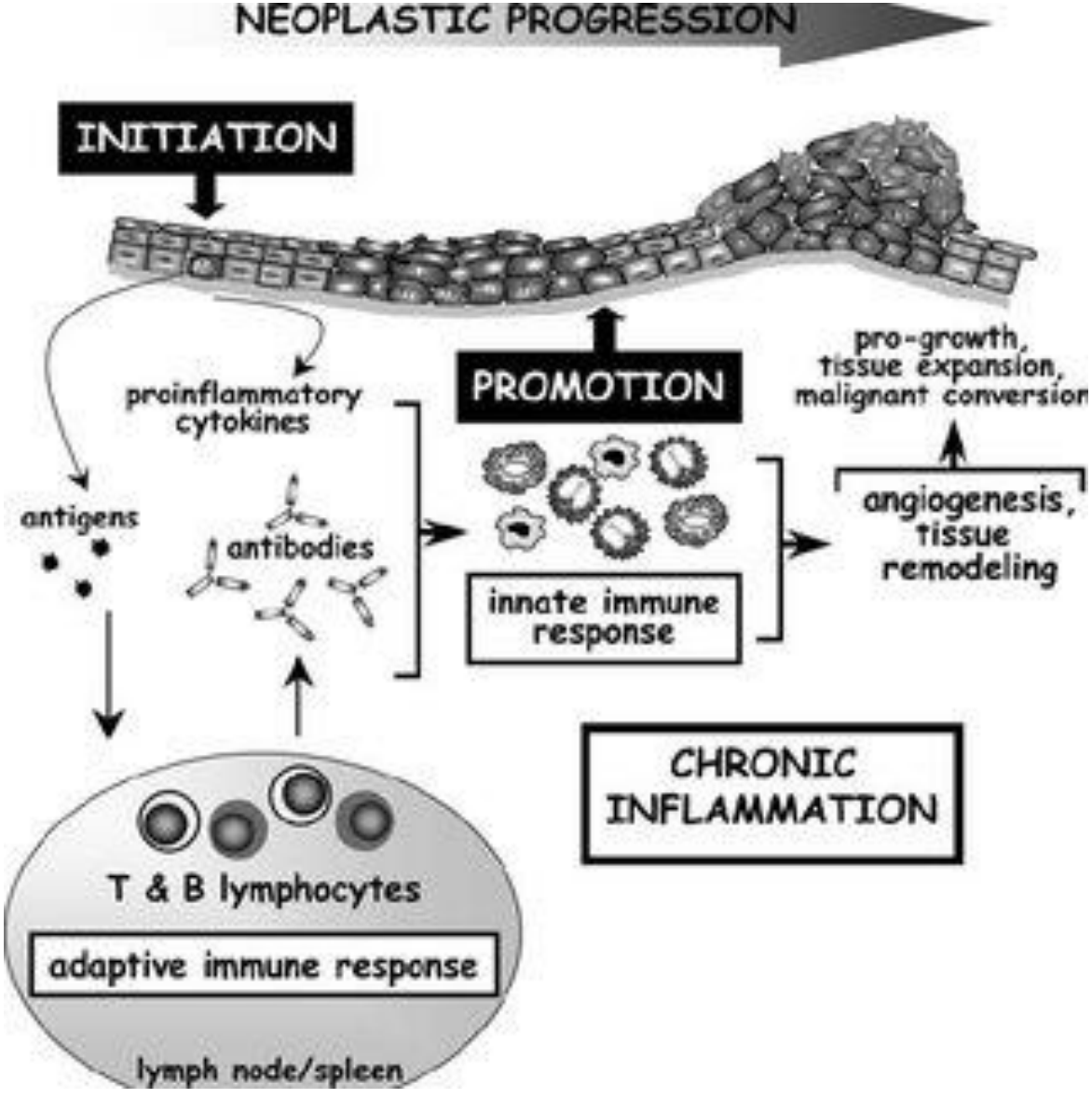






Jin-Wei Miao Li-Jiang Liu Jie Huang
Int. J. Oncol, 2014

Anticorpos e inflamação



Antígenos tumorais e respostas imunes contra tumores

RESPOSTAS IMUNES CONTROLAM O CRESCIMENTO DE TUMORES

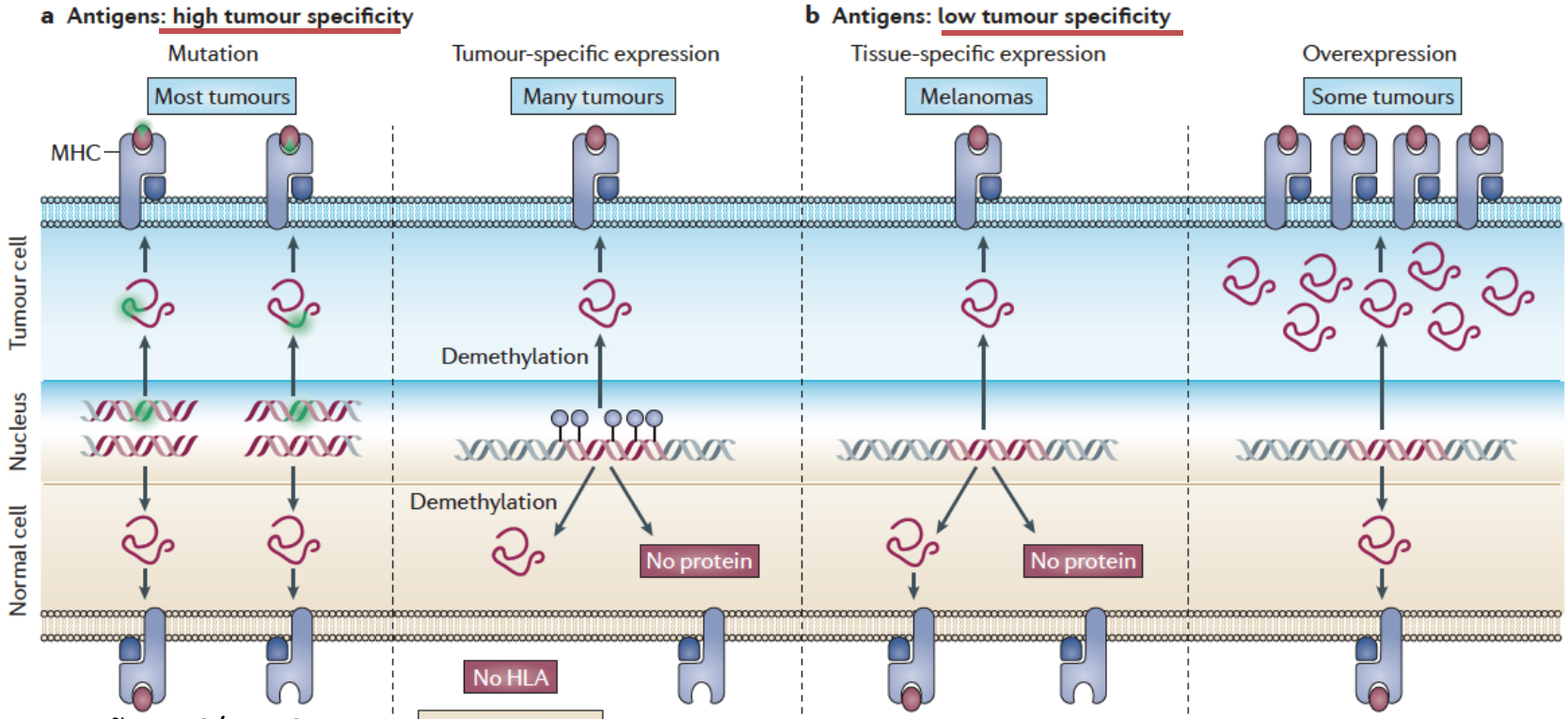
- Indivíduos imunossuprimidos ou imunodeficientes apresentam maior risco de desenvolvimento de neoplasias do que indivíduos imunocompetentes;

- Sistema imune reconhece antígenos tumorais, mesmo que a causa do tumor não seja infecção;

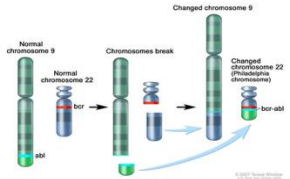
- Câncer é uma doença crônica, e a exposição continuada a antígenos tumorais, Assim como sinalização crônica por citocinas e outros mediadores inflamatórios levam ao disparo de mecanismos de controle de resposta imune;

- Células tumorais apresentam mecanismos de evasão das respostas imunes;

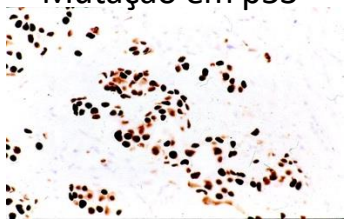
ANTÍGENOS TUMORAIS



mutação BRC/ABL CML

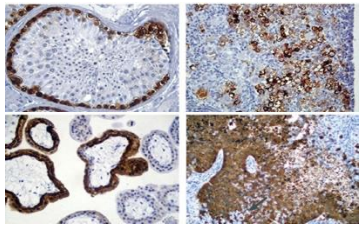


Mutação em p53

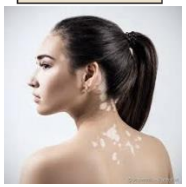


Gonzalez-Angulo A M et al. Clin Cancer Res 2004;10:6215

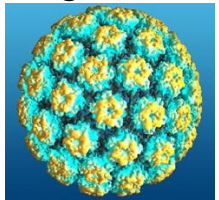
Antígenos câncer/testis



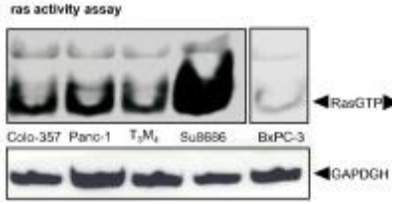
Simpson A et al. Nat Rev 2005;5:615.



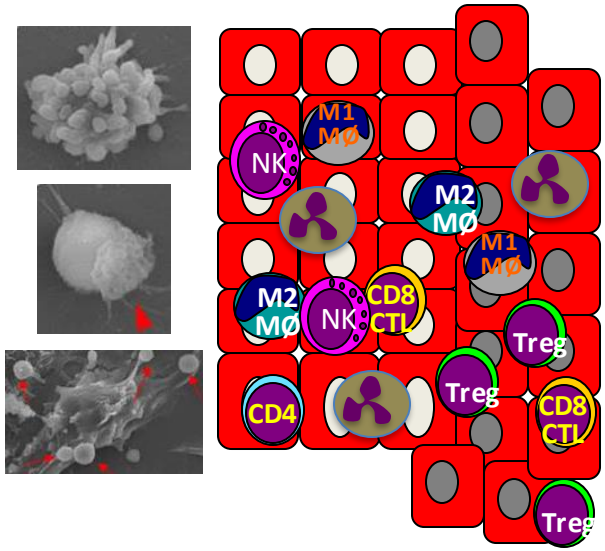
Antígenos virais



Amplificação de Kras



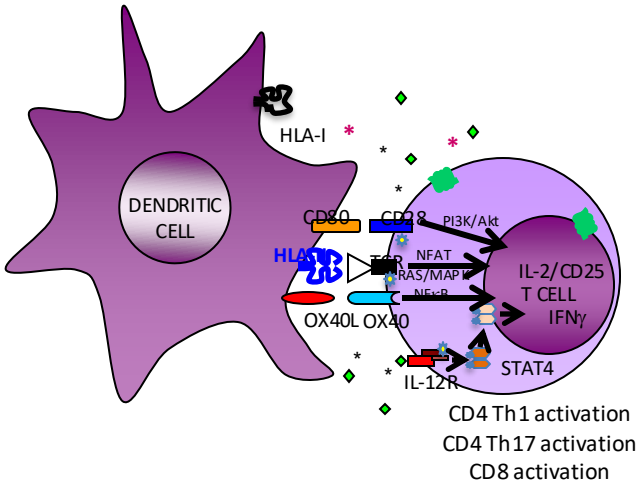
SINAIS INFLAMATÓRIOS NO MICROAMBIENTE TUMORAL
ATIVAÇÃO DE APCs



DNA
ATP
HMBG1

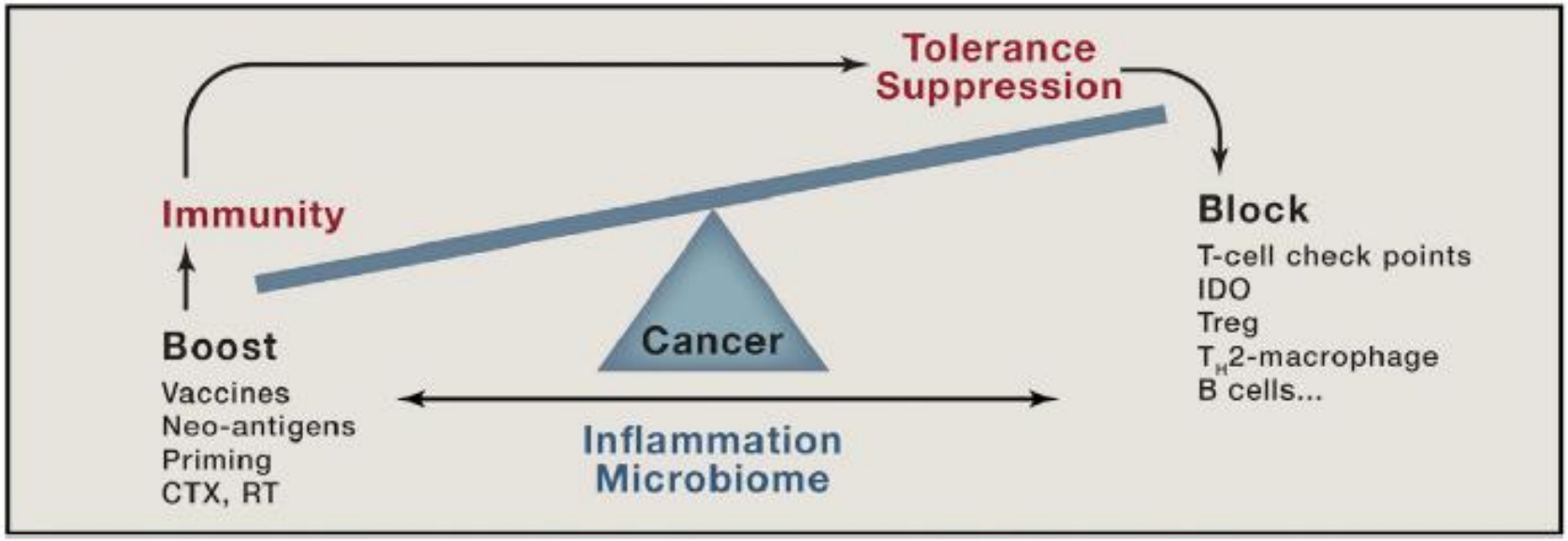
STING
MDA5
AIM2
XBP-1
UPR

Citocinas pró-inflamatórias
Expressão MHC-II

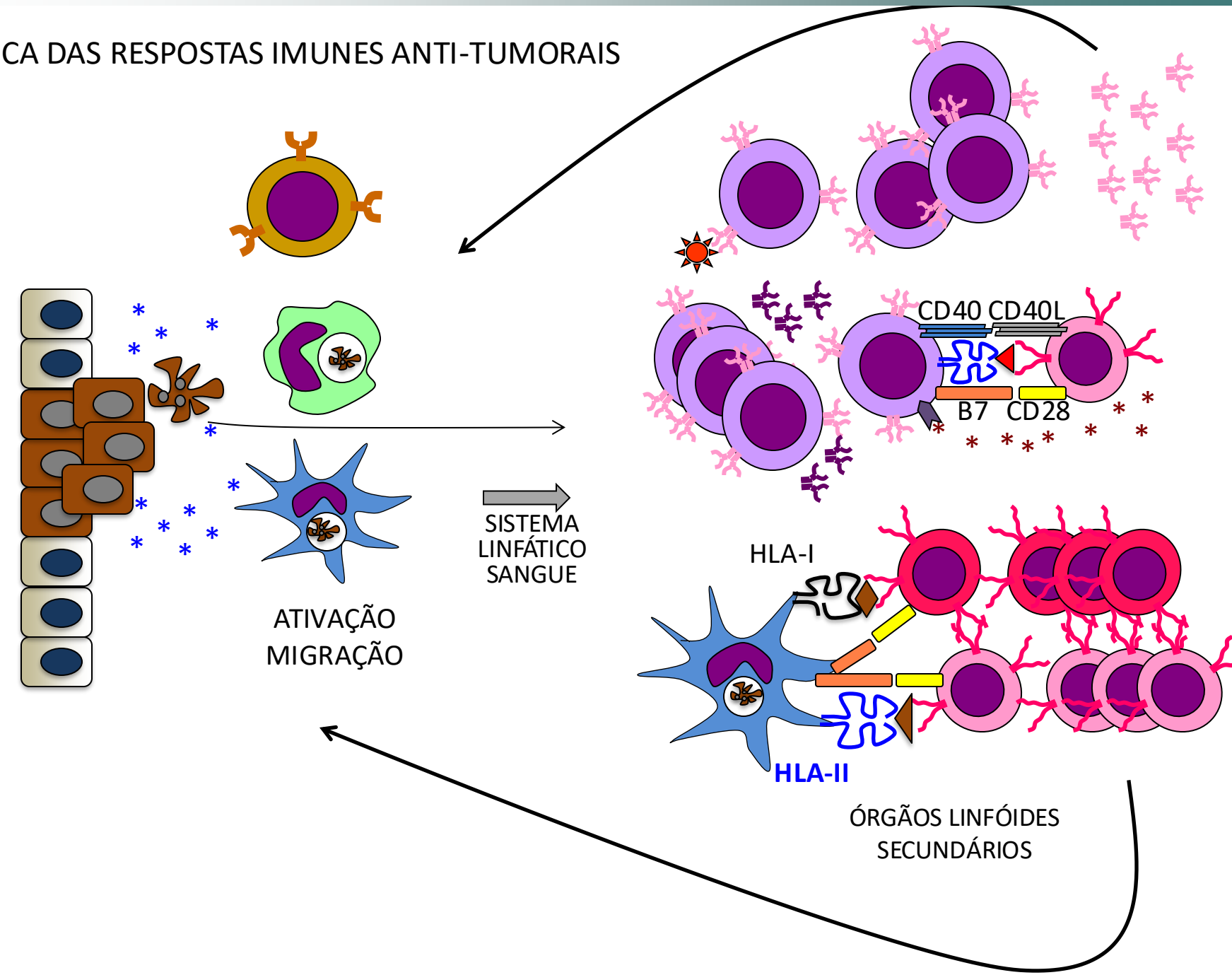


CD4 Th1 activation
CD4 Th17 activation
CD8 activation

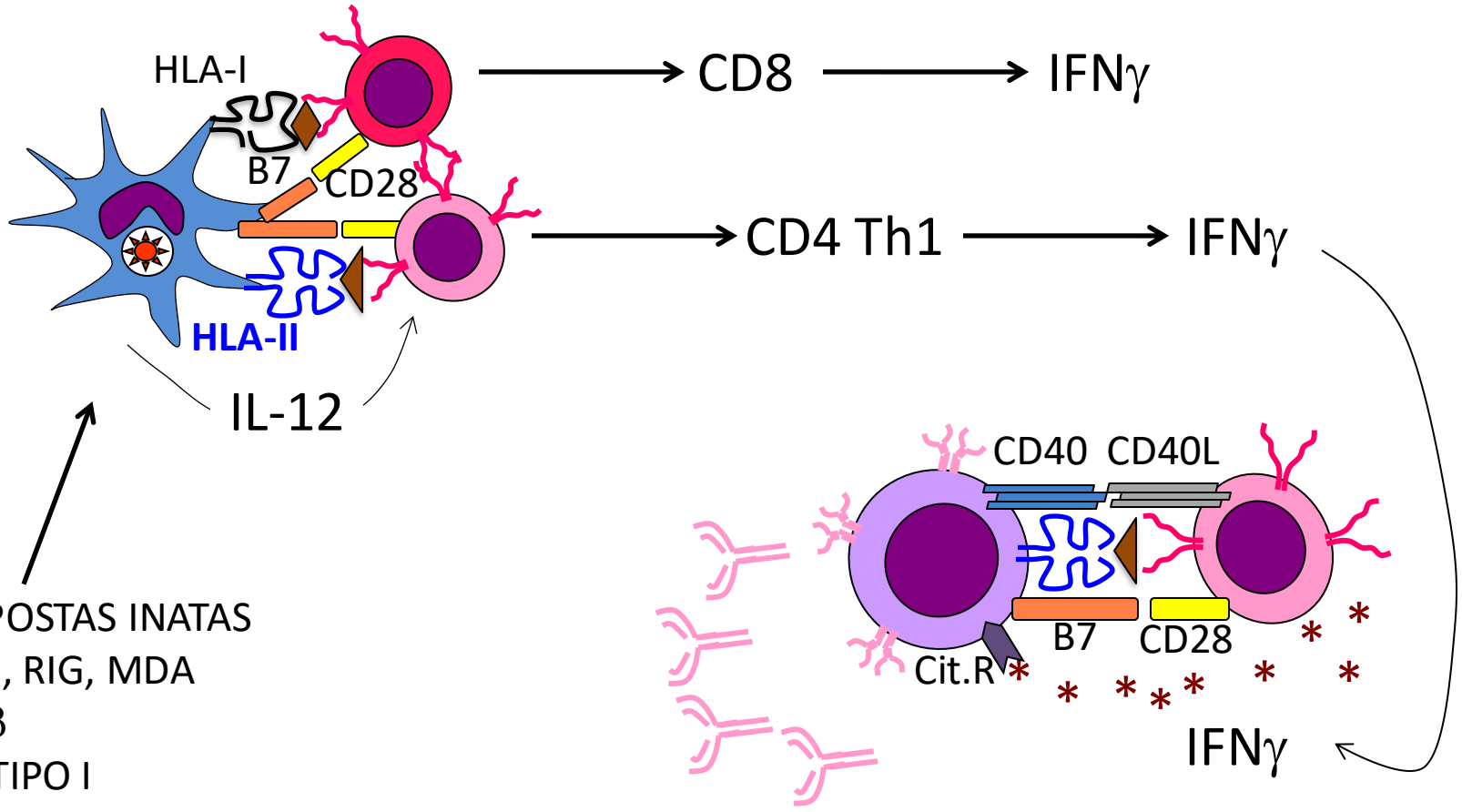
INFLAMAÇÃO E RESPOSTAS IMUNES ADAPTATIVAS



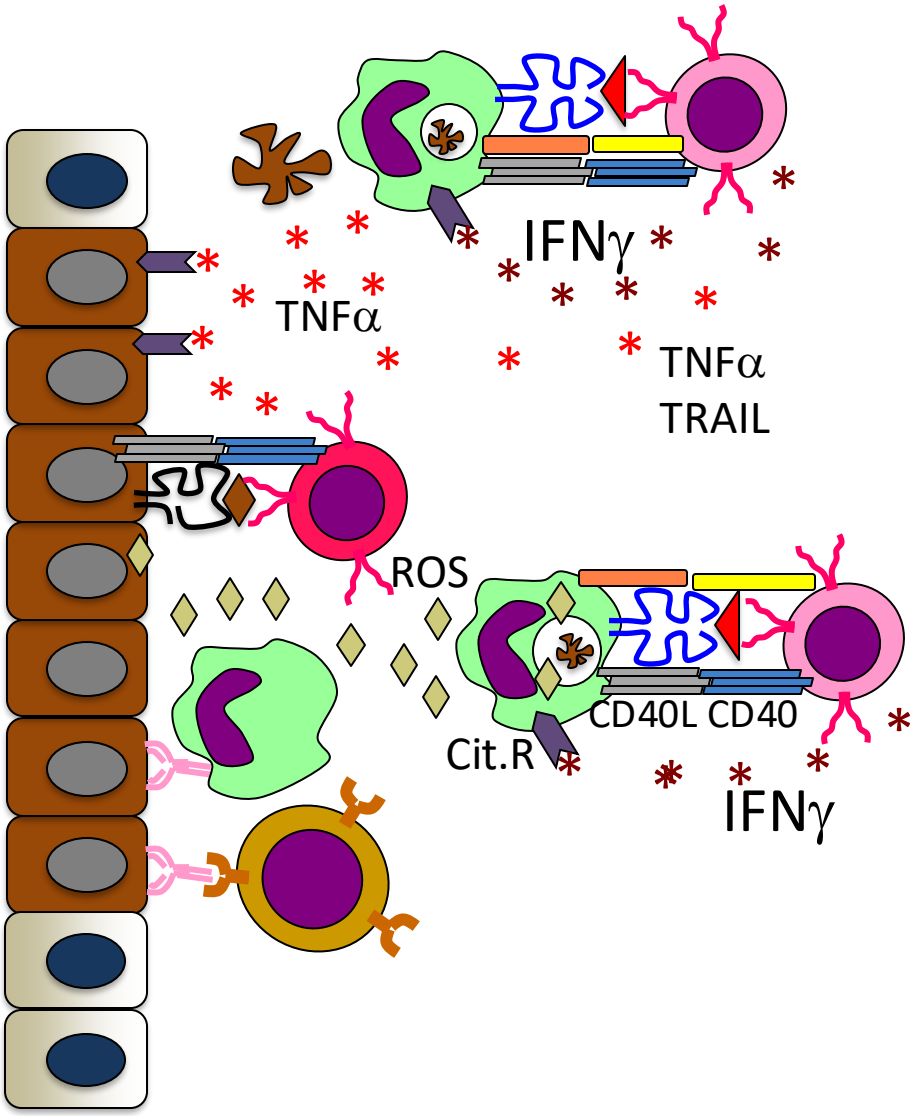
DINÂMICA DAS RESPOSTAS IMUNES ANTI-TUMORAIS



ACTIVATION ANTI-VIRAL (TUMOR) IMMUNE RESPONSES

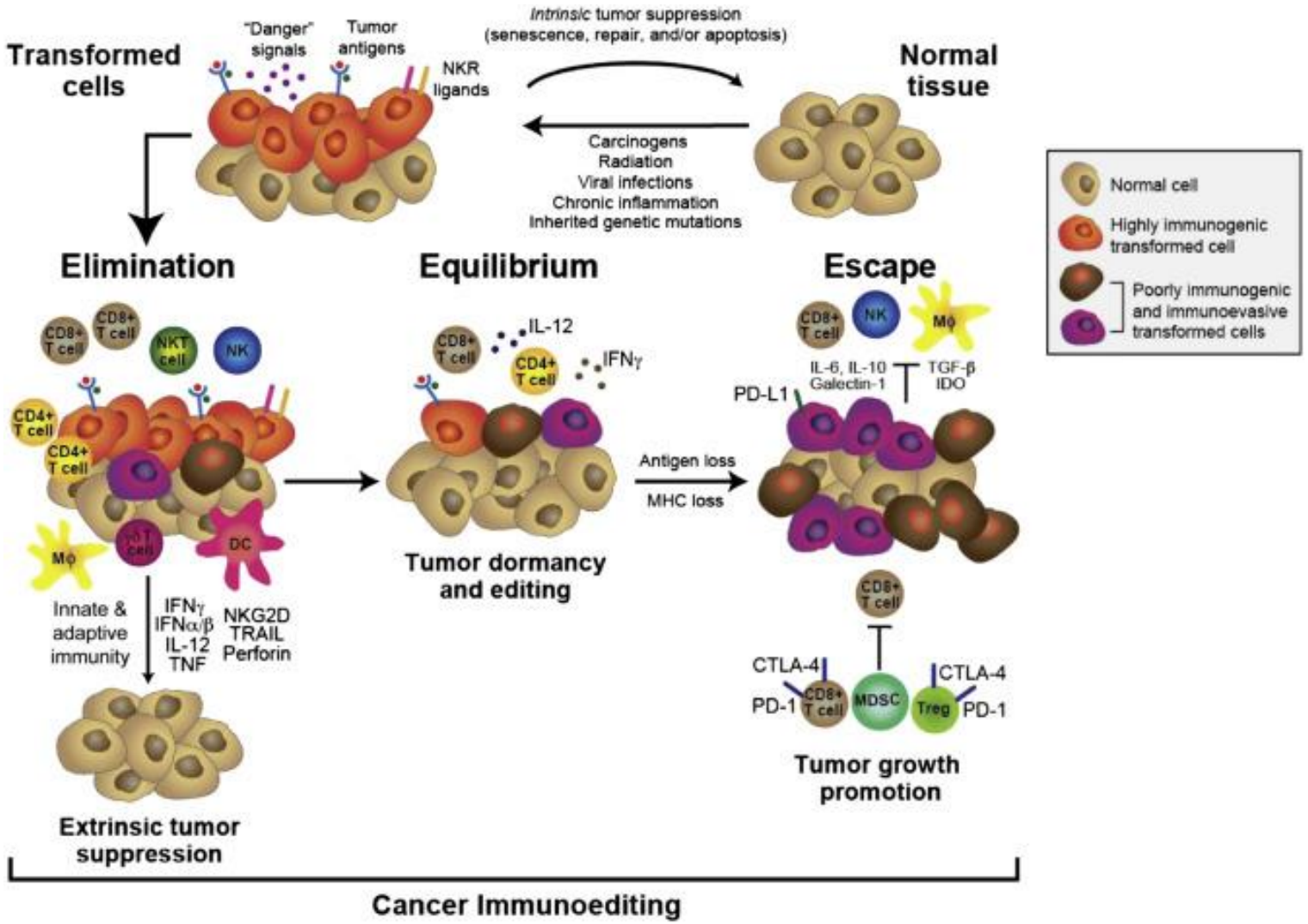


RESPOSTAS IMUNES ADAPTATIVAS CONTRA TUMORES



Imunoedição e Escape

IMUNOEDIÇÃO E ESCAPE



"We may one day be able to use immunotherapy to artificially induce equilibrium and convert cancer into a chronic but controllable disease."
Mark Smith, Peter MacCallum Cancer Center, Australia

Dunn and Schreiber, 2002

ESCAPE

- Células tumorais – comportamento de tecido imunoprivilegiado

- Microambiente tumoral
  - Indução de fenótipo tolerogênico em APCs
  - Recrutamento de células reguladoras
  - Hipóxia e metabolismo levando a imunossupressão

- Efeitos sistêmicos
  - Disparo de respostas reguladoras
  - Produção de células mielóides com viés supressor

- Controle de respostas adaptativas – checkpoint blockade

ESCAPE – células tumorais

Redução da apresentação por HLA-I (inibição da expressão de Tapasina, de subunidades do imunoproteasoma);

Expressão de HLA-G (inibição da atividade de CD8 e NK);

Resistência à apoptose mediada por TNFα e TRAIL;

Resistência ao efeito citostático de TGFβ;

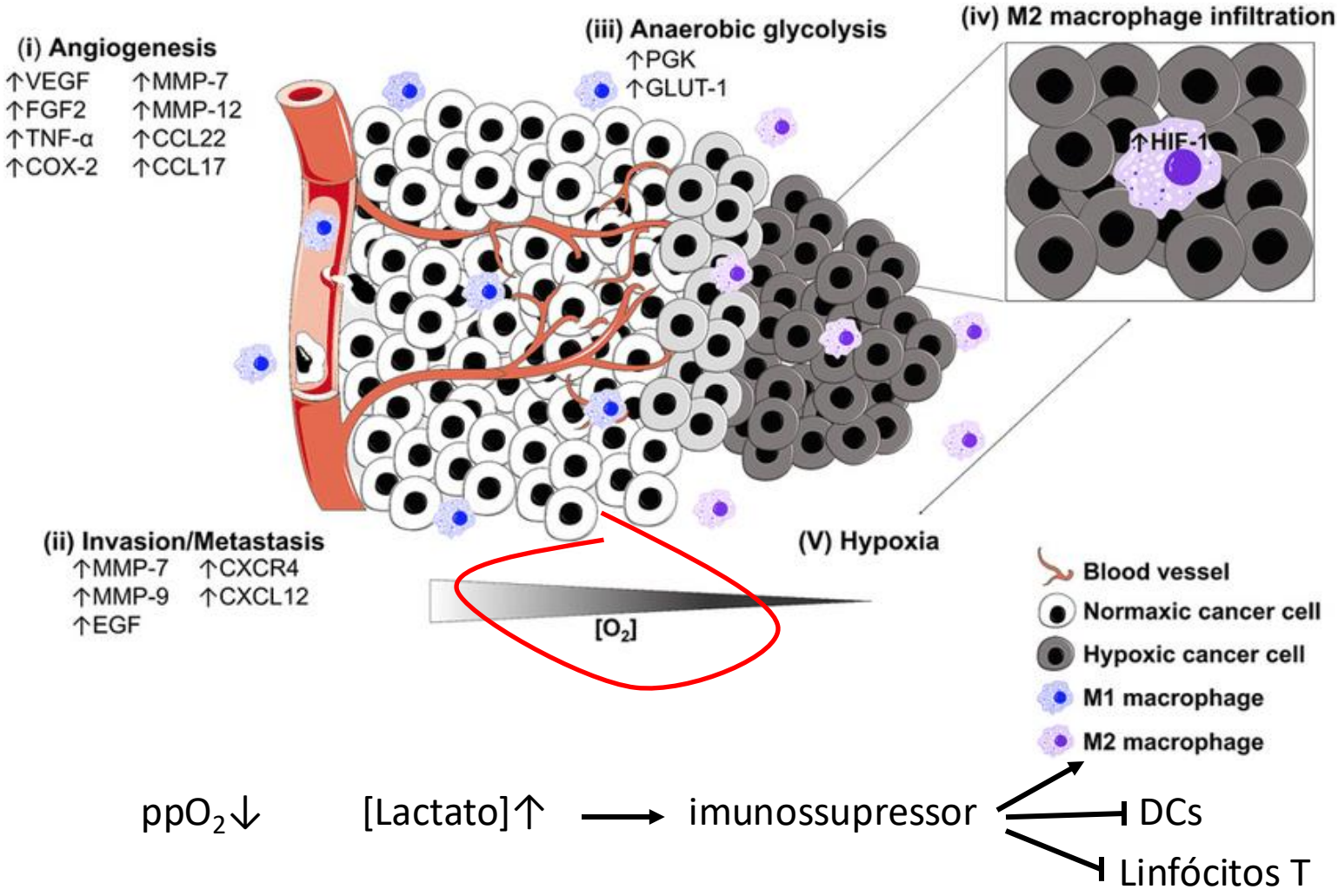
Secreção de citocinas reguladoras (IL-10 e TGFβ);

Secreção de quimiocinas que recrutam células T reguladoras e células mielóides (CCL20 e CCL2);

Expressão de IDO, TDO, produção de kinurenina (indução de fenótipo T Regulador), ativação de GCN2 por depleção de triptofano, indução de morte celular;

Expression of PD-L1.

ESCAPE – Microambiente tumoral

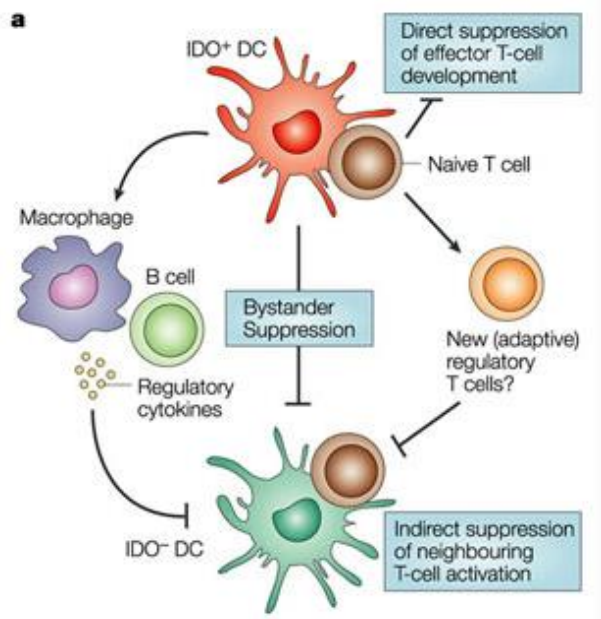


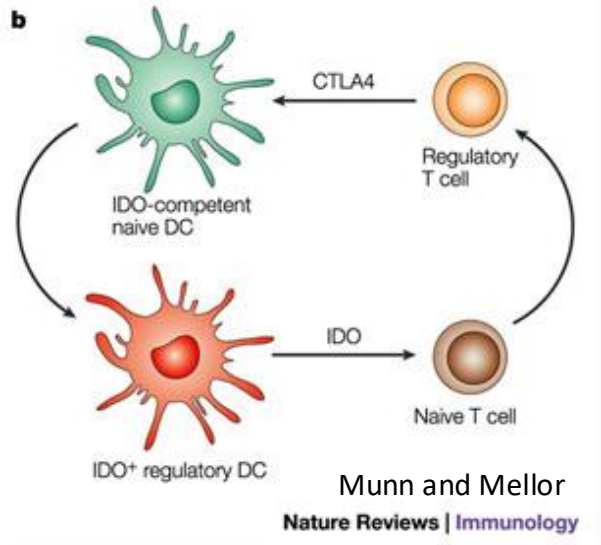
$ppO_2\downarrow$ [Lactato]↑ → imunossupressor → DCs

Linfócitos T

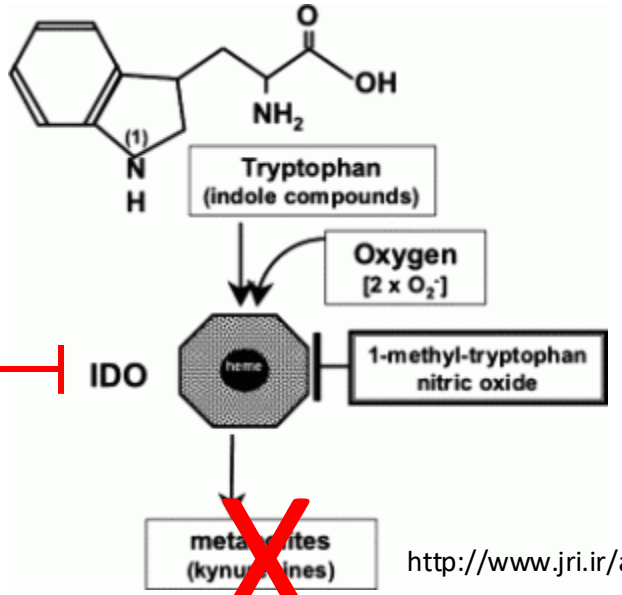
ESCAPE – APCs tolerogênicas

ESCAPE – APCs tolerogênicas





INDOLEAMINA 2,3 DIOXIGENASE (E TDO)



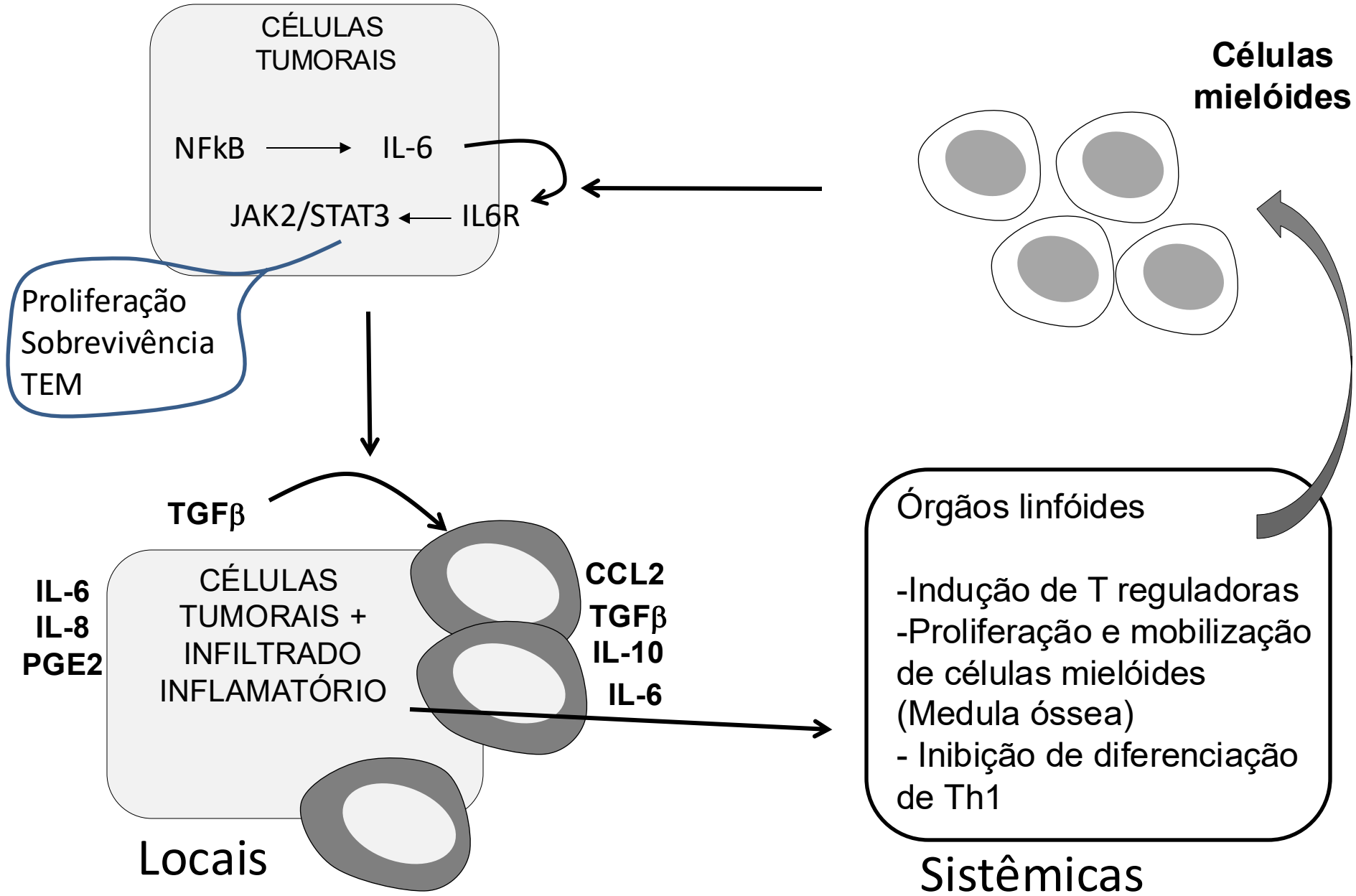
1 metil triptofano

http://www.jri.ir/article/382

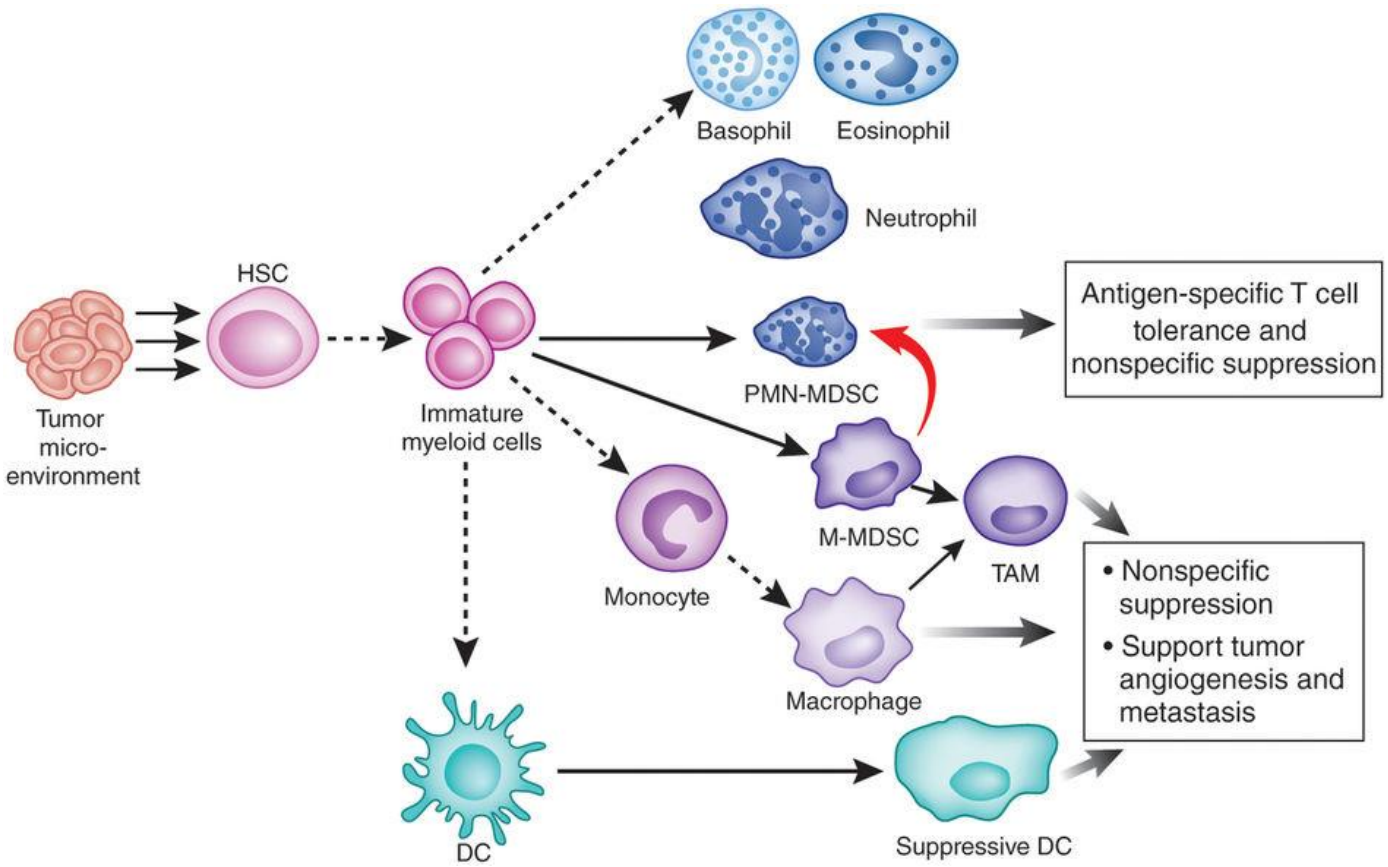
INDUÇÃO DE CÉLULAS T REGULADORAS

Resposta anti-tumoral ↑

ESCAPE – indução de respostas sistêmicas



ESCAPE - CÉLULAS MIELÓIDES

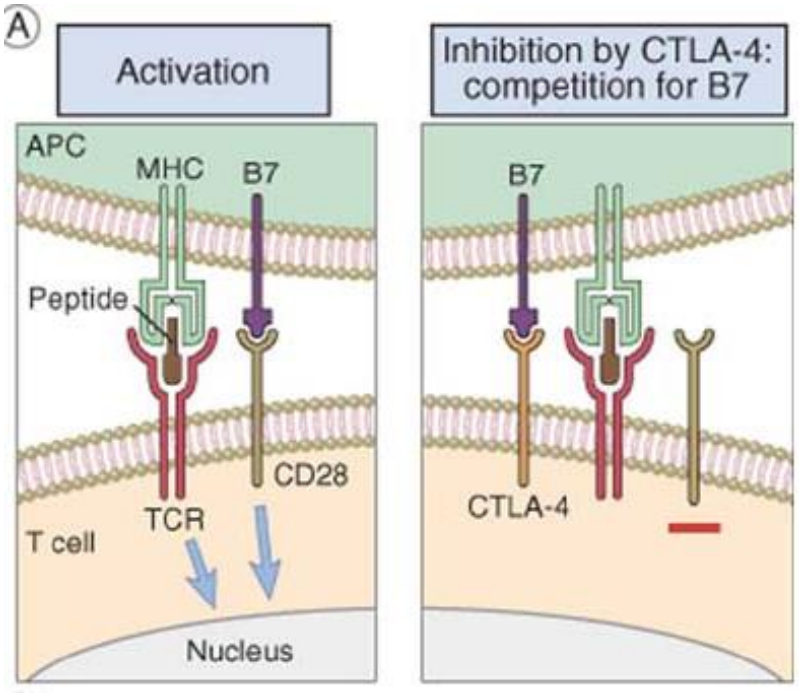


ESTRESSE OXIDATIVO
CITOCINAS SUPRESSORAS
ATIVIDADE DE ARGINASE
EXPRESSÃO DE IDO
EXPRESSÃO DE PD-L1

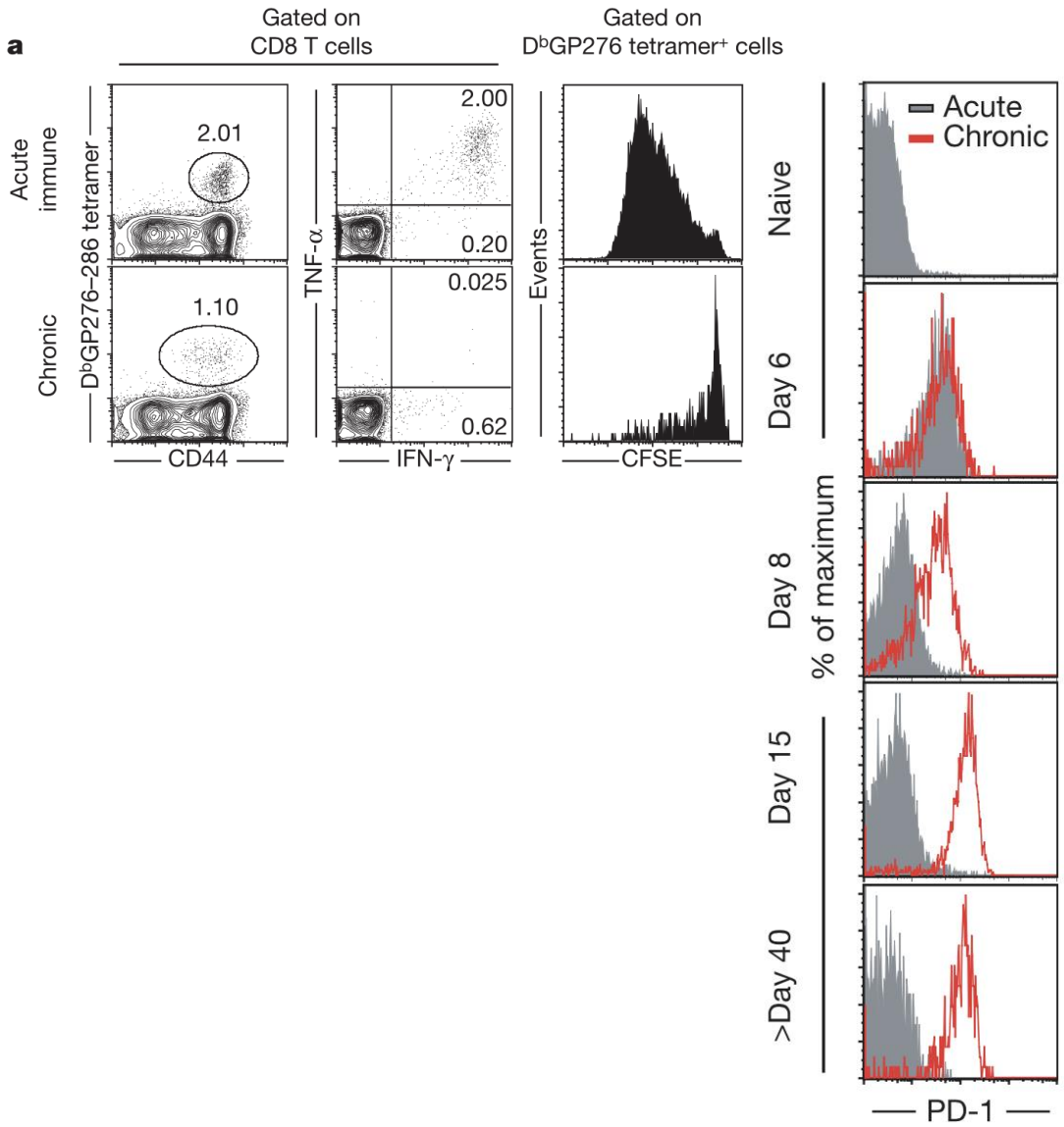
Efeito de respostas imunes crônicas

Imunomodulação

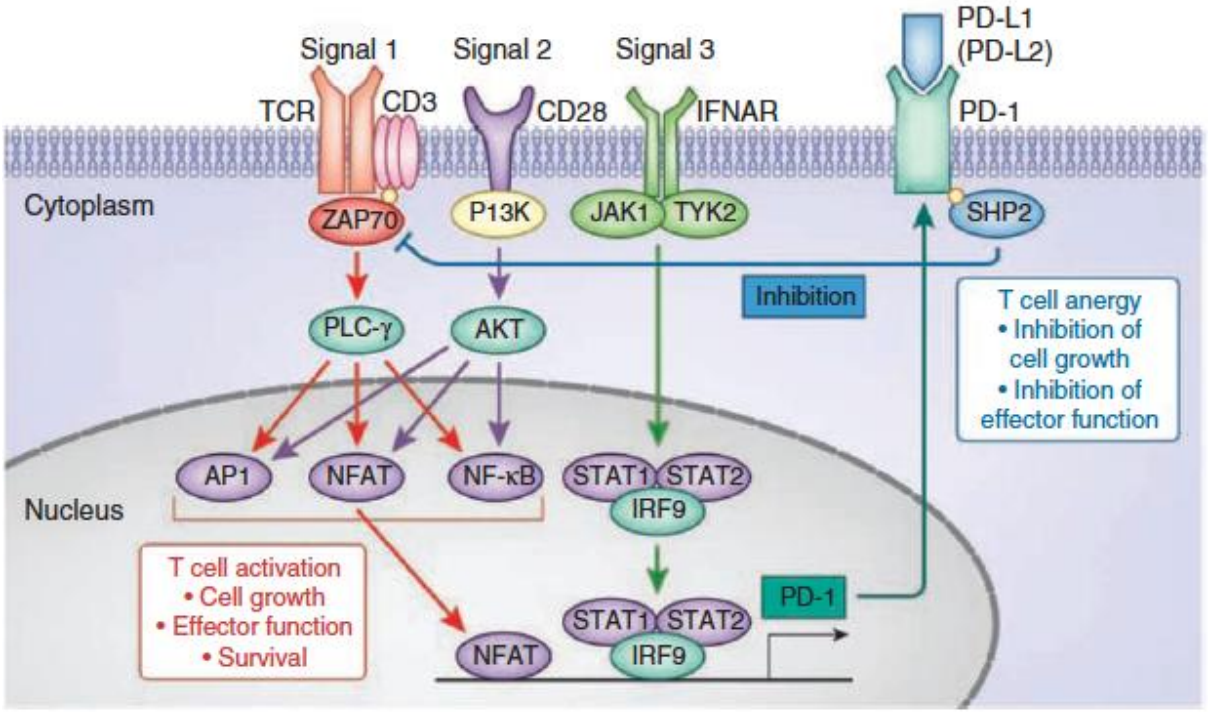
CTLA-4 - Cytotoxic T Lymphocyte Associated Protein 4



Indução de fenótipo tolerogênico
em DCs – amplificação do sinal negativo


a
Gated on
CD8 T cells
Gated on
DbGP276 tetramer+ cells
Acute
immune
Chronic
DbGP276–286 tetramer
2.01
1.10
CD44
TNF-α
2.00
0.20
0.025
0.62
IFN-γ
Events
CFSE
Naive
Day 6
Day 8
Day 15
>Day 40
% of maximum
Acute
Chronic
PD-1

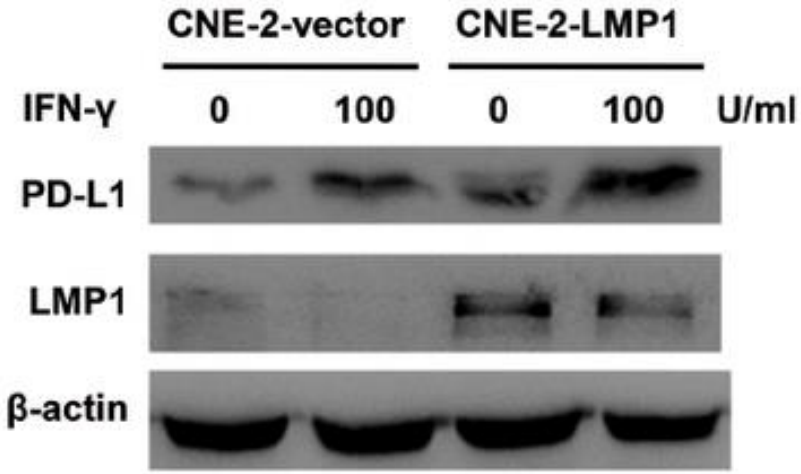
PD-1/PD-1L – T CELL EXHAUSTION

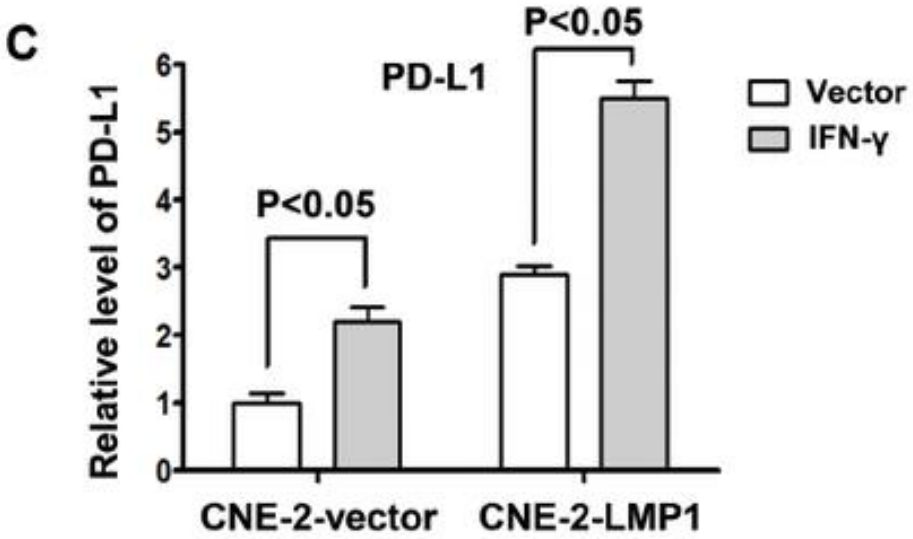


A rheostat for immune responses: the unique properties of PD-1 and their advantages for clinical application

Taku Okazaki[1], Shunsuke Chikuma[2], Yoshiko Iwai[3], Sidonia Fagarasan[4] & Tasuku Honjo[2]

IFNγ INDUZ EXPRESSÃO DE PD-L1

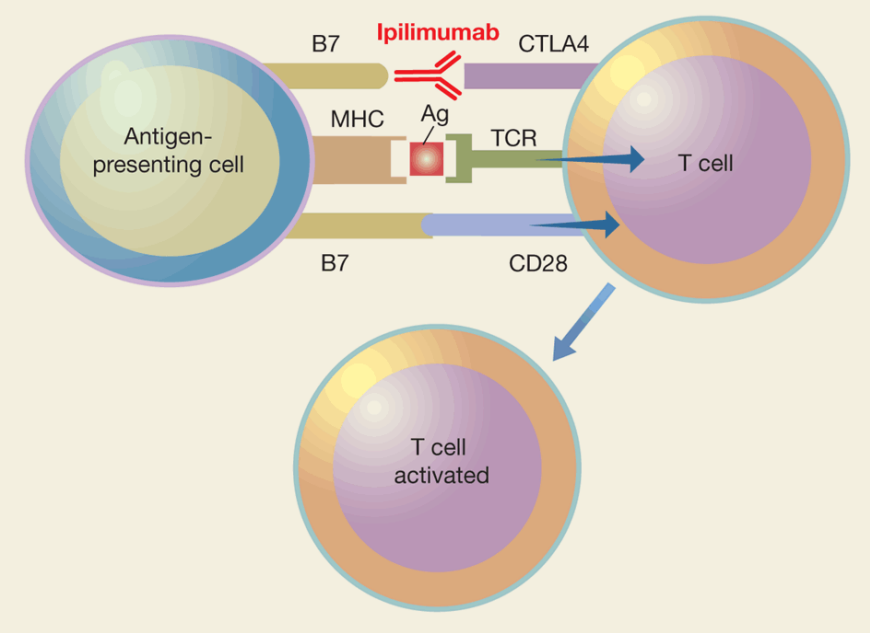


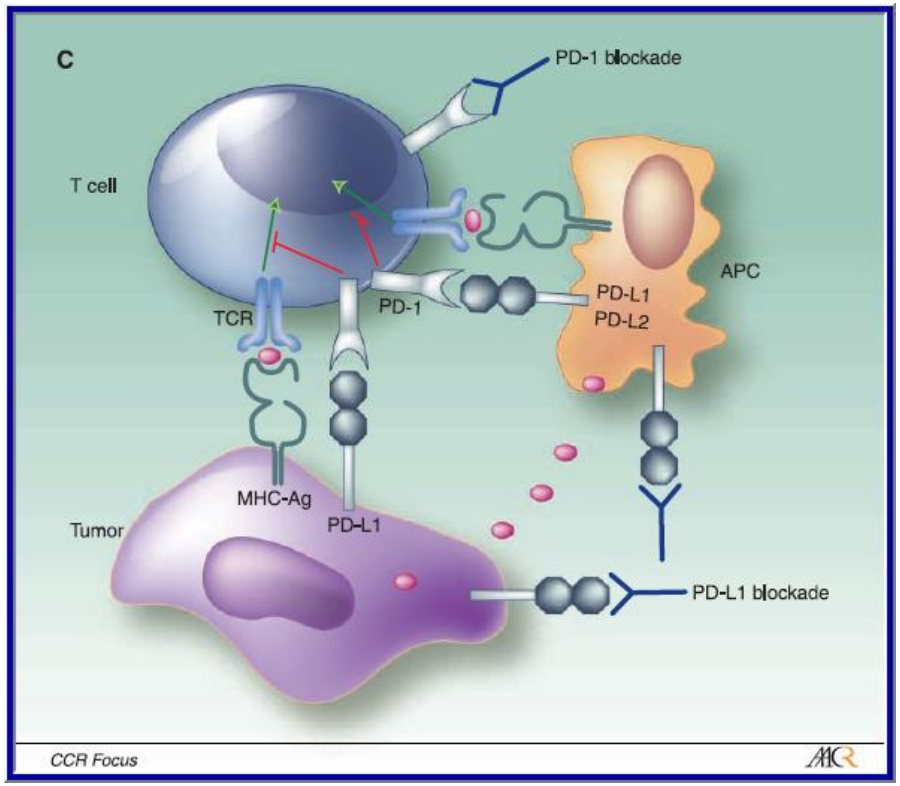


OPORTUNIDADES TERAPÊUTICAS - IMUNOMODULAÇÃO

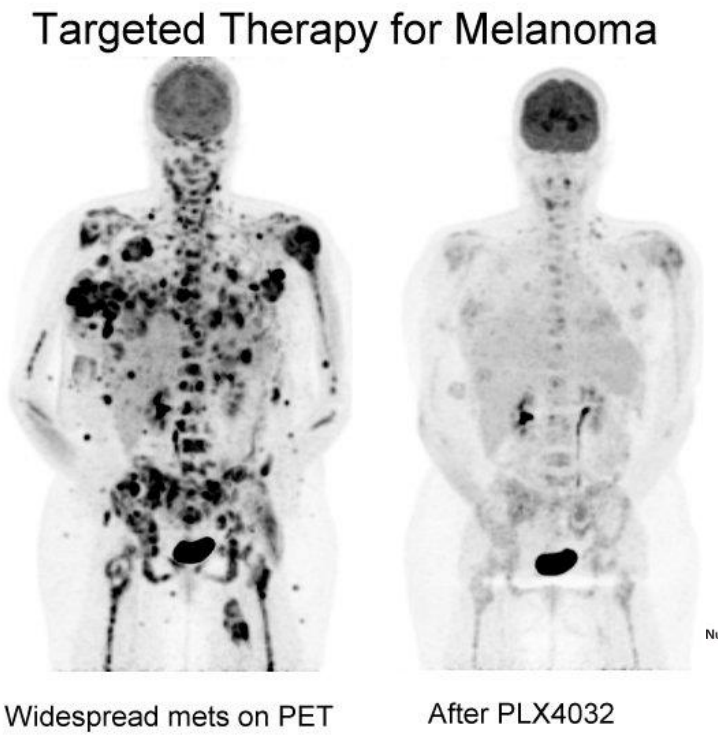
Imunomodulação é a alteração de respostas imunes do organismo com agentes que ativam ou suprimem suas funções

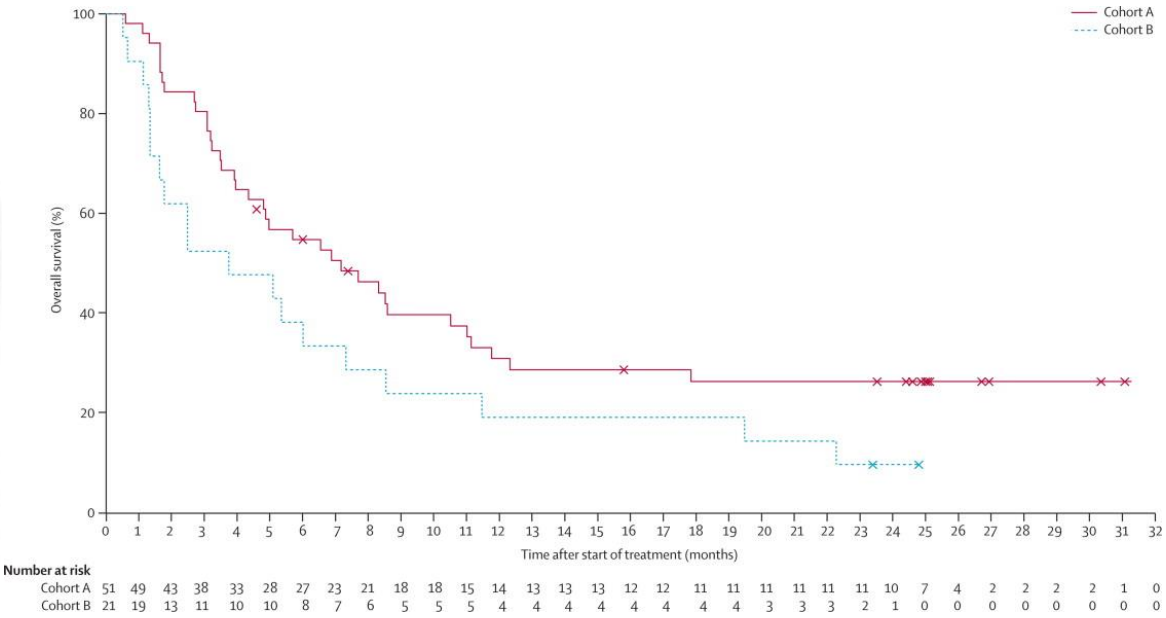
OPORTUNIDADES TERAPÊUTICAS - IMUNOMODULAÇÃO





IMPILIMUMAB (ANTI-CTLA-4)

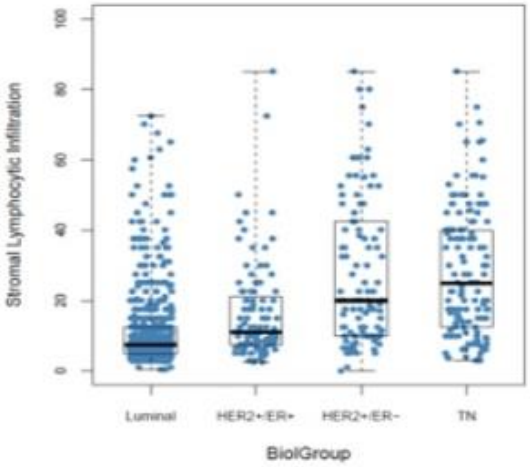


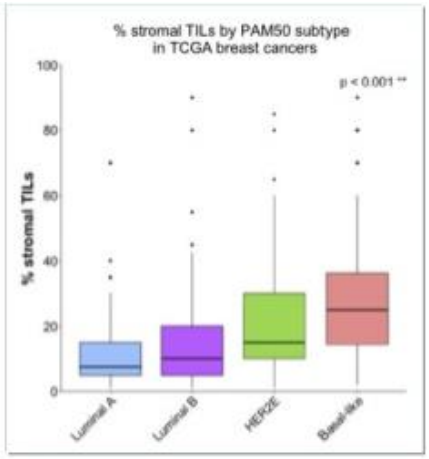


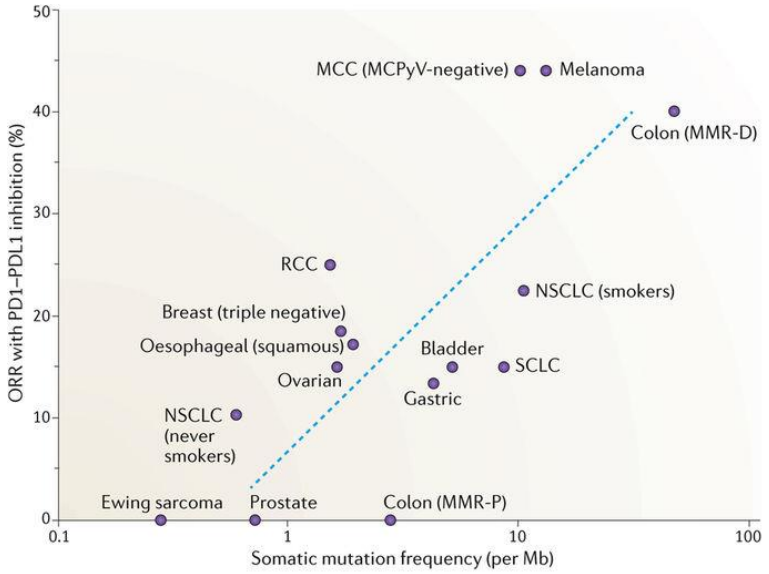
THE LANCET Oncology

Ipilimumab in patients with melanoma and brain metastases: an open-label, phase 2 trial.
Prof Kim Margolin, MD'Correspondence information about the author Prof Kim MargolinEmail the author Prof Kim Margolin, Marc S Ernstoff, MD, Omid Hamid, MD, Donald Lawrence, MD, David McDermott, MD, Igor Puzanov, MD, Jedd D Wolchok, MD, Prof Joseph I Clark, MD, Mario Sznol, MD, Theodore F Logan, MD, Jon Richards, MD, Tracy Michener, PharmD, Agnes Balogh, MS, Kevin N Heller, MD, F Stephen Hodi, MD

TUMORES COM MAIOR INFILTRAÇÃO POR LINFÓCITOS T E MAIOR FREQUÊNCIA DE MUTAÇÕES SÃO MELHORES CANDIDATOS PARA TRATAMENTO COM ANTICORPOS CONTRA CHECKPOINT BLOCKADE

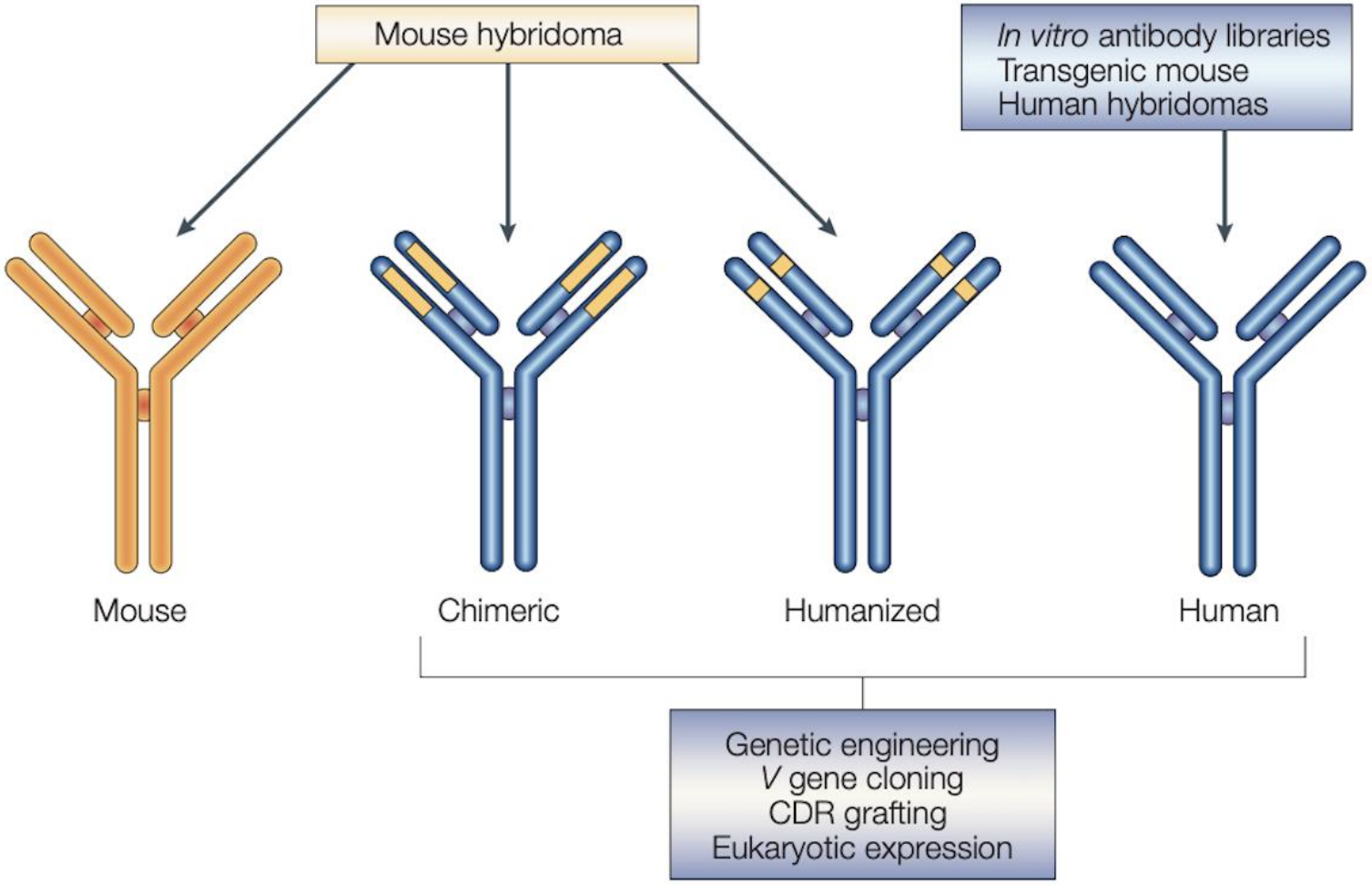






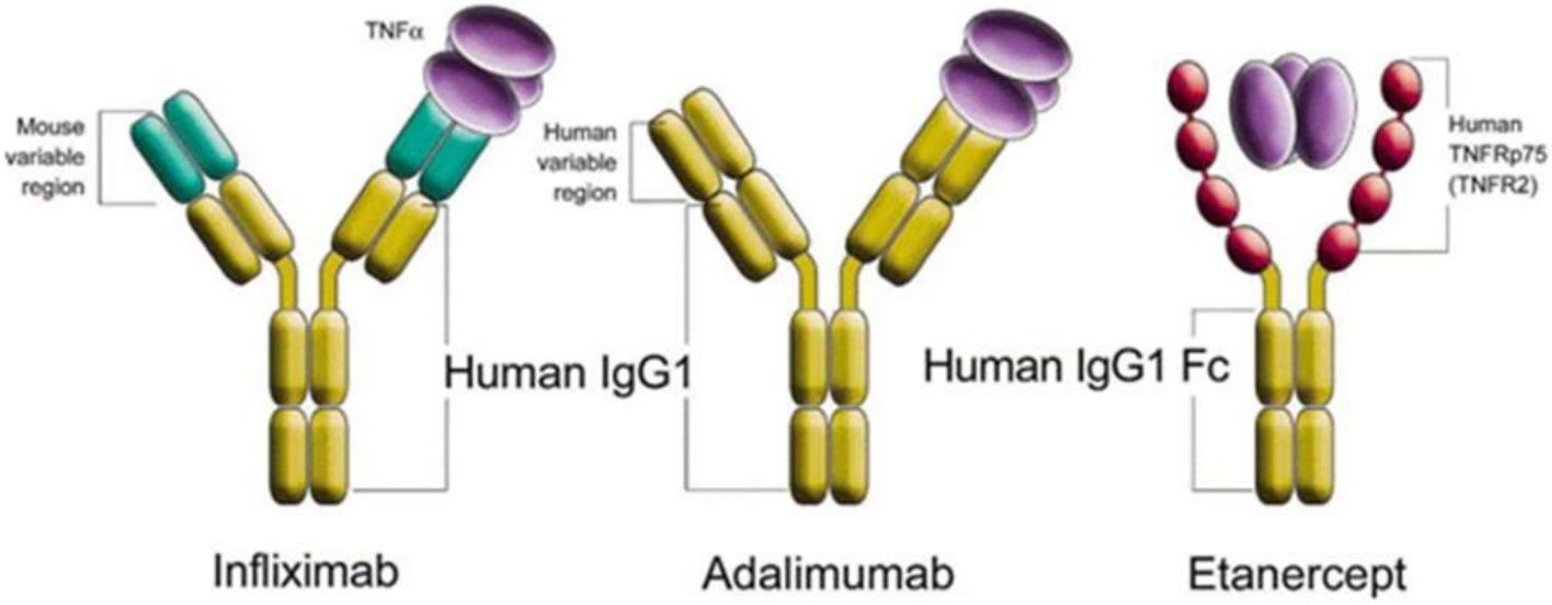
Loi S, et al. J Clin Oncol 2013Onc 2016
Luen, et al, Breast, 2016
Stanton, Adams, Disis. Jama

Anticorpos

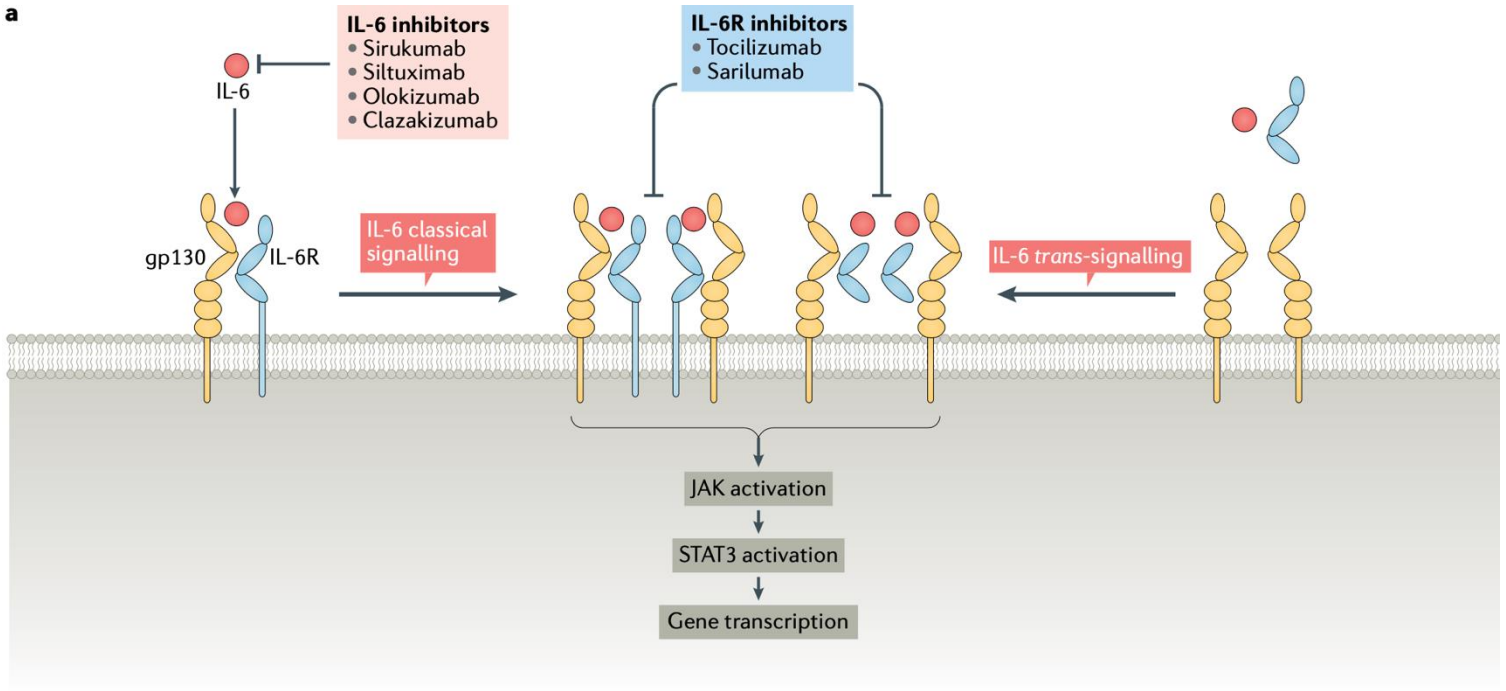

Mouse hybridoma
In vitro antibody libraries
Transgenic mouse
Human hybridomas
Mouse
Chimeric
Humanized
Human
Genetic engineering
V gene cloning
CDR grafting
Eukaryotic expression

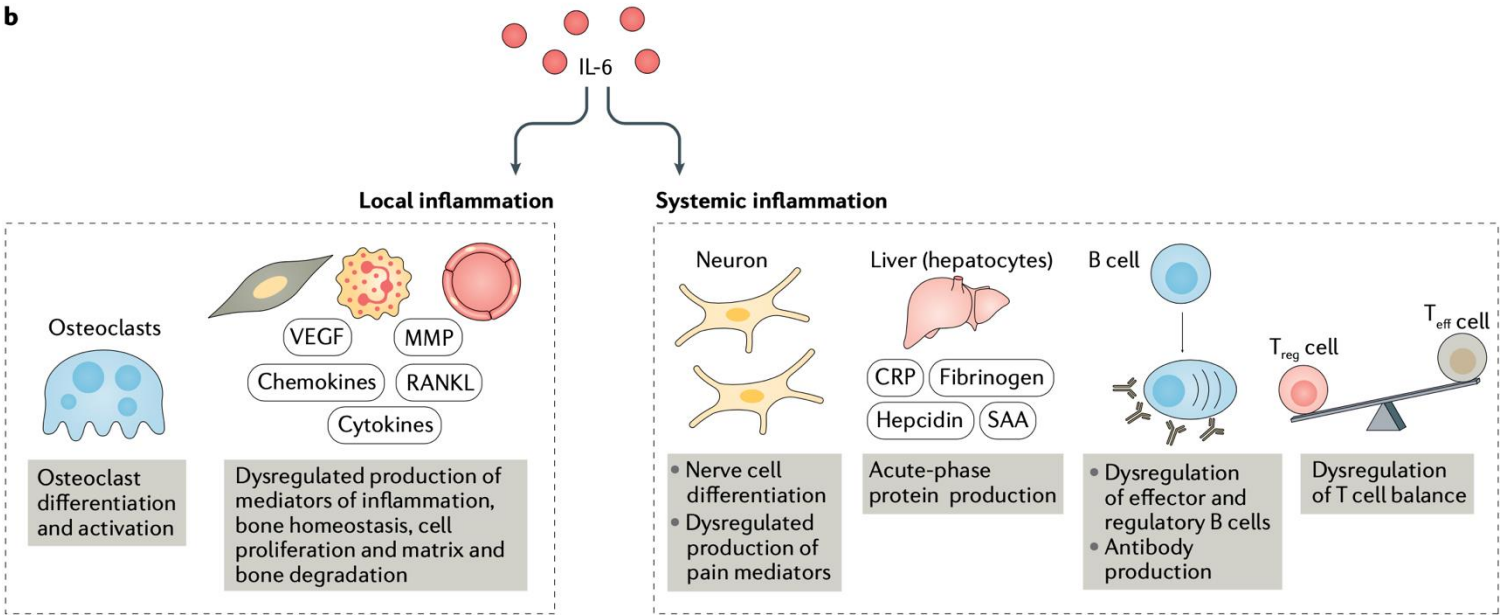
Anticorpos TNFα

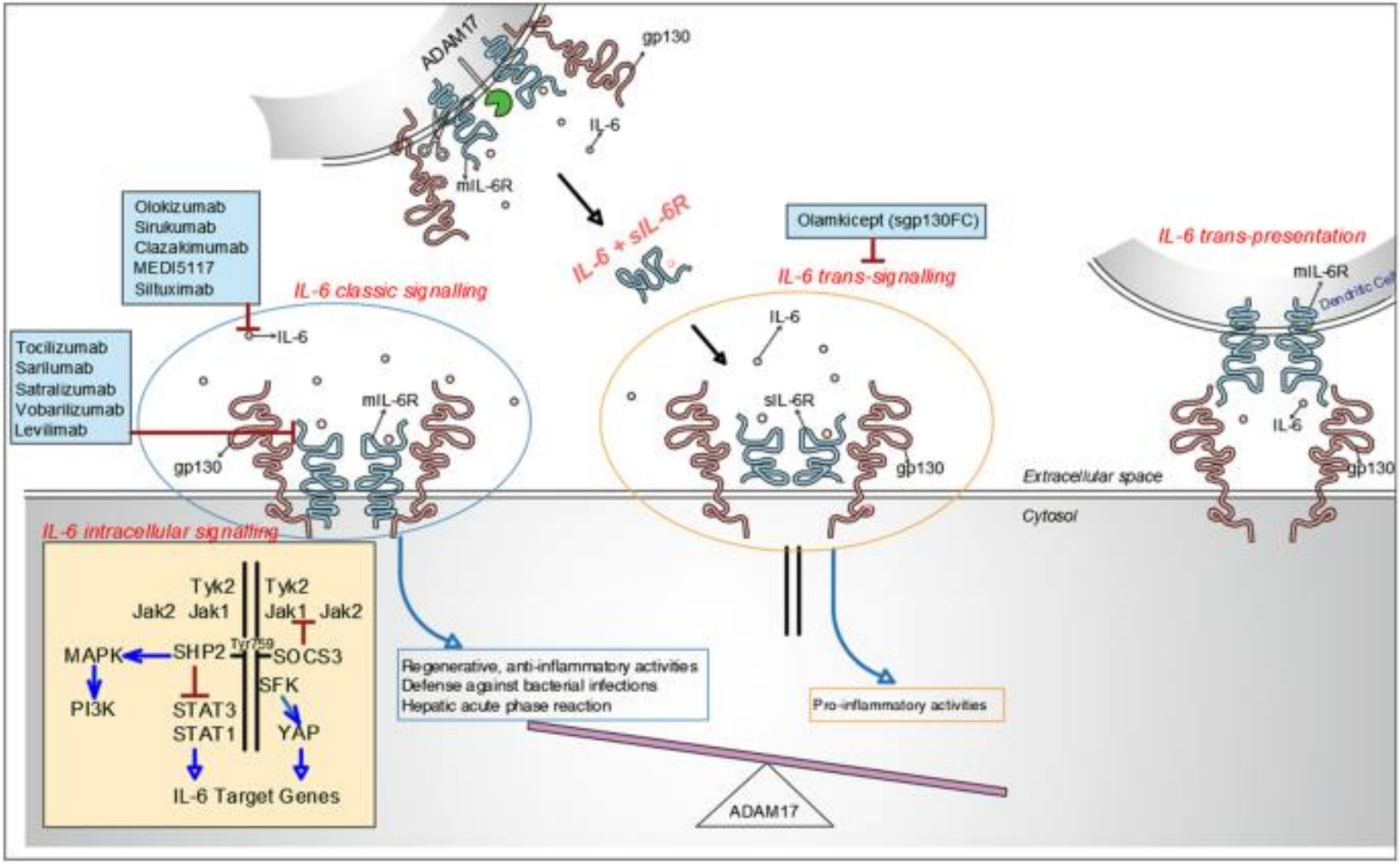
TNFα – citocina medeia respostas inatas e adaptativas, secretada por macrófagos, linfócitos, em alguns casos DCs e NK.



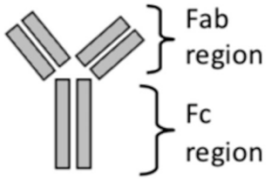
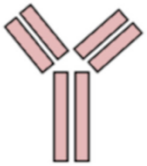
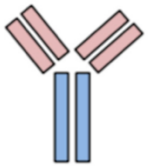
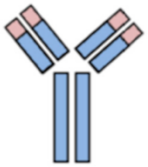
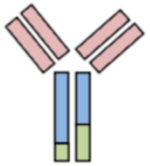
Inibidores de IL-6 e seu receptor



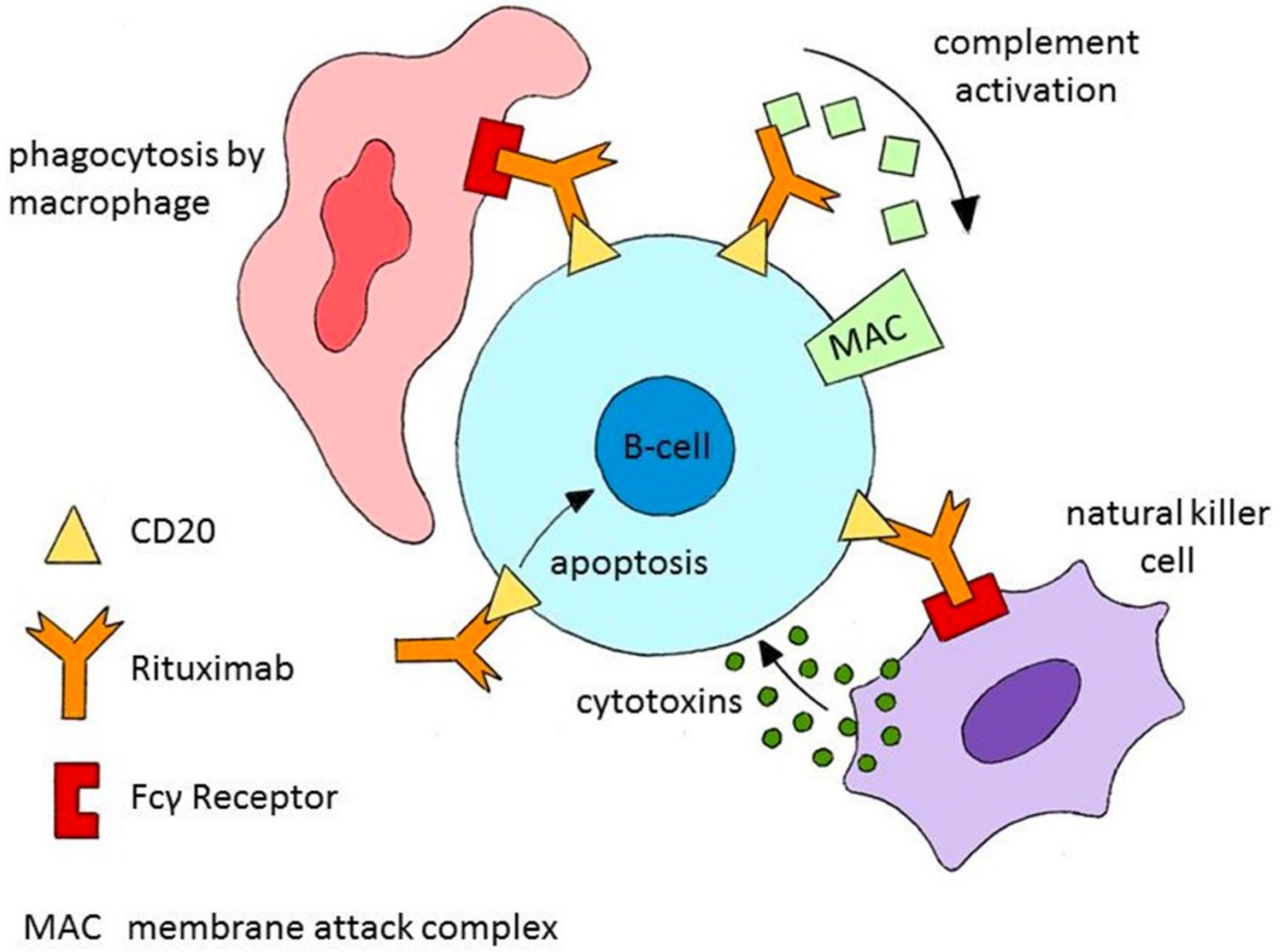



ADAM17
gp130
IL-6
mIL-6R
IL-6 + sIL-6R
Olokizumab
Sirukumab
Clazakimumab
MEDI5117
Siltuximab
IL-6 classic signalling
Tocilizumab
Sarilumab
Satralizumab
Vobarilizumab
Levilimab
gp130
Olamkicept (sgp130FC)
IL-6 trans-signalling
sIL-6R
IL-6 trans-presentation
Dendritic Cell
Extracellular space
Cytosol
IL-6 intracellular signalling
Tyk2
Jak2
Jak1
Tyk2
Jak1
Jak2
MAPK
SHP2
Tyr759
SOCS3
SFK
PI3K
STAT3
STAT1
YAP
IL-6 Target Genes
Regenerative, anti-inflammatory activities
Defense against bacterial infections
Hepatic acute phase reaction
Pro-inflammatory activities
ADAM17

Anticorpos para eliminação de linfócitos B

Generation	1st Generation		2nd Generation		3rd Generation
mAb Structure 	Murine (100% rodent)  Suffix: -***o***mab	Chimeric (65% human)  Suffix: -***xi***mab	Humanised (>90% human)  Suffix: -***zu***mab	Fully human  Suffix: -***u***mab	Modified Fc region (chimeric or humanised) 
Immunogenicity	Higher → Lower				
Anti-CD20 mAbs	*Not in clinical use due to short half-life, poor efficacy and high risk of adverse reactions*	**Rituximab** Biosimilars: **Truxima** **Rixathon** *Unlicensed use in neurology (table 2)*	**Ocrelizumab** *Licensed for relapsing and primary progressive MS*	**Ofatumumab** *Currently in phase III clinical trials for MS*	**Ublituximab (TG-1101)** (chimeric) *Currently in phase III clinical trials for MS*
Anti-CD19 mAbs					**Inebilizumab (MEDI-551)** (humanised) *Currently in clinical trials for MS and NMOSD*

Rituximab – tratamento contra linfomas, doenças autoimunes (Myastenia gravis, encefalite, neuromielite, MS)



Citocinas

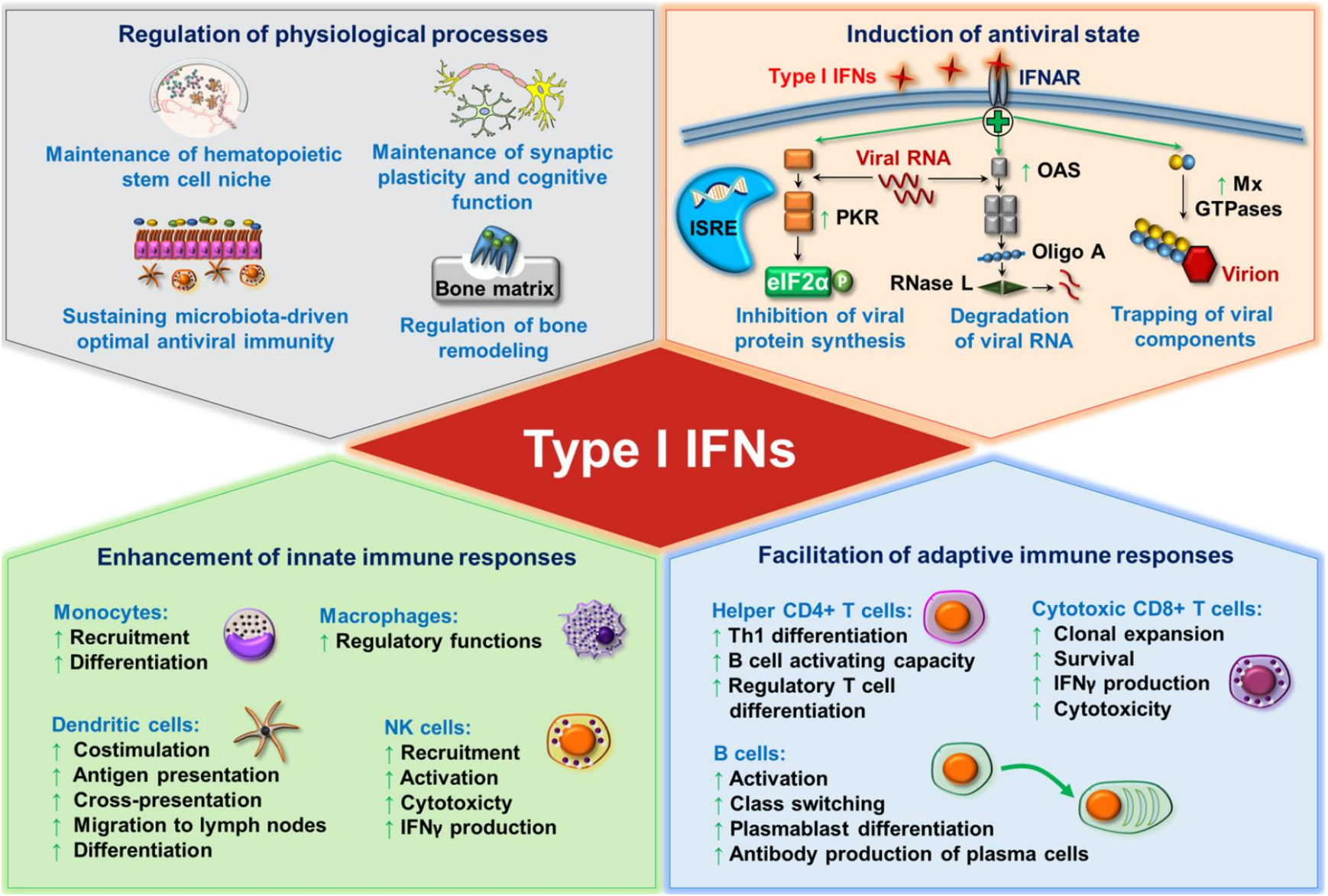
- terapia para estimular o sistema imune – ATIVAÇÃO

ex. IL-2, IFN tipo I – terapia contra câncer
IL-2, primeira droga aprovada pelo FDA no tratamento contra câncer
IFN tipo I, um dos primeiros tratamentos contra doenças infecciosas crônicas, por exemplo, infecção por HCV (vírus da Hepatite C)

- terapia para inibir a sinalização de citocinas em doenças inflamatórias - INIBIÇÃO

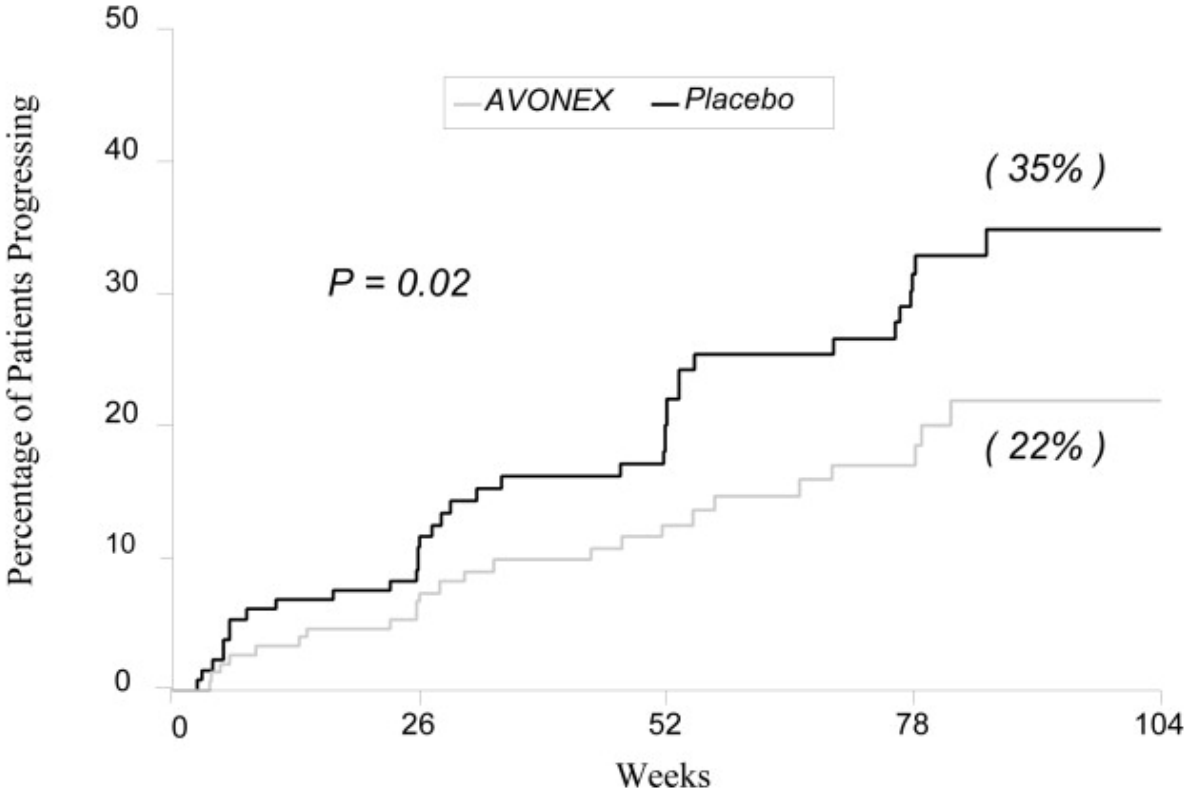
ex. anti-IL-6 e anti-TNFα – terapia contra doenças reumáticas, tempestade de citocinas, doença de Castleman

IFN tipo 1 – recombinante, peguilado (conjugado com polietilenoglicol) ativação de respostas anti-virais



Tratamento de pacientes com esclerose múltipla usando IFNbeta

Figure 1: Time to Onset of Sustained Disability Progression in Patients with MS in Study 1[1]

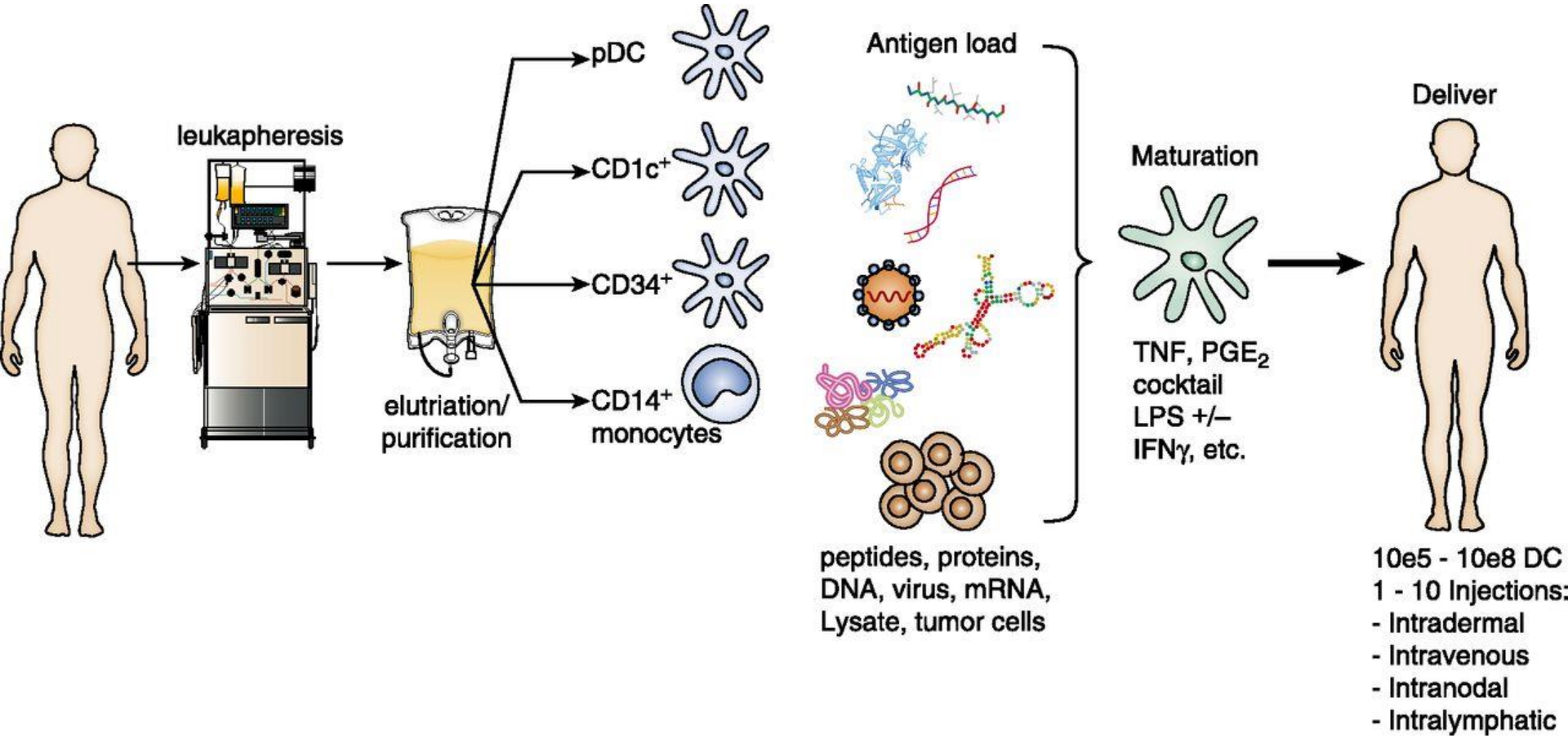


1 Kaplan-Meier Methodology; *Disability progression was defined as at least a 1 point increase in EDSS score sustained for at least 6 months.*

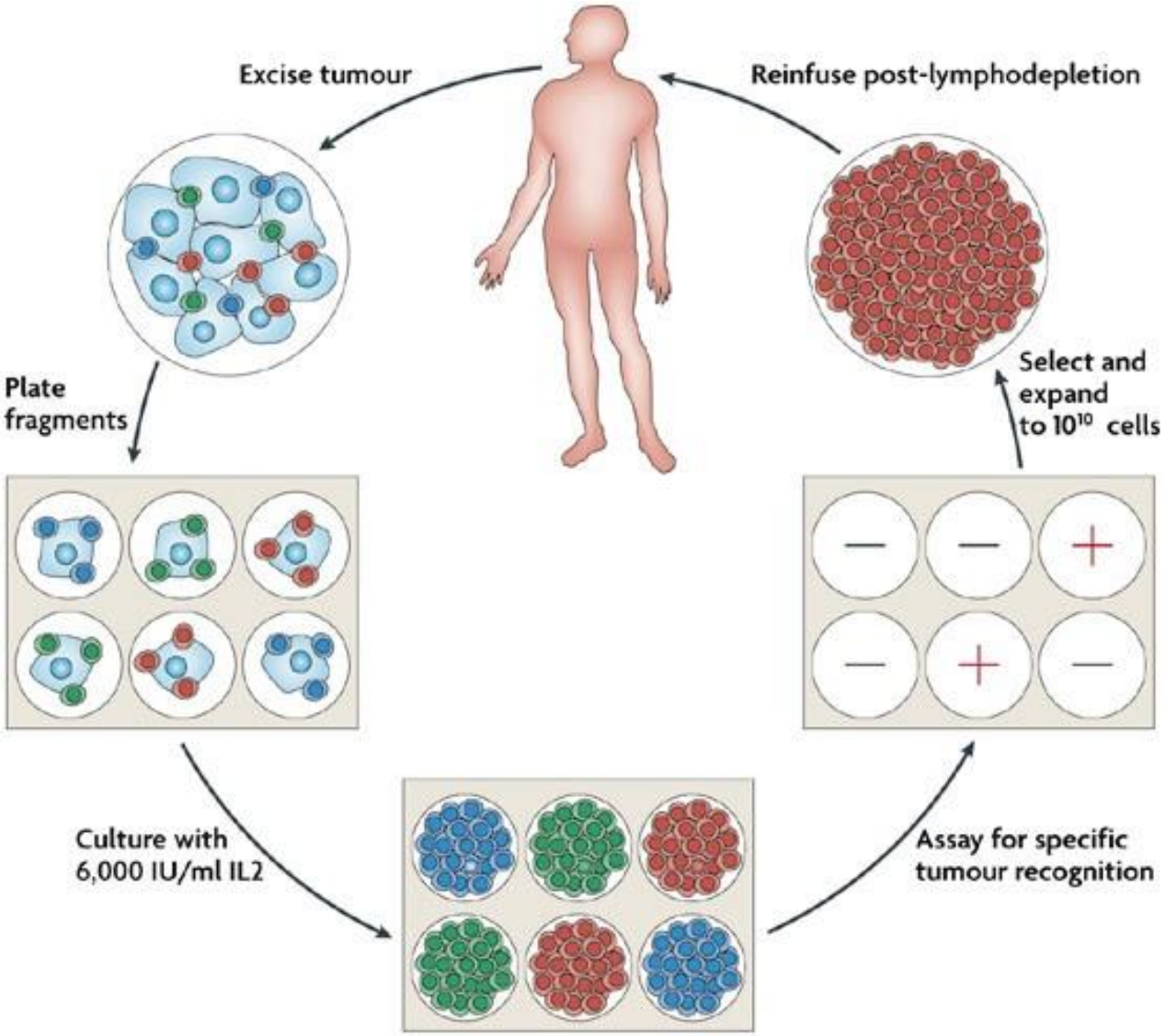
The distribution of confirmed EDSS change from study entry (baseline) to the end of the study is shown in Figure 2. There was a statistically significant difference between the AVONEX and placebo groups in confirmed change for patients with at least 2 scheduled visits (p = 0.006).

Transferência adotiva de células

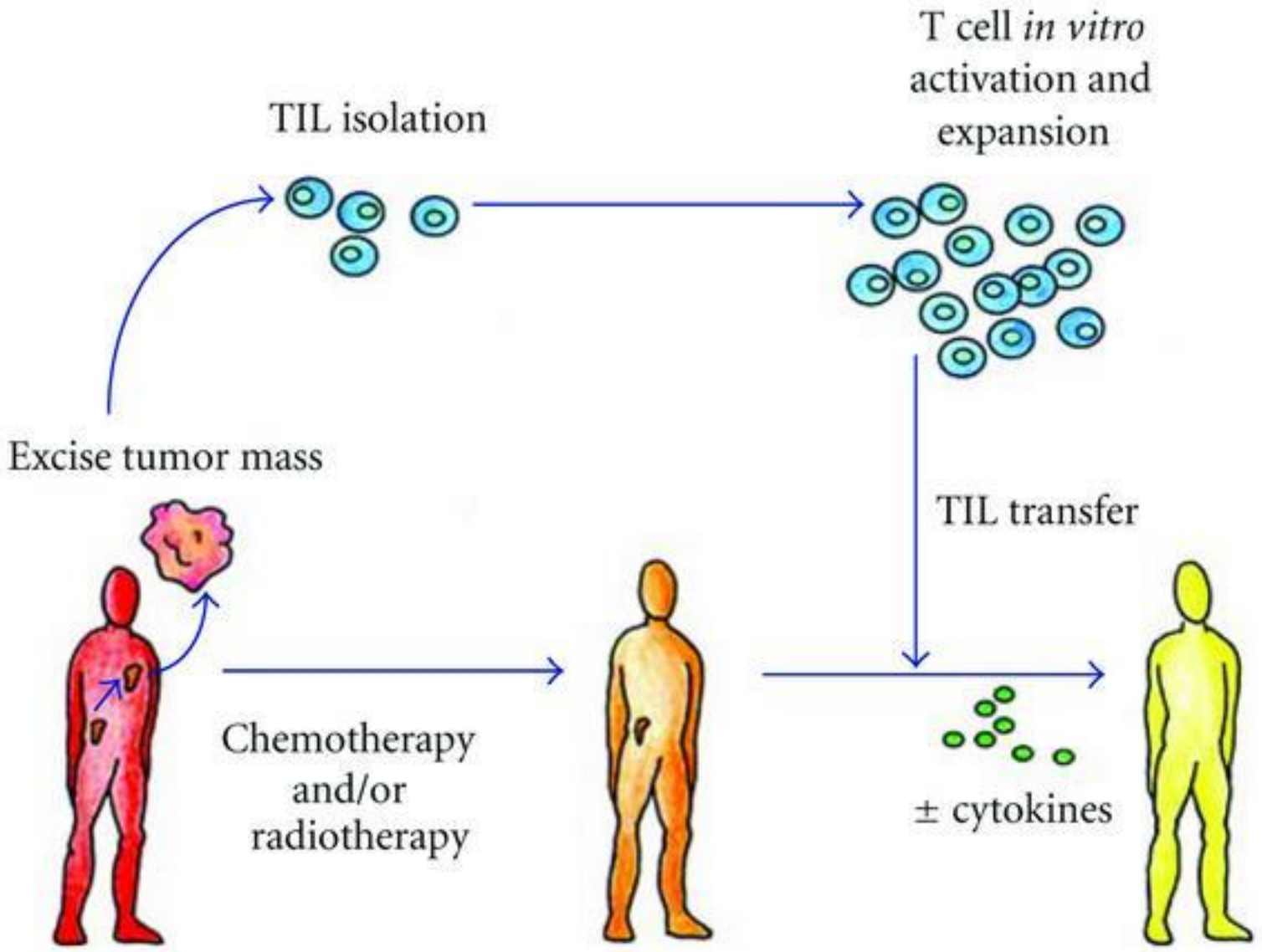
DCs carregadas com antígeno para ativação de linfócitos T



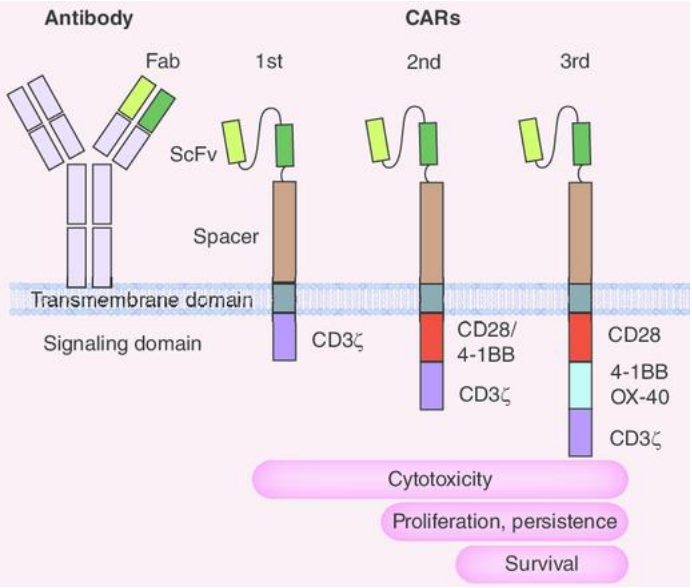
Transferência adotiva de linfócitos T

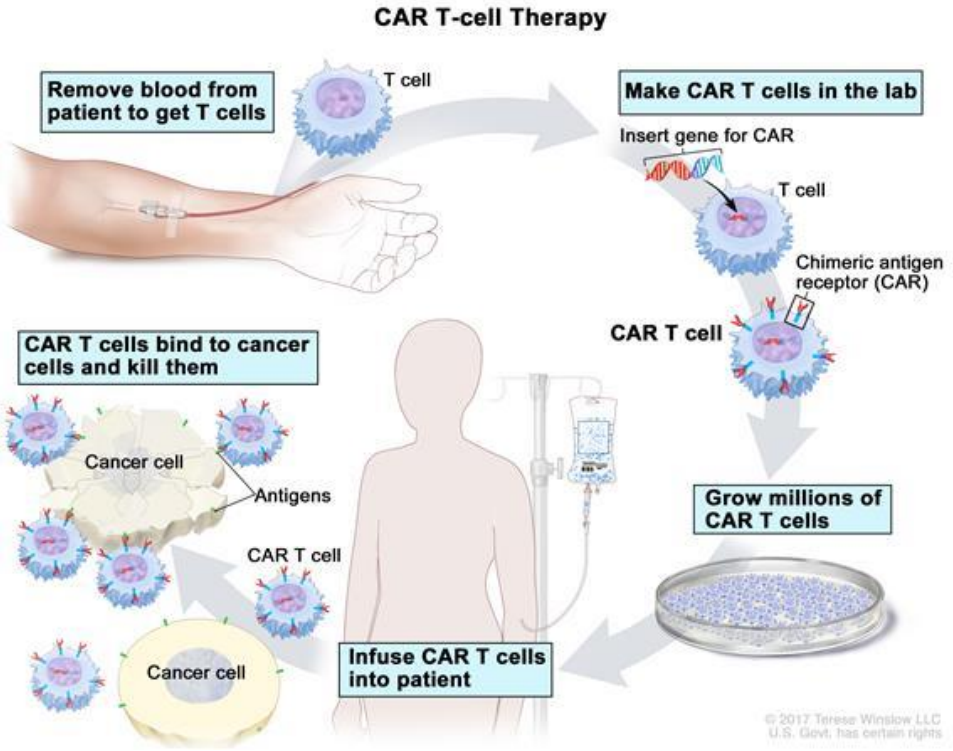


Transferência adotiva de linfócitos T



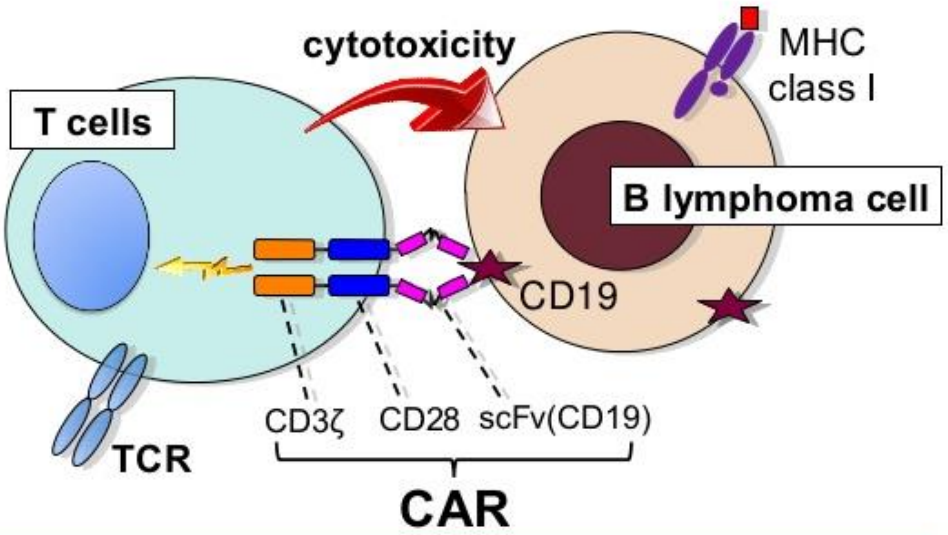
CAR T Cells – Chimeric antigen receptor





CAR T Cells – Chimeric antigen receptor

Cytotoxicity of CD19-specific CAR-expressing T Lymphocytes against B Cell Lymphoma



CD19-CAR T cells, which are engineered to express extracellular single-chain immunoglobulin variable fragments to CD19, linked to cytoplasmic T cell activation domains including CD3-ζ, showed remarkable therapeutic benefits toward $CD19^+$ B cell malignancies.

NK CAR e mielóide CAR

NK

podem ser diferenciada a partir de diversas fontes

células vivem menos

secretam IFNγ, mas também outras citocinas não secretadas por T ativadas (GM-CSF, IL-3)

apresentam outros mecanimos de reconhecimento e indução de morte de alvos, indendentes do CAR. Ex. Citotoxicidade mediada por anticorpos, regulação negativa de MHC nas células alvo e ativação de citotoxicidade.

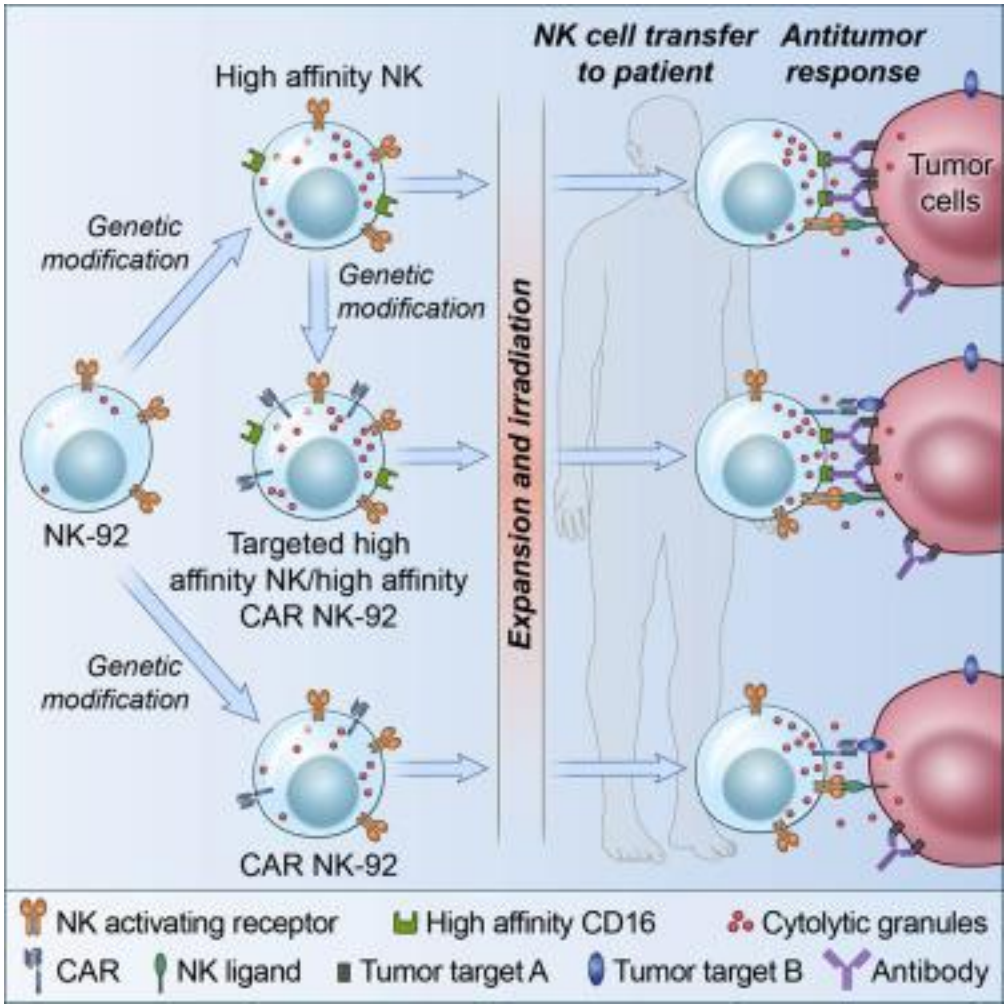
Mielóide

podem ser diferenciadas a partir de monócitos circulantes

facilmente recrutadas para o microambiente tumoral, em tumores sólidos

CAR DCs ativadas migram para órgãos linfóides secundários

difícil de modificar geneticamente


NK cell transfer to patient
Antitumor response
High affinity NK
Genetic modification
Genetic modification
Tumor cells
Expansion and irradiation
NK-92
Targeted high affinity NK/high affinity CAR NK-92
Genetic modification
CAR NK-92
NK activating receptor
High affinity CD16
Cytolytic granules
CAR
NK ligand
Tumor target A
Tumor target B
Antibody