Combination immunotherapy to tackle immune-desert cancers

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Today's Topic

- **Current status of cancer immunotherapy**
- **Overcoming resistance with combination strategies**
- **STING-based immunotherapy to tackle immune-desert microenvironment of peritoneal carcinomatosis**

Era of cancer immunotherapy

Immune checkpoint blockade in cancer !!

PD1 and CTLA-4: critical regulators of cancer-immunity

CTLA4

3. Priming and activation
(APC & T cell)

4. Trafficking of T cells to tumors

5. Infiltration of T cells into tumors

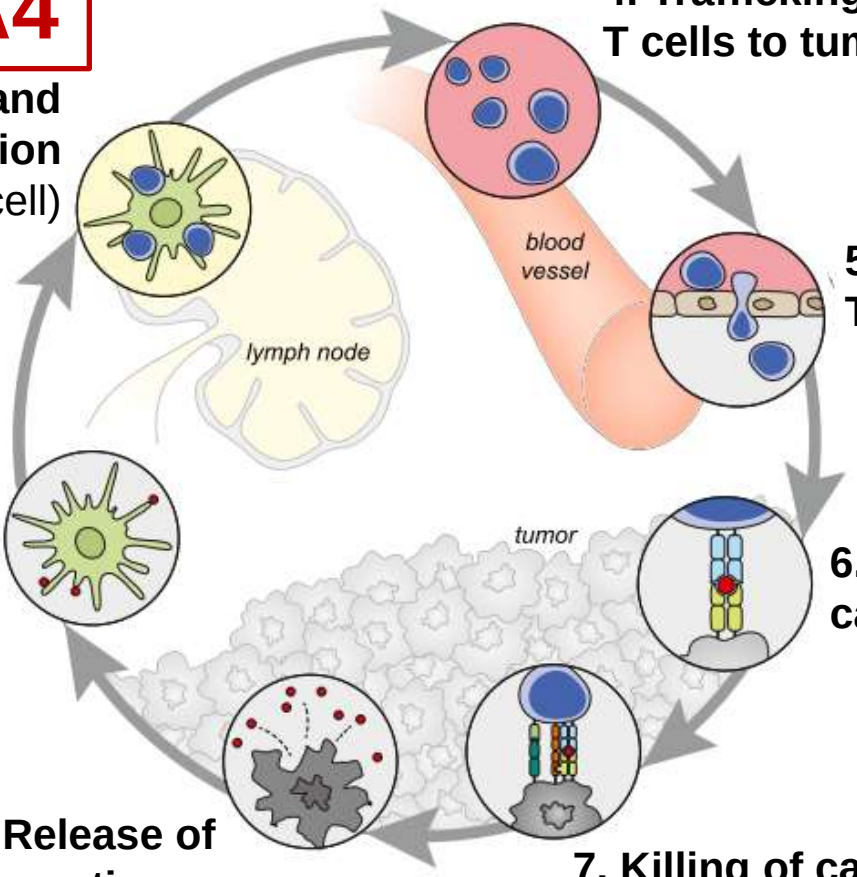
6. Recognition of cancer cell by T cells

7. Killing of cancer cells
(T cell & cancer cell)

PD1

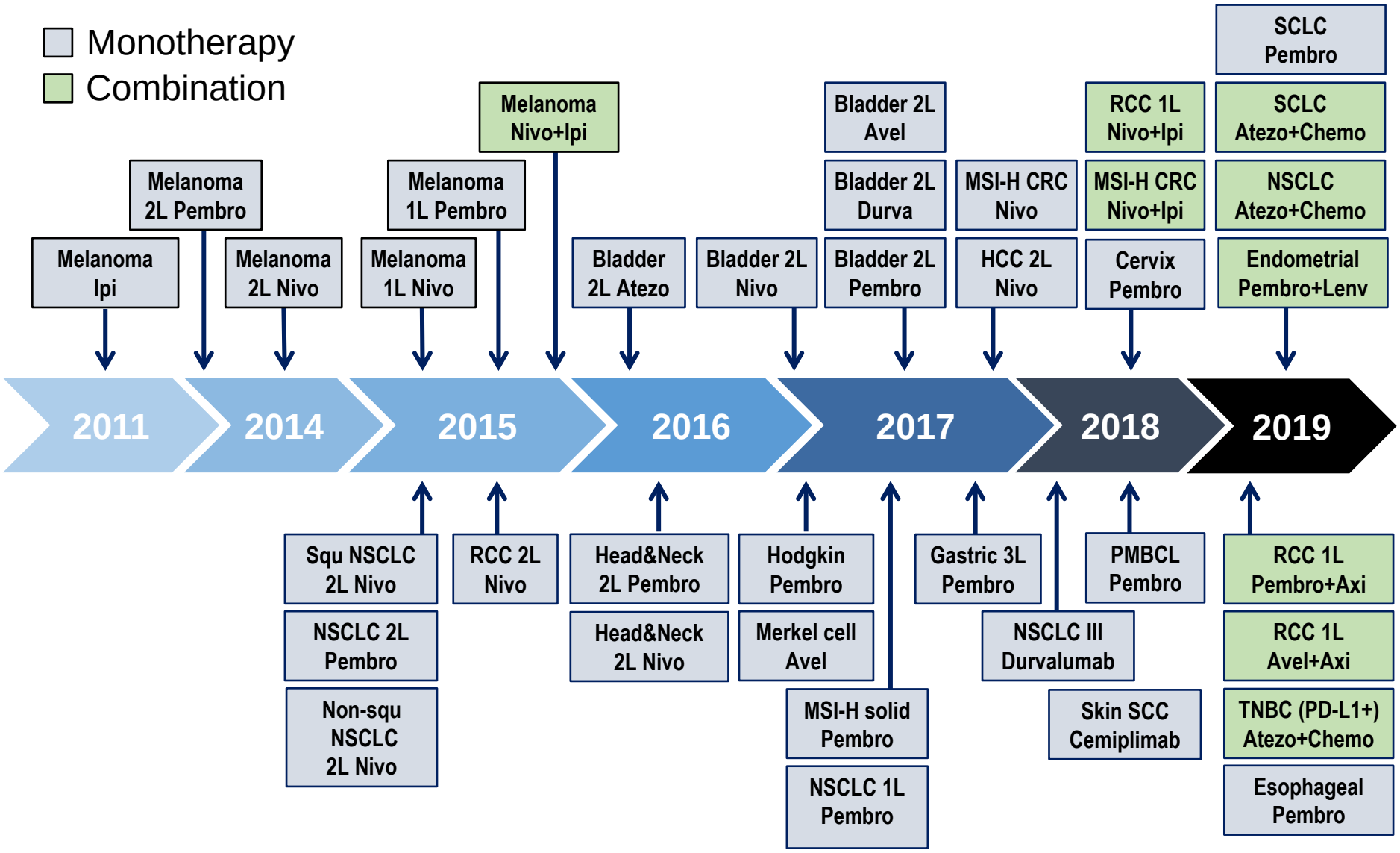
1. Release of tumor antigens
(tumor cell death)

2. Cancer antigen Presentation
(DC/APC)

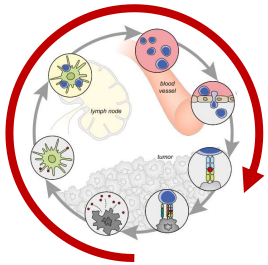


Adapted from Chen and Mellman. Immunity 2013

FDA approved immunotherapies
6 drugs in >15 tumor types

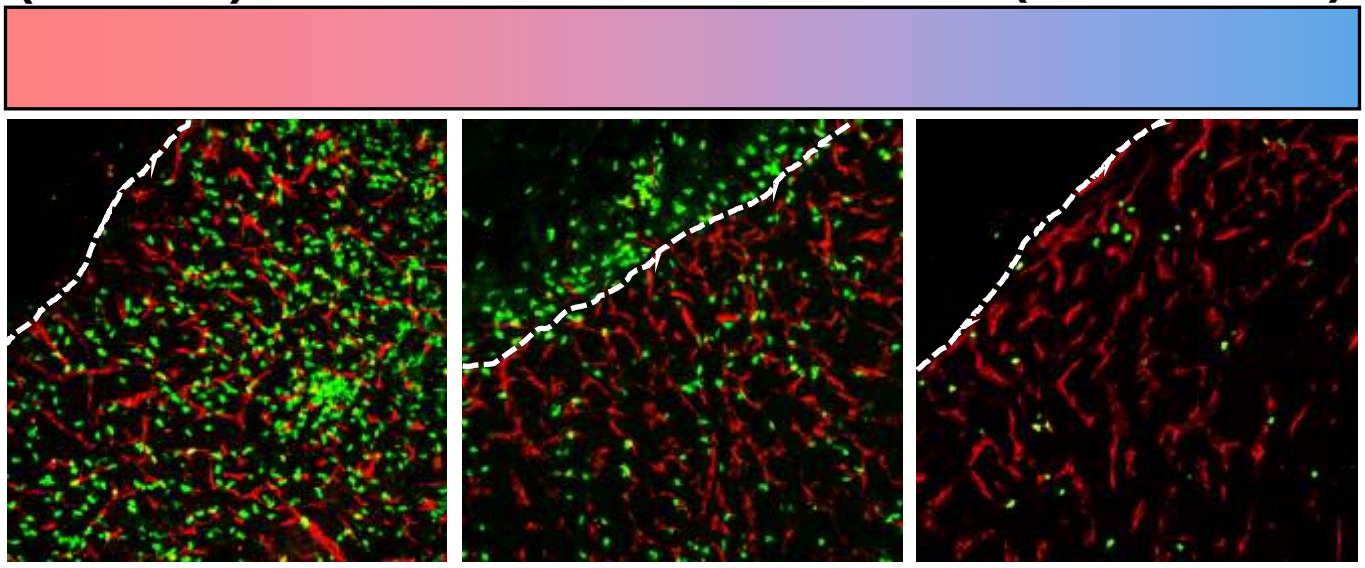


Hot vs. Cold tumors

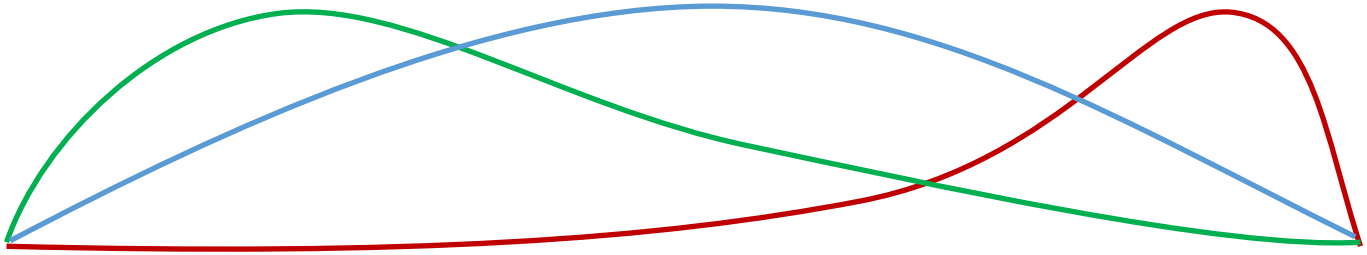


Hot tumor (Inflamed)

Cold tumor (non-Inflamed)

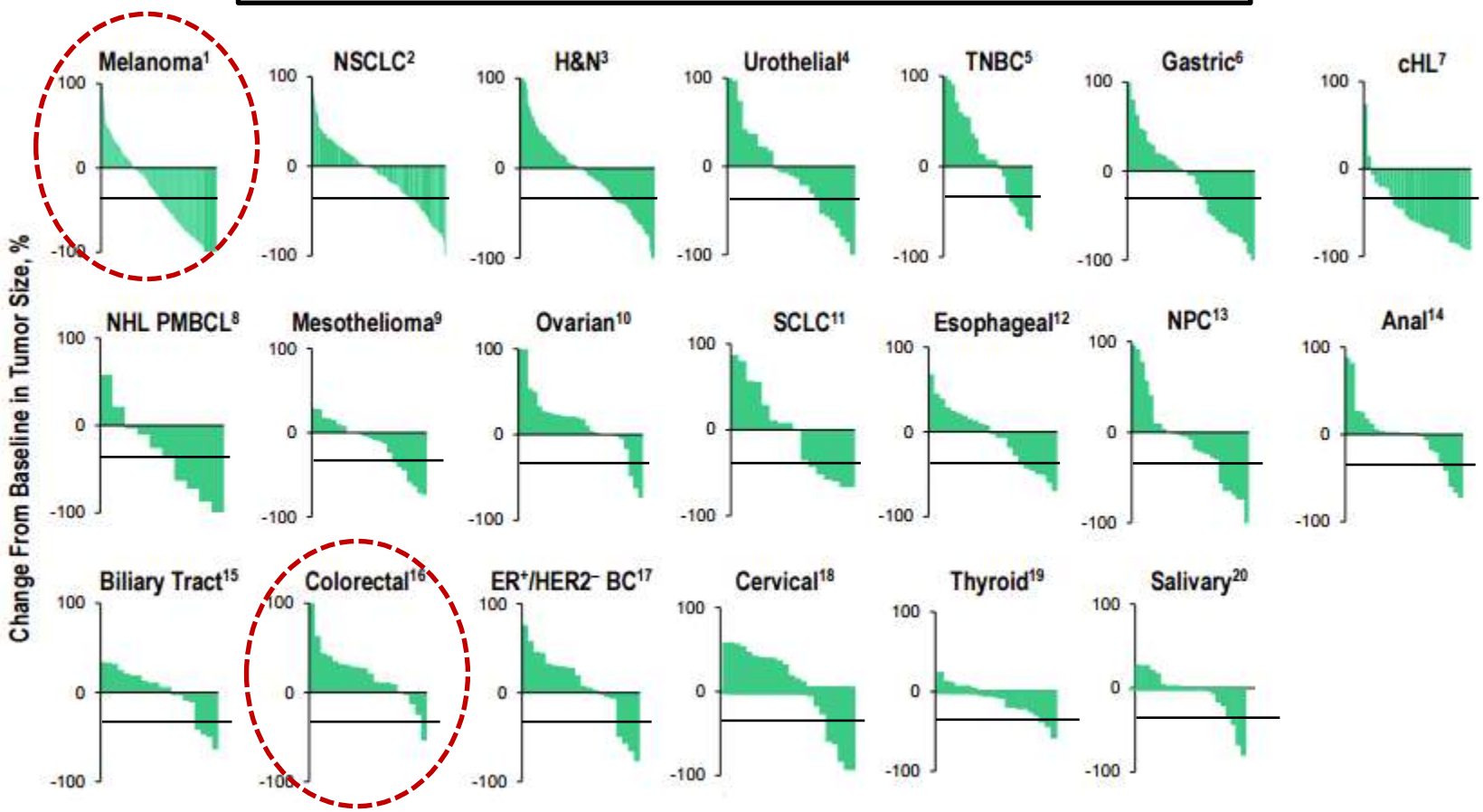


종양내 면역세포 침윤	종양 경계에 면역세포 존재	종양내 면역세포 부재
T세포 침윤, IFNγ, PD-L1, checkpoint	비정상 암혈관, 미세환경TAM, MDSCs	낮은 MHC 발현 빠른 종양증식 속도



ICI monotherapy showed a limited efficacy

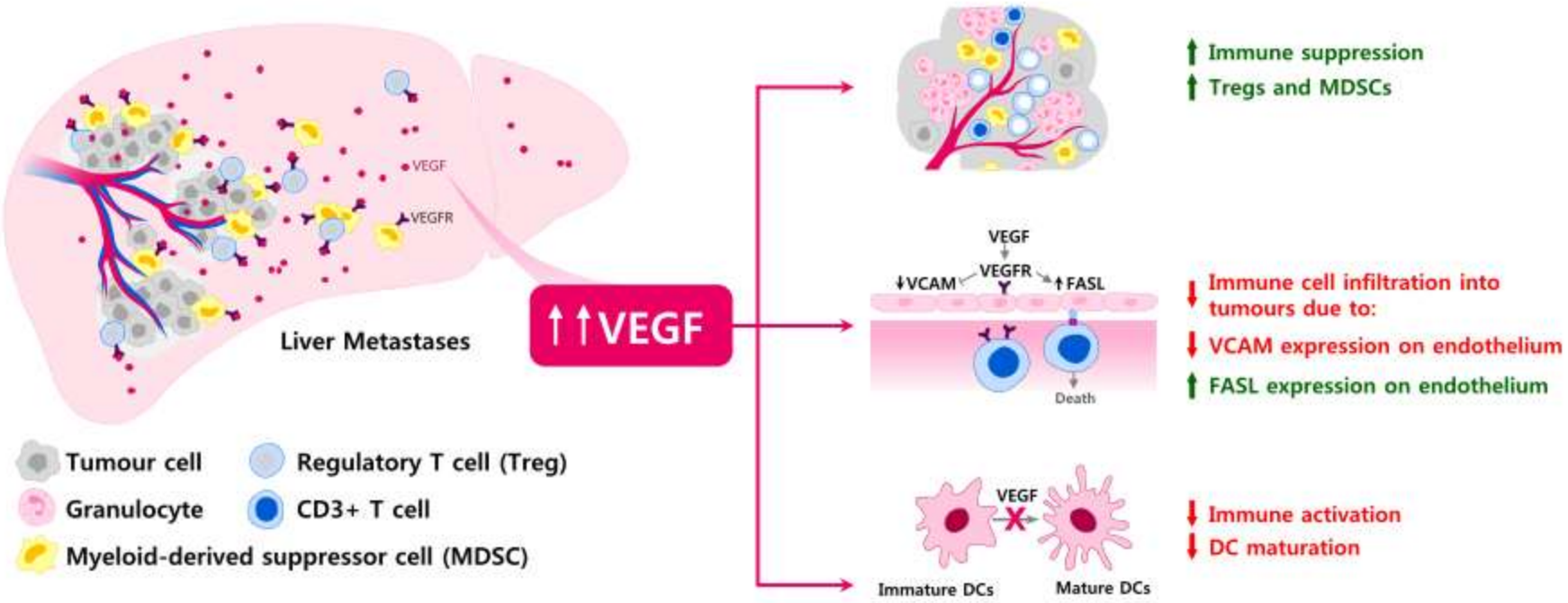
Only 20~30% response rate for solid cancers



Adopted from ASCO 2016

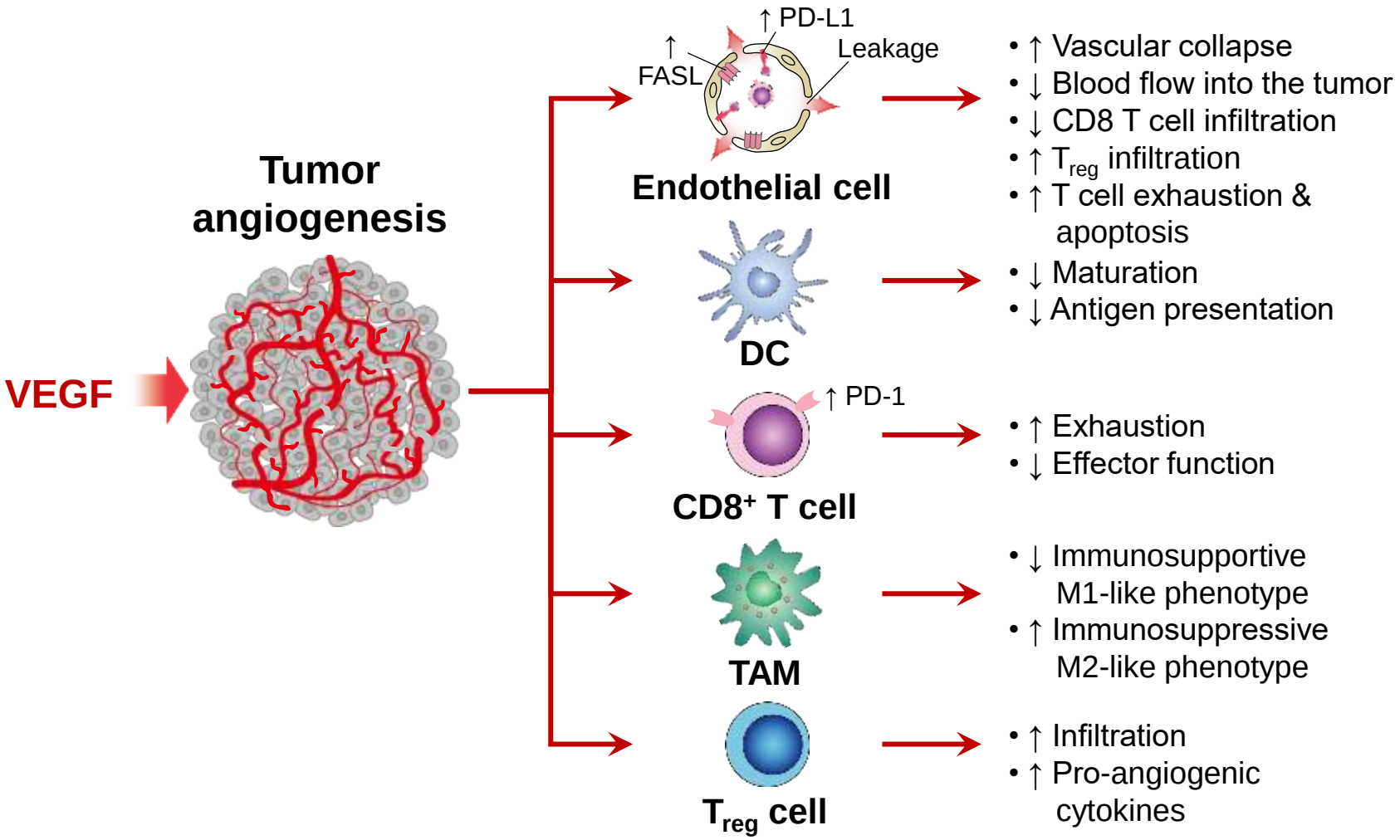
Tissue-specific immunoregulation

- **High levels of VEGF in the liver** support the hypothesis of VEGF-dependent modulation of **liver-specific mechanisms of immune tolerance**



Chen & Hurwitz. Cancer J 2018

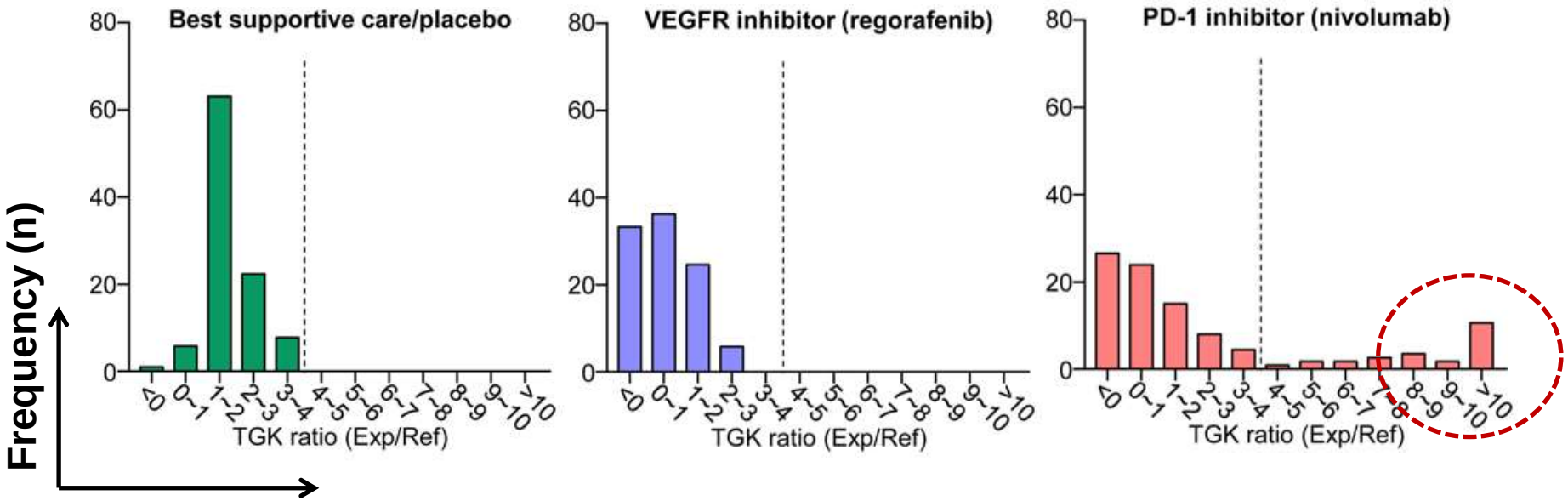
VEGF negatively impacts cancer immunity at multiple steps



Lee, Yang, Chon, and Kim. Exp. Mol. Med 2020

Cancer immunotherapy: Hyperprogressive disease

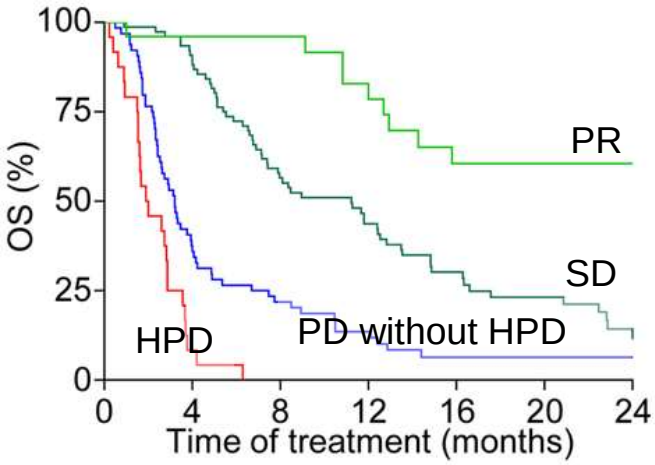
Advanced HCC patients

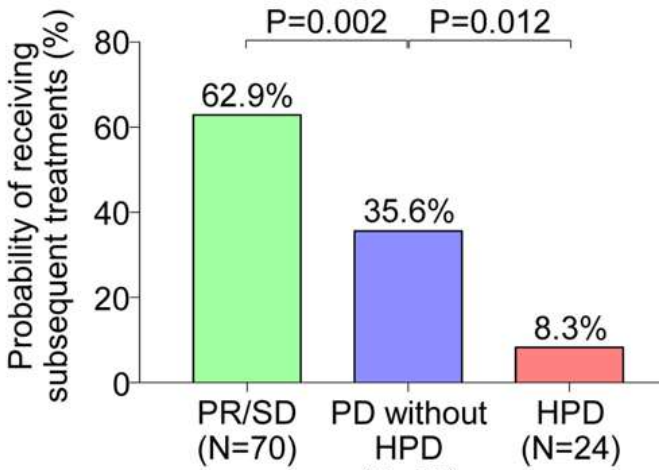


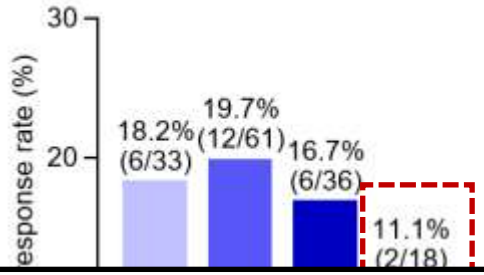
Tumor growth kinetic ratio between Experimental and Reference period

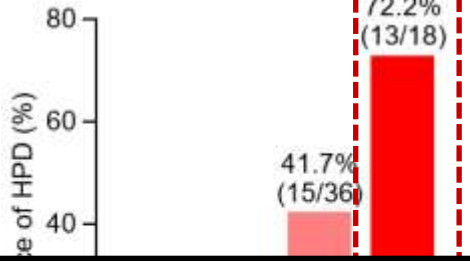
Kim and Chon. *Journal of Hepatology 2020 (IF20.582)*

Cancer immunotherapy: Hyperprogressive disease







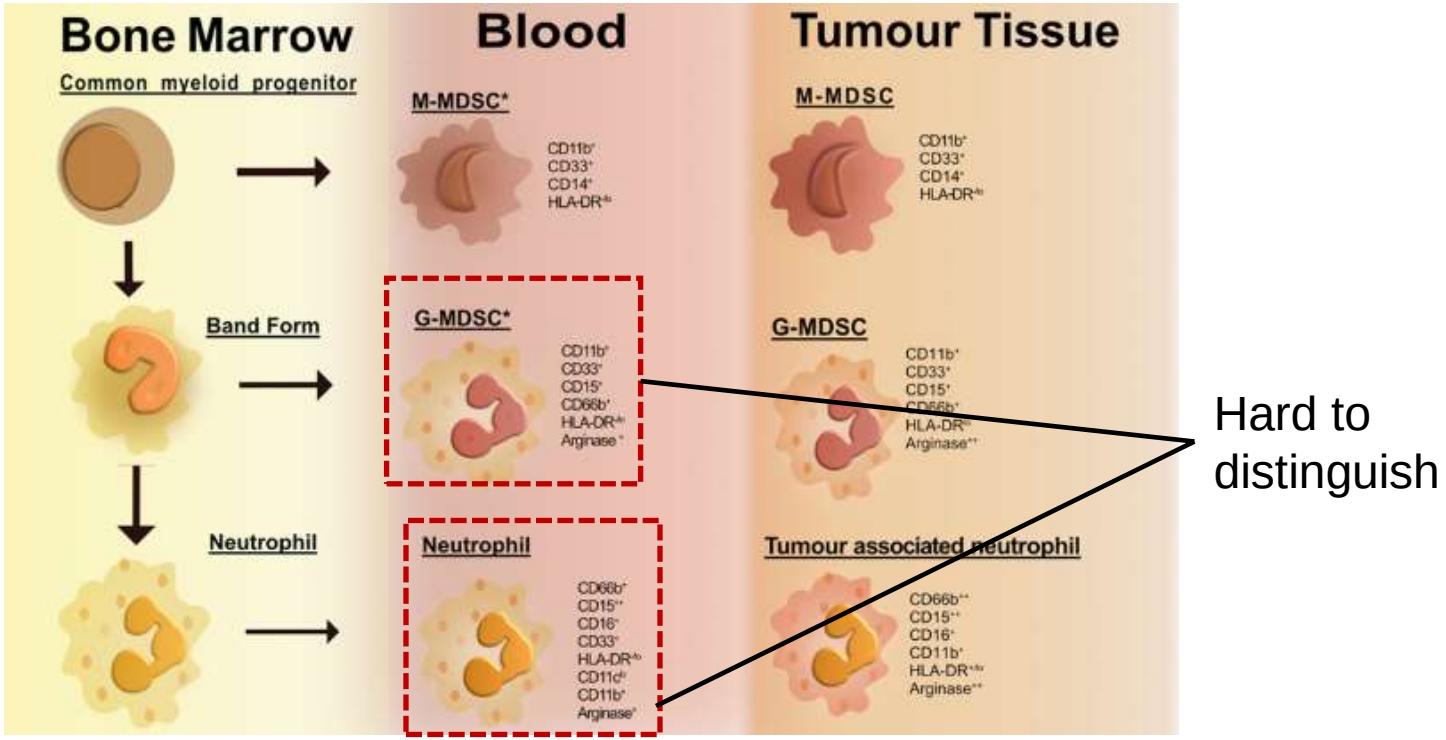


- Occurs in **a fraction** of patients
- **Dismal prognosis**
- **Deprivation of chances for subsequent treatment**
- Associated with **high NLR**

Kim and Chon. *Journal of Hepatology 2020 (IF20.582)*

Immunosuppressive myeloid cells

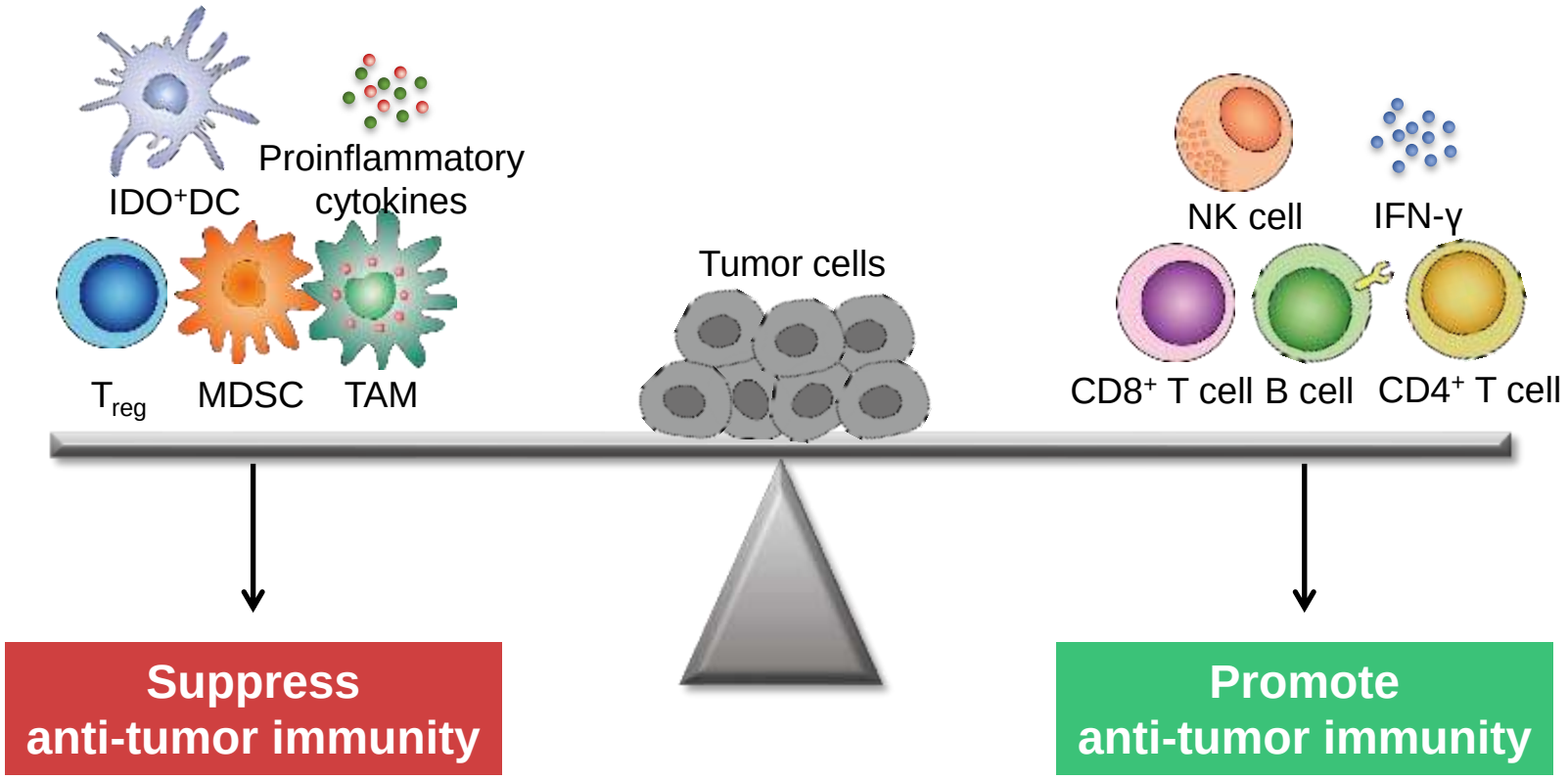
- High neutrophil in RCC → Poor prognosis ! (IMDC risk factor)
- **Neutrophil in CBC = Neutrophil + PMN-MDSC**
- MDSC: immunosuppressive myeloid cells



Immune effectors vs. suppressors

Neutrophil to Lymphocyte ratio

≈ Suppressor to Effector ratio



Summary of Part I

- **Dramatic and durable responses**
- **Limited efficacy (20~30% Response rate)**
- **Stroma-dependent variable responses**
- **Hyperprogression in a fraction of patients**

Today's Topic

- Current status of cancer immunotherapy
- **Overcoming resistance with combination strategies**
- STING-based immunotherapy to tackle immune-desert microenvironment of peritoneal carcinomatosis

Complexity of cancer-immunity cycle

CTLA4

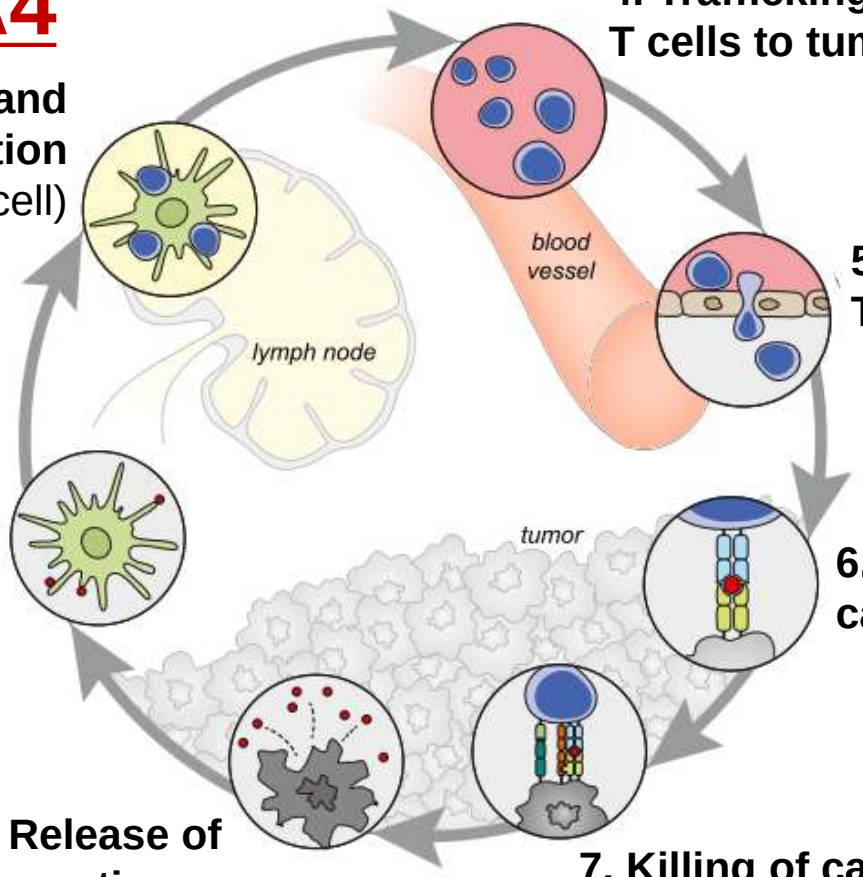
CD28/B7-1
CD137/CD137L
OX40/OX40L
CTLA-4/B7-1
PD-L1/PD-1
PD-L1/B7-1

3. Priming and activation
(APC & T cell)

4. Trafficking of T cells to tumors

CX3CL1, CXCL9
CXCL10, CCL5
VEGF

VEGF



5. Infiltration of T cells into tumors

LFA1/ICAM1
Selectins
VEGF

2. Cancer antigen Presentation
(DC/APC)

TNF-α, IL-1, IFN- α
CD40/CD40L
IL-4,10,13, VEGF

6. Recognition of cancer cell by T cells

TCR
reduced MHC

VEGF

1. Release of tumor antigens
(tumor cell death)

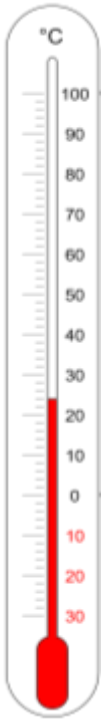
7. Killing of cancer cells
(T cell & cancer cell)

PD1

IFNγ
PD-L1/PD1
PD-L1/B7-1
IDO, TGFβ, LAG3
BTLA, VISTA,
Arginase

Stimulatory factors
Inhibitors

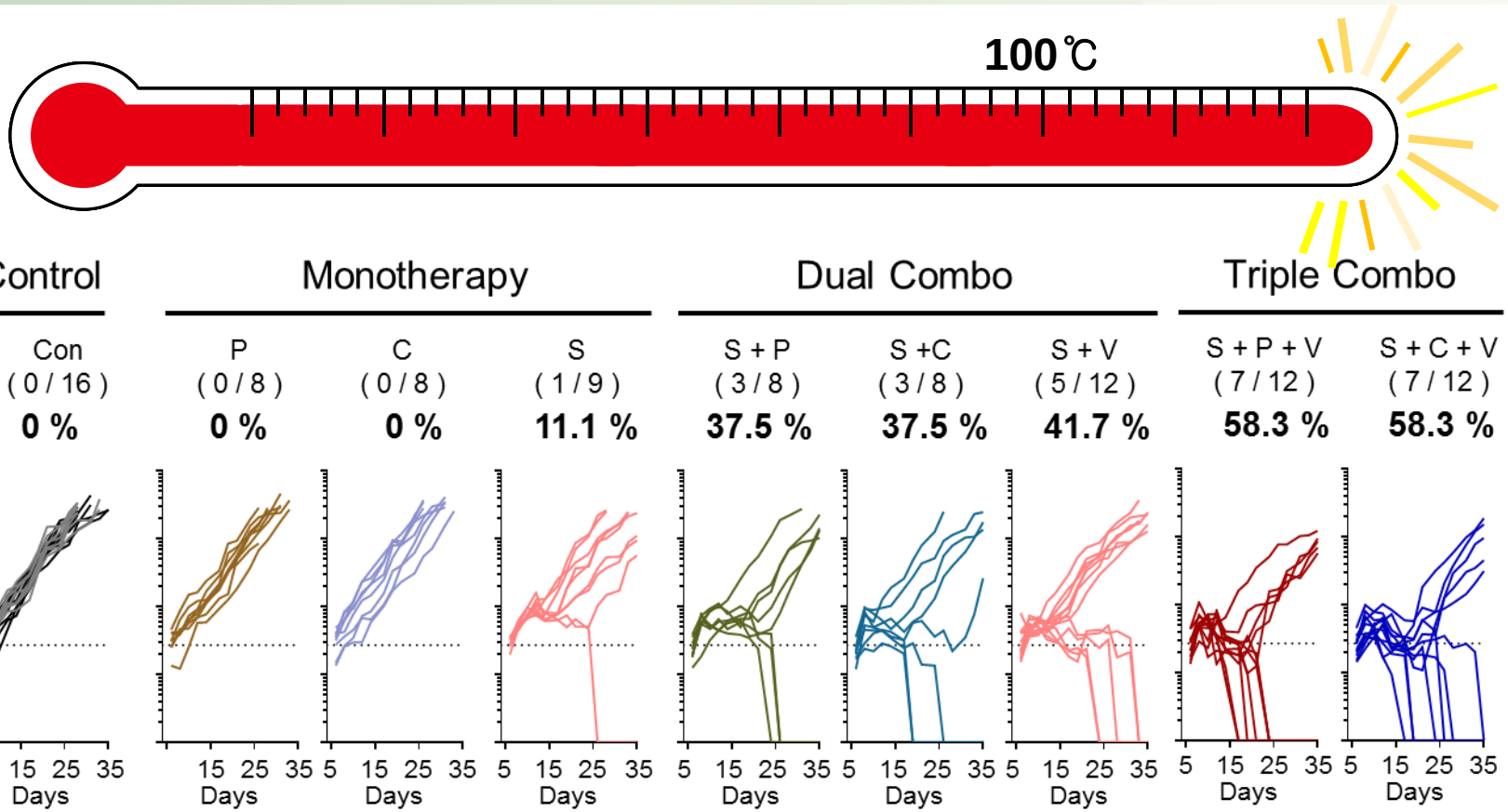
Optimal Combination Immunotherapy:
Beyond Immunologic Boiling Point



All or None Responses

We have to inflame tumors beyond immunological boiling point !

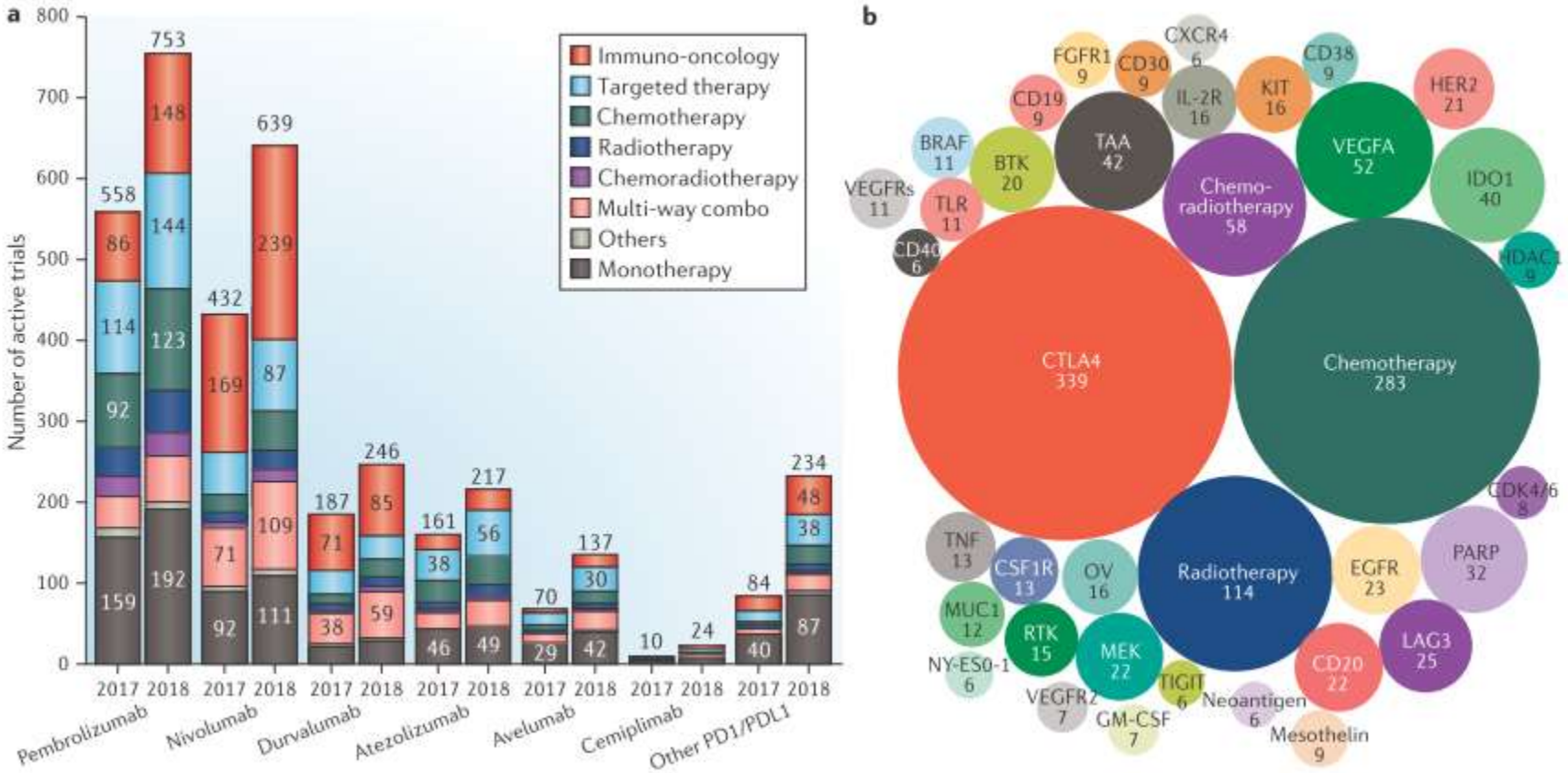
Optimal Combination Immunotherapy:
Beyond Immunologic Boiling Point



P: anti-PD1 **C**: anti-CTLA4
S: STING agonist **V**: anti-VEGFR2

Yang, Chon, Kim. J. Clin. Invest 2019 (IF 12.282)

Landscape of ongoing cancer immunotherapy clinical trials



- **진행중인 임상연구 총 수:** 2,250
- **병용 임상연구 총 수:** 1,716
  - 240개의 서로 다른 표적

Tang J et al, Nature reviews Drug discovery. 2018;17(12):854.

Overcoming Resistance to Immunotherapy

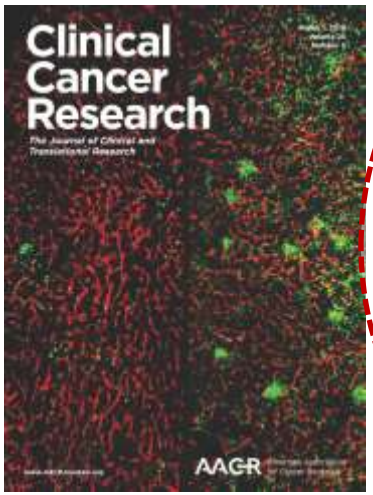
Goal	Candidate Intervention
1. Promote innate immunity	• Local Radiation • TLR agonist • STING agonist • Targeted IFNα/β • Oncolytic Virus • Vaccinia virus, Reovirus, Herpesvirus • Oncolytic bacteraia
2. Induce tertiary lymphoid structure	• Intratumoral LIGHT • Lymphotoxin

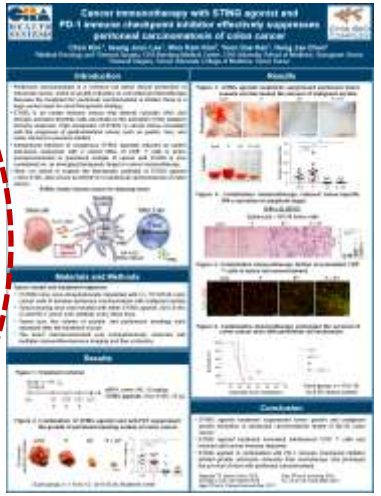
3. Stromal modulation	• Anti-angiogenic agent
	  • Lenvatinib, Cabozantinib, Regorefenib
	  • ABTAA (Ang2-binding/Tie2-activating Ab)
	• Anti-CDXXX
	• EtB receptor inhibitor

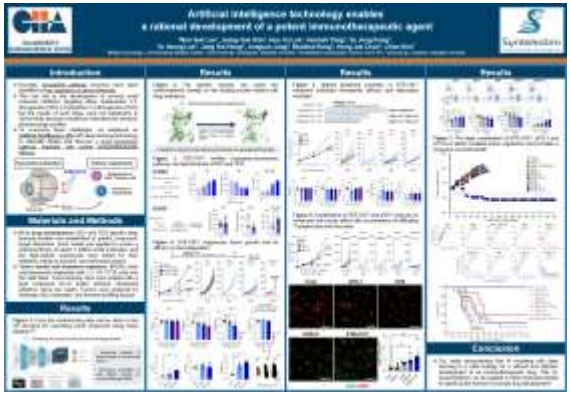
4. Inhibit immunosuppressive oncogene pathways	• MerTK inhibitor • JAK inhibitors • IDO or TDO inhibitor • Anti-TIGIT antibody • Anti-GITR antibody • AhR inhibitor
5. Microbiome modulation	• Probiotics • Prebiotics

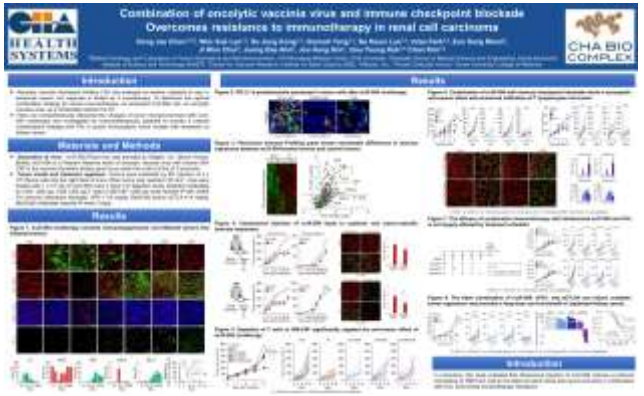
Overcoming Resistance to Immunotherapy

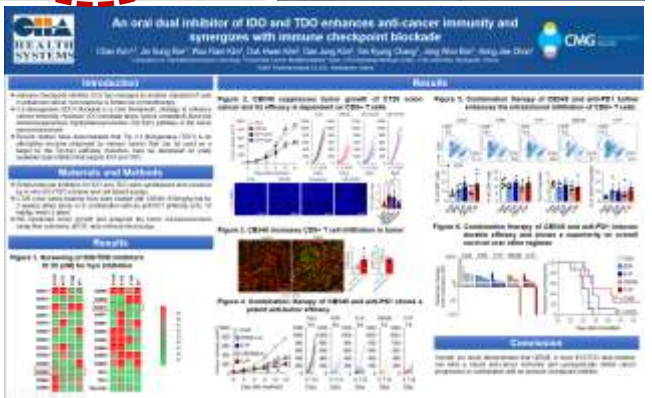
Our experiences since 2015



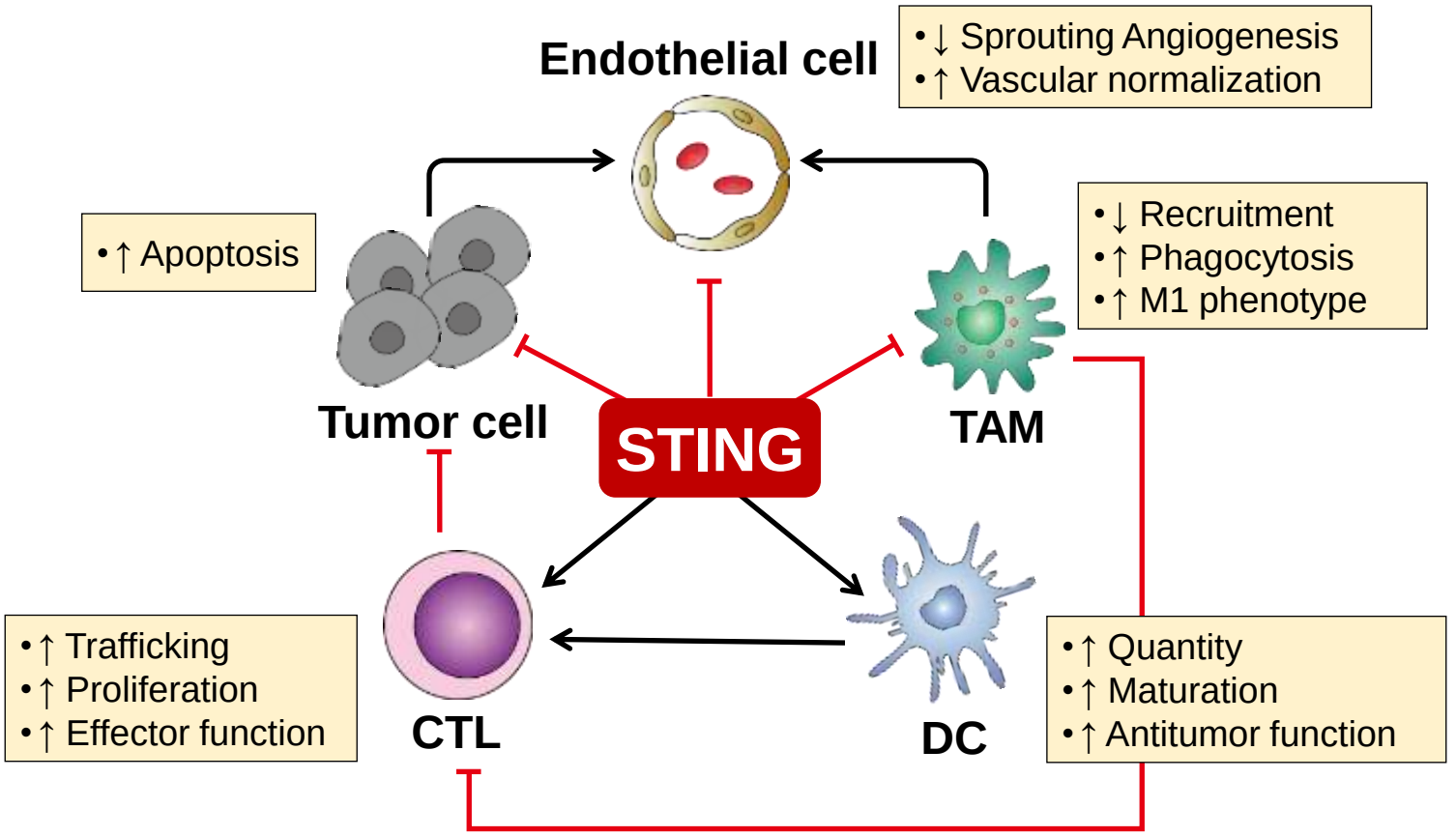








STING regulates both angiogenesis and immunity



Yang, Chon, Kim. J. Clin. Invest 2019

Thank you for listening !