



SITC 2017

November 8-12
NATIONAL HARBOR
MARYLAND

Gaylord National Hotel
& Convention Center



Society for Immunotherapy of Cancer

November 8-12 • NATIONAL HARBOR, MD

SITC
2017

An Immunogram for the Cancer-Immunity Cycle: Towards Personalized Cancer Immunotherapy

Takahiro Karasaki M.D.

Japanese Association of Cancer Immunology (JACI)



Society for Immunotherapy of Cancer

#SITC2017

Presenter Disclosure Information

Takahiro Karasaki

The following relationships exist related to this presentation:

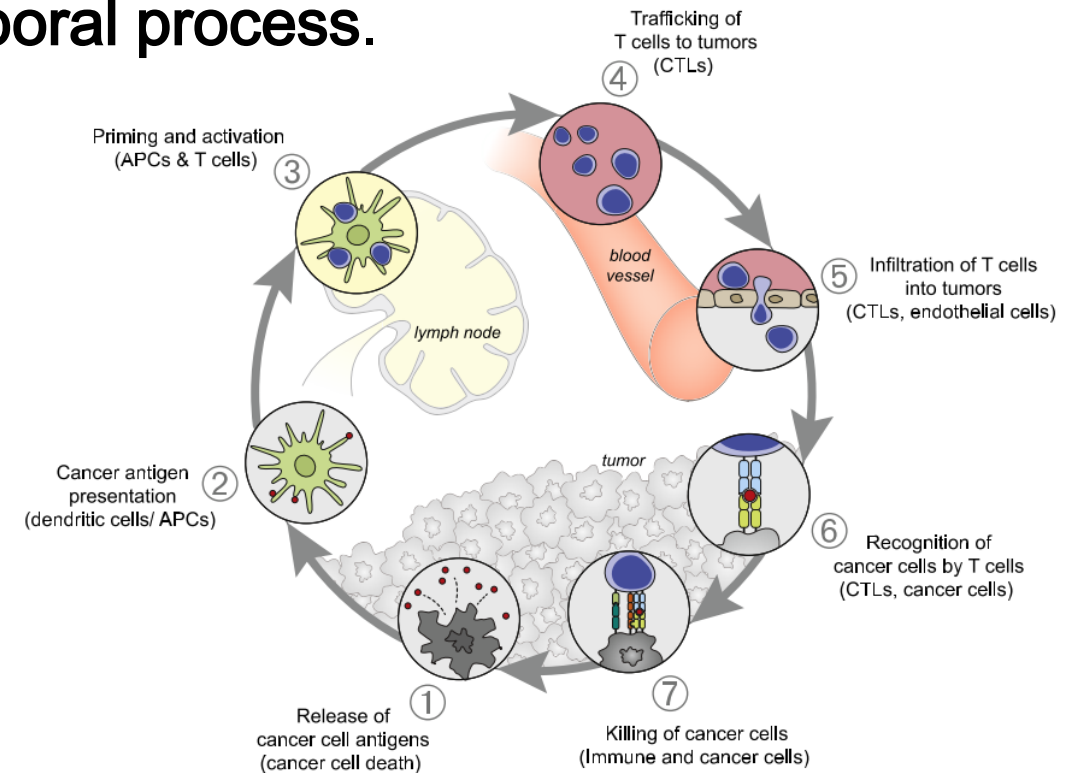
<No Relationships to Disclose>

Objectives

- Anti-tumor immunity is a **dynamic spacio-temporal process**.

→ The Cancer-Immunity Cycle (CIC)

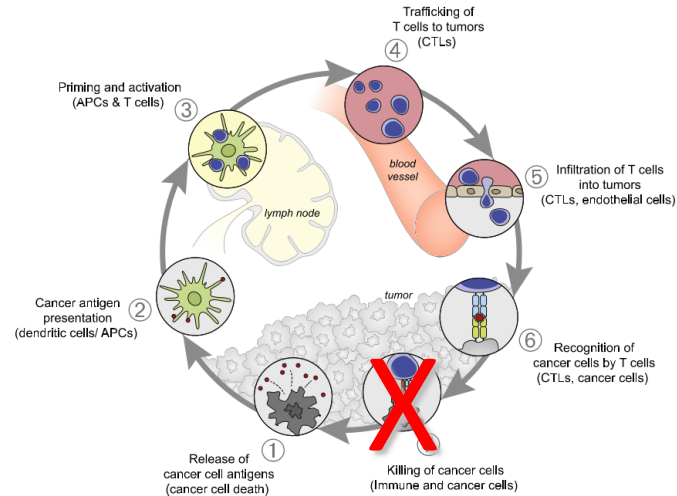
- Comprehensive assessment of “**CIC status**” is important for successful cancer immunotherapy.
- We recently developed an “**Immunogram for CIC**” to **evaluate** and **visualize** “CIC status” in each patient.



The Cancer-Immunity Cycle

Chen DS & Mellman I. Immunity 2013;39:1-10

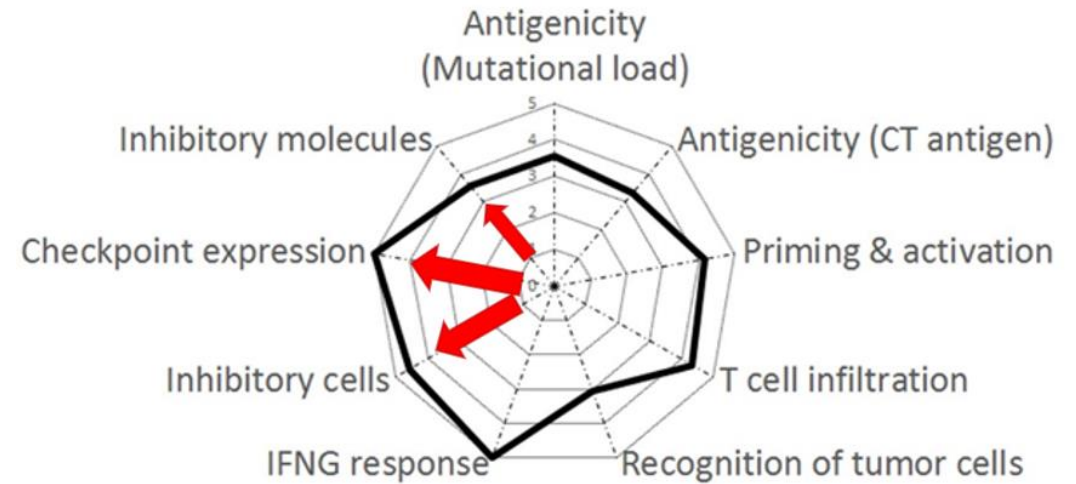
“The Cancer-Immunity Cycle”



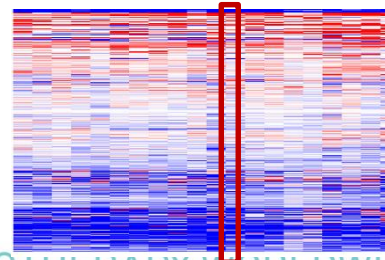
Chen DS & Mellman I. Immunity 2013

Describe the status of cancer immunity cycle in each patient using NGS data

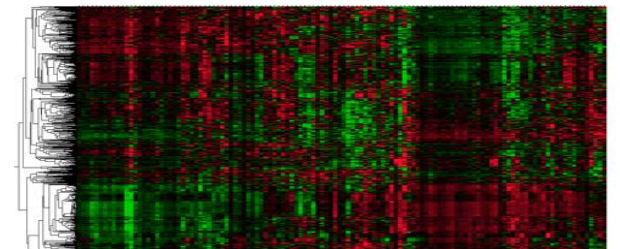
Immunogram for the Cancer-Immunity Cycle



NGS data of each patient



TCGA data for standardization

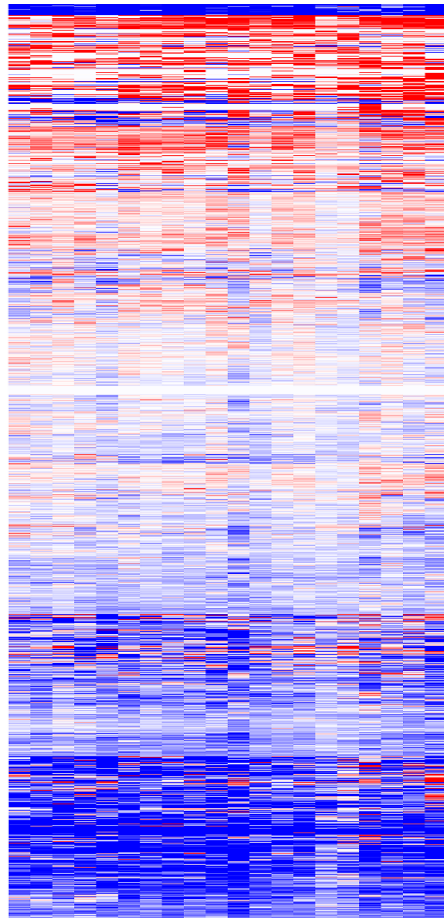


Methods

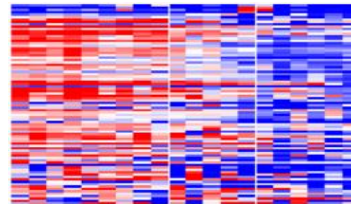
- Surgically resected non-small cell lung carcinoma:
N=25 (13 Ad, 11 Sq, 1 LCNEC)
- NGS data analyses
RNA-Seq (tumor) -> expression analyses
Whole-exome sequencing (tumor & normal) -> somatic mutation analysis
- TCGA-LUAD & LUSC data (n=1035) for standardization

Methods modified from *Karasaki T, et al.*

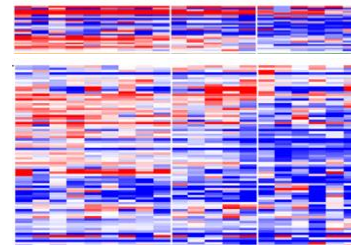
RNAseq
Expression Analysis → Extraction of
immune-related
genes



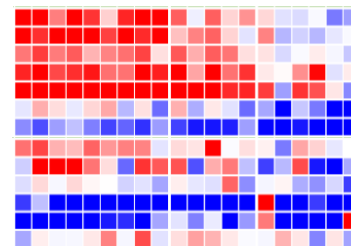
T cell



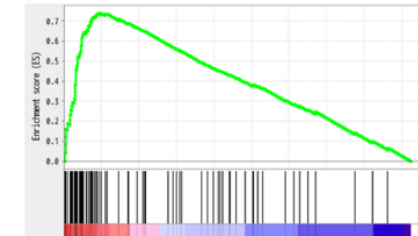
Tregs
MDSC



Inhibitory
molecules

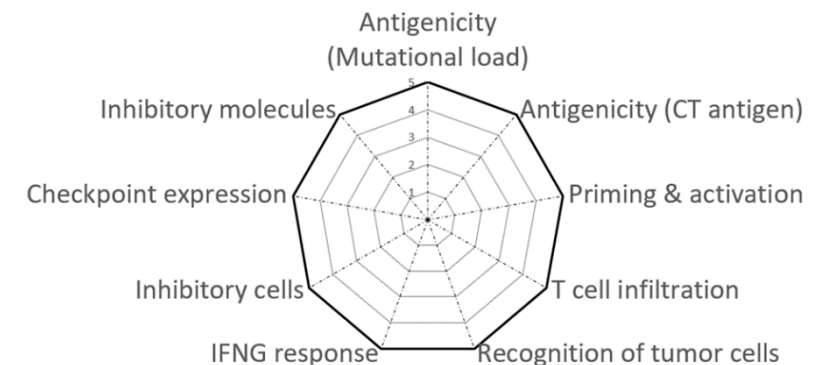


→ Scoring
(ssGSEA etc.)



Normalization
using TCGA data

Immunogram score (x9)



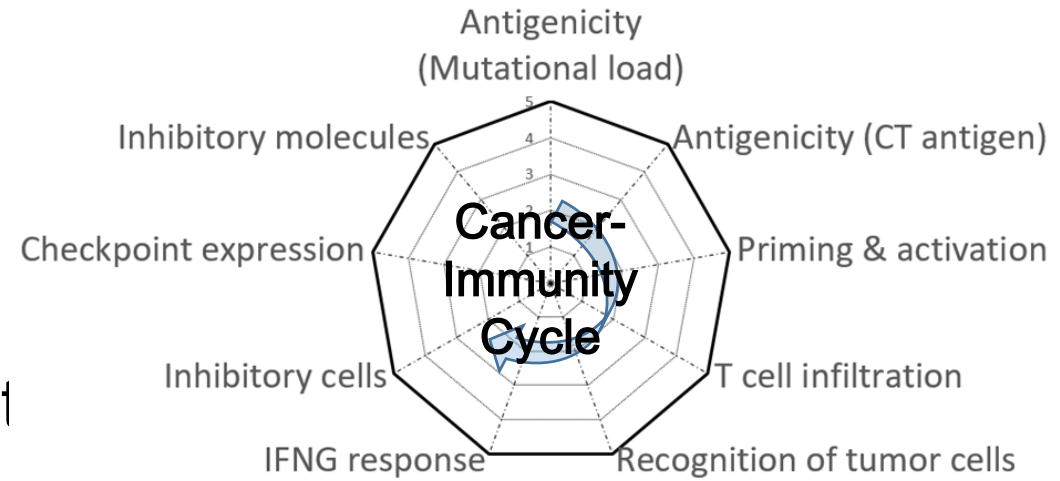
Calculation of Immunogram Scores

Antigenicity:

1. Missense mutational load
2. Expressed CT-Antigen load

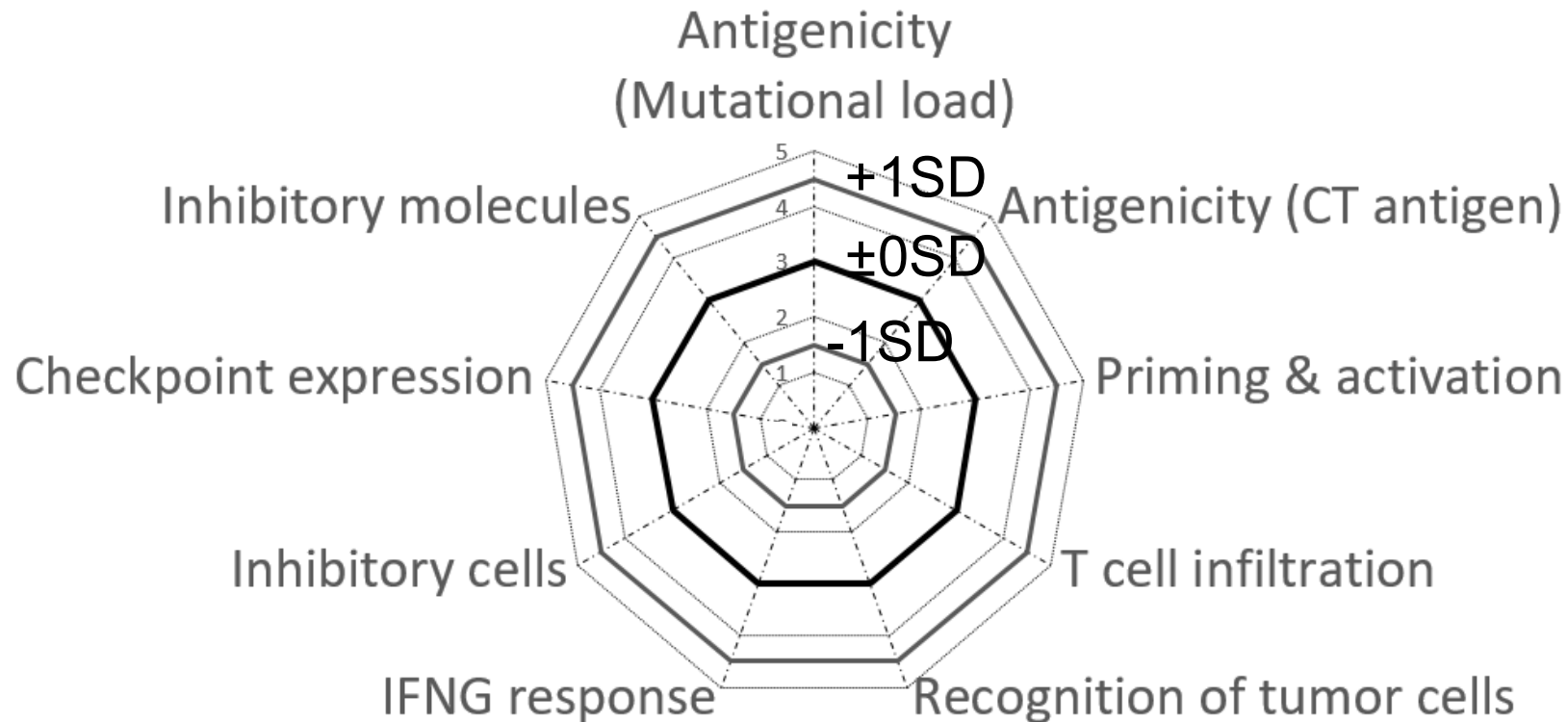
Priming & activation (activated DC enrichment)
T cell infiltration (activated CD8 T cell" enrichment),
IFNG response, **Recognition of tumor cells** (antigen presentation),
Inhibitory cells (enrichment of Tregs & MDSC):
→ scoring by ssGSEA

Checkpoint & inhibitory molecule expression:
→ scoring by mean FPKM (geometric)



Methods modified from *Karasaki T, et al. J Thorac Oncol 2017;12:791-803*

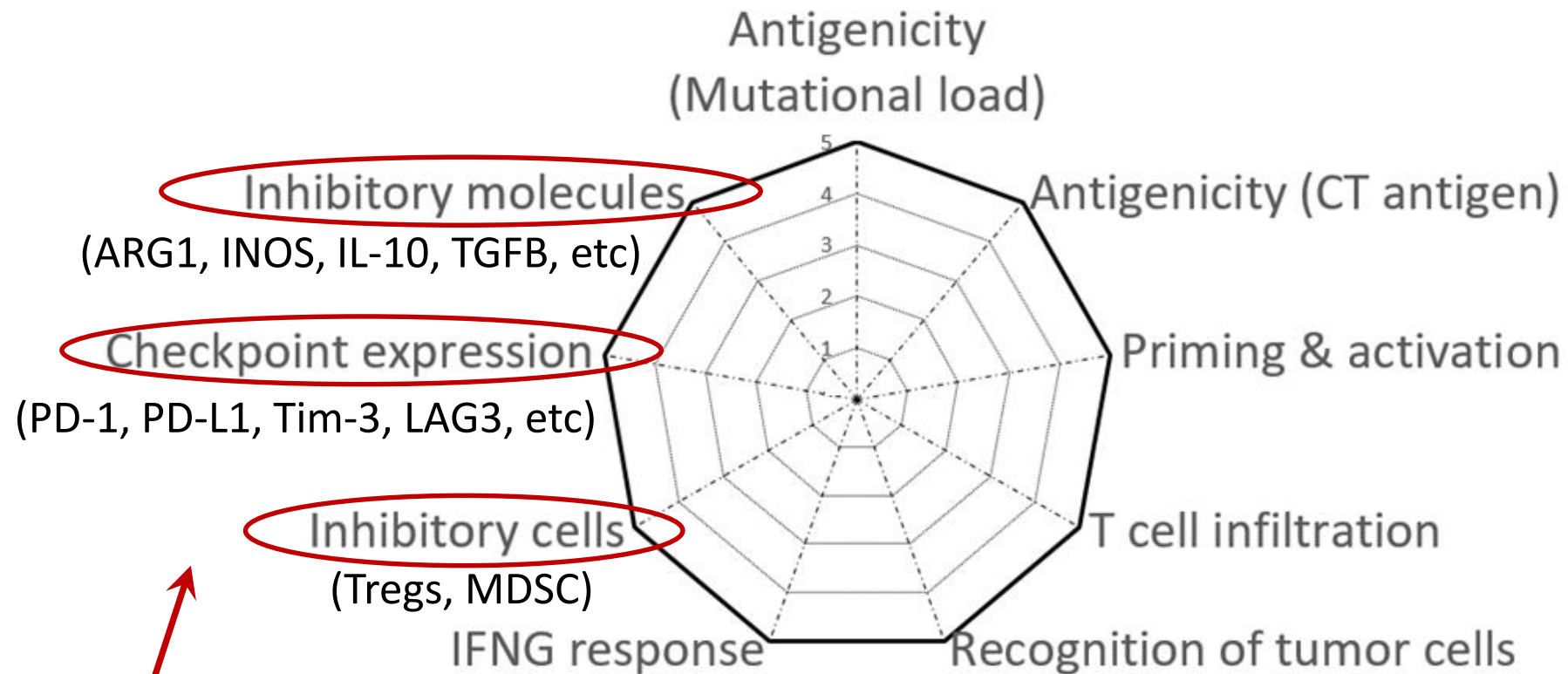
Immunogram for the Cancer-Immunity Cycle



3 : Mean score of TCGA LUAD/LUSC cohort
 >3 : higher than TCGA mean (max:5)
 <3 : lower than TCGA mean (min:1)

Methods modified from *Karasaki T, et al. J Thorac Oncol 2017;12:791-803*

Immunogram for the Cancer-Immunity Cycle

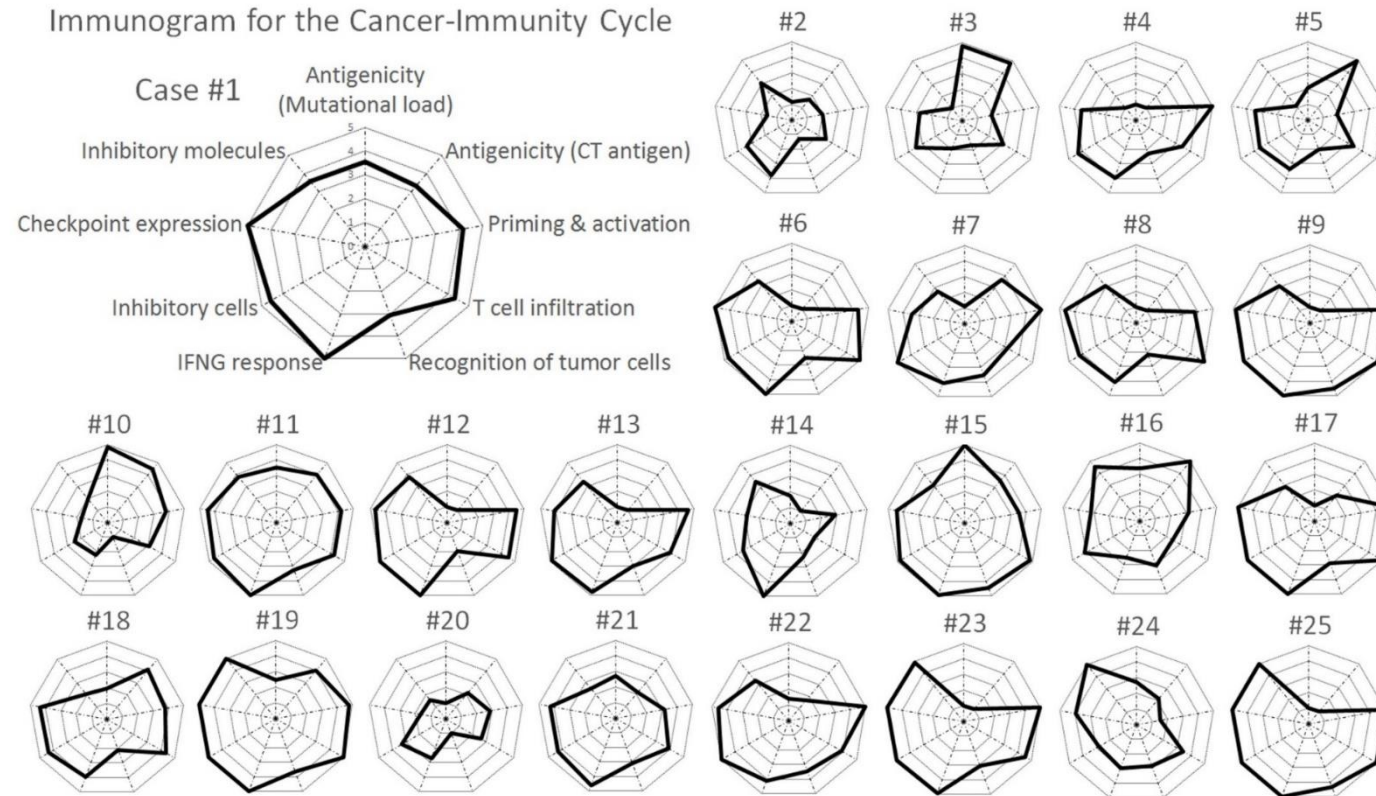


High scores of these axes
reflect immune **suppression**

Methods modified from *Karasaki T, et al.*
J Thorac Oncol 2017;12:791-803

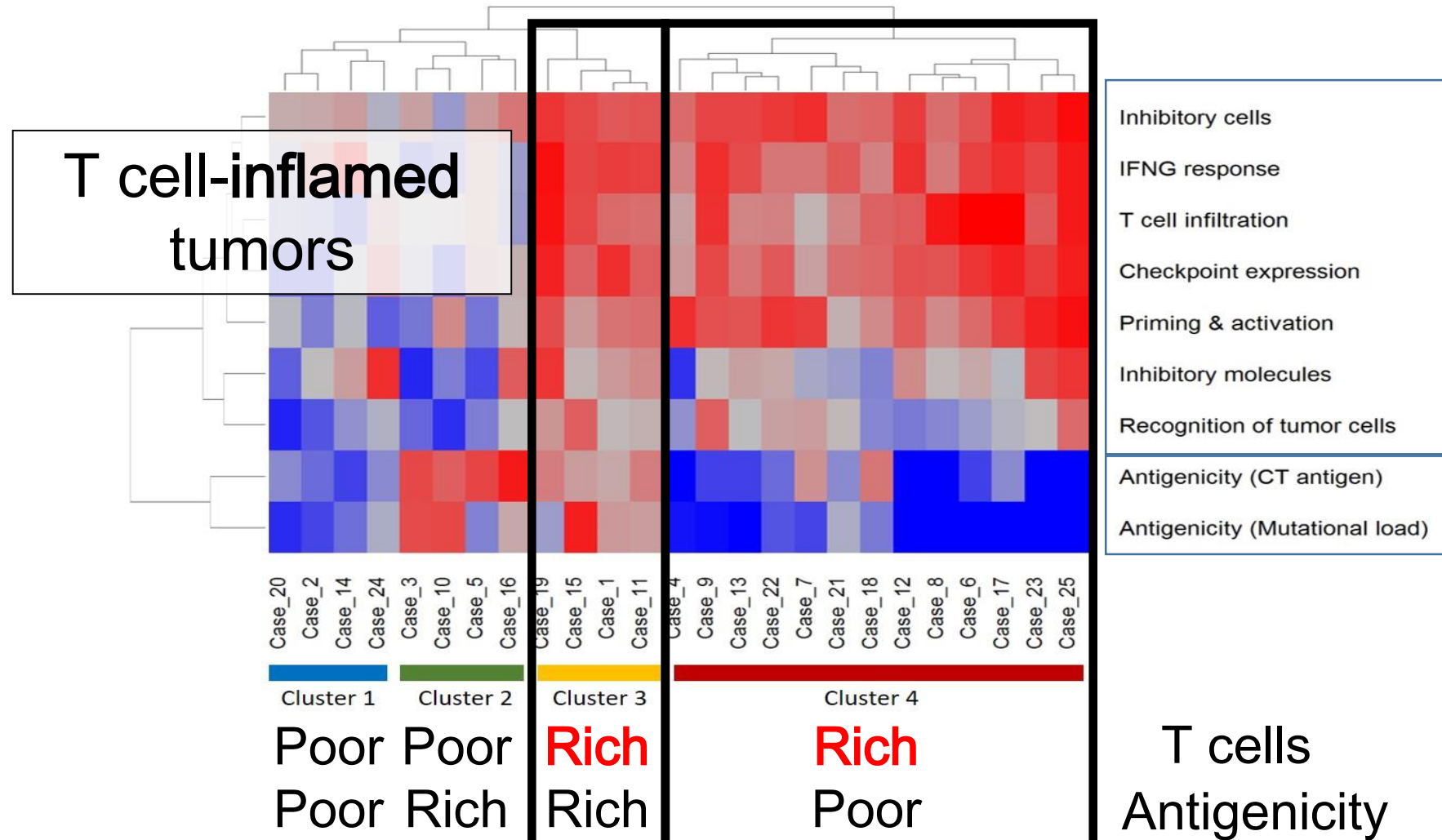
Results

Immunograms of 25 NSCLC patients

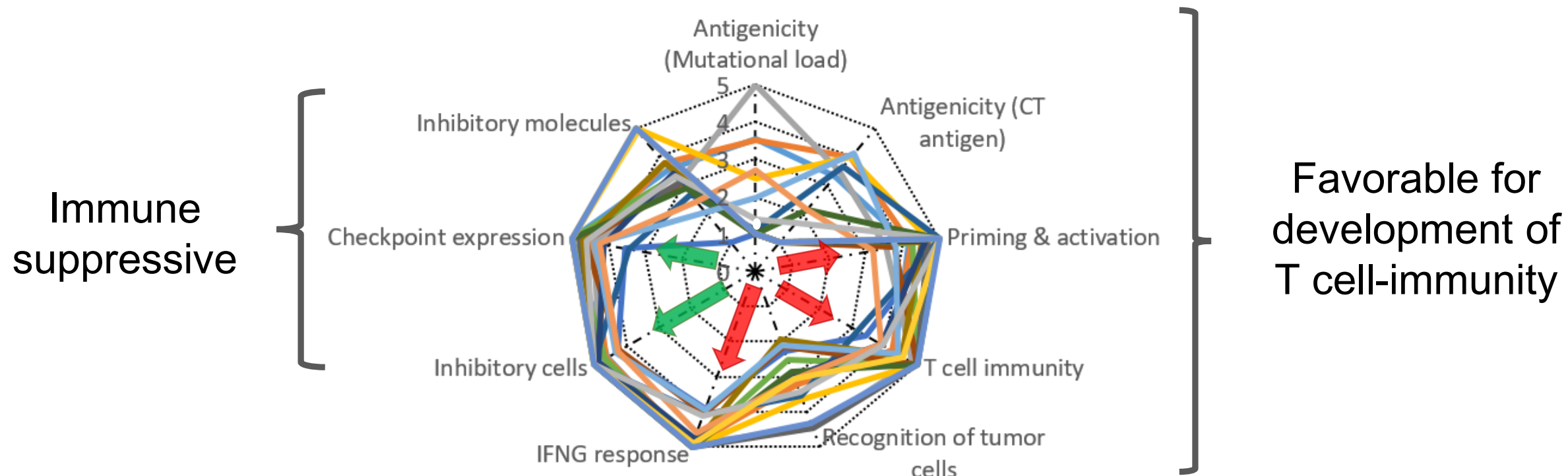


Various patterns of immunograms were observed
→ Each patient has their own pattern of immunosuppressive microenvironment

Clustering by immunogram scores demonstrated 4 clusters



T cell-inflamed tumors



Gene signatures of:

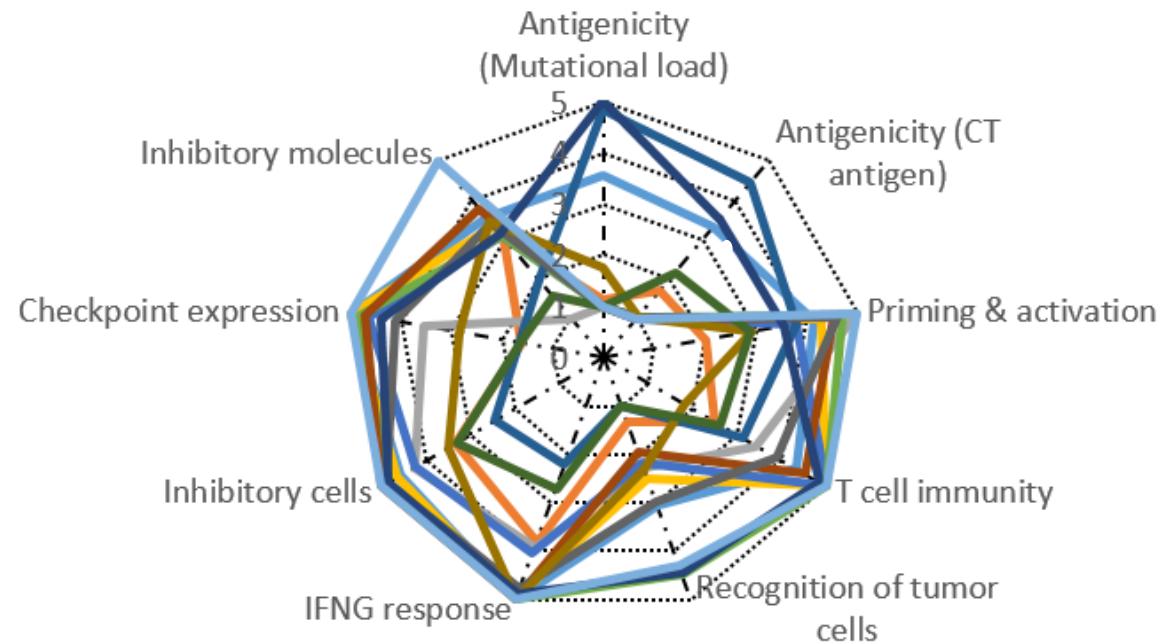
activated DCs, abundant T cells, IFN γ response

⇔ inhibitory cells (Treg & MDSC) and checkpoint molecules

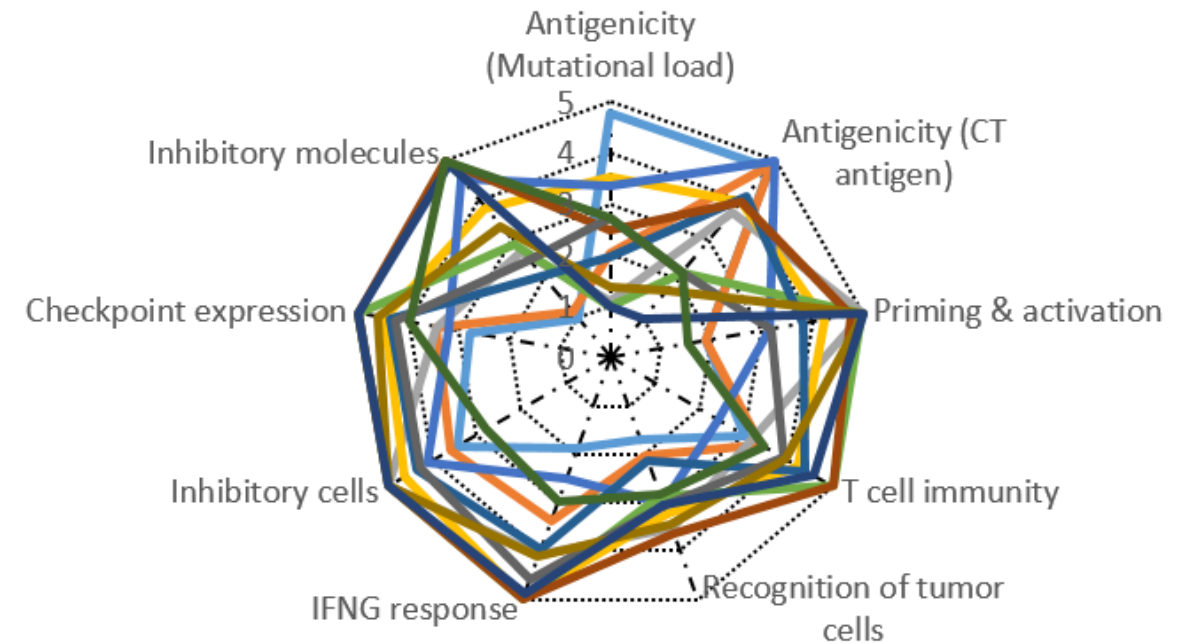
→ Existence of **counter regulatory immunosuppressive microenvironment**

Each immunogram score had no correlation with histology

Adenocarcinoma



Non-adenocarcinoma



Age, gender and TNM stage also did **not** correlate with each immunogram scores.

Clinical Relevance

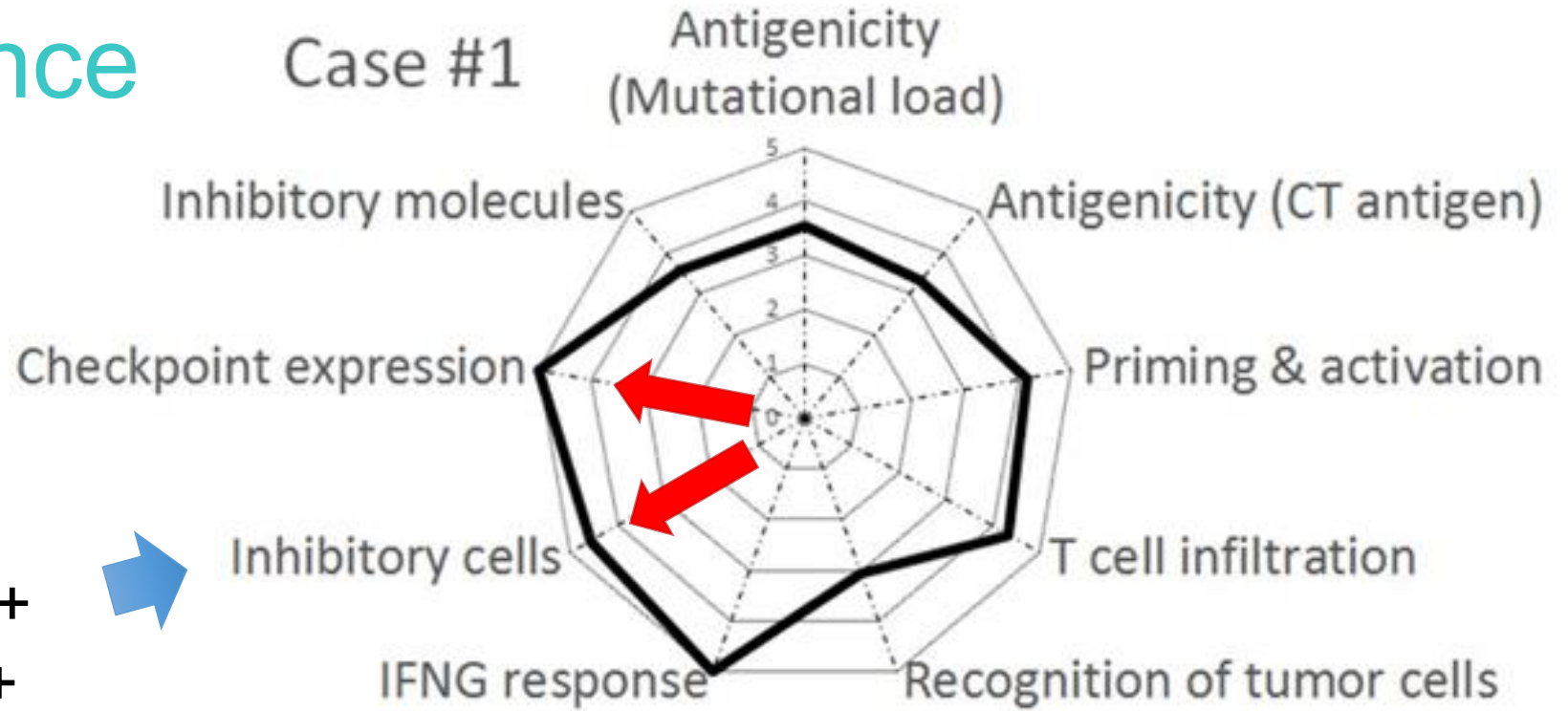
PD-1 ++++++

TIM-3 ++++

LAG3, CTLA-4 ++



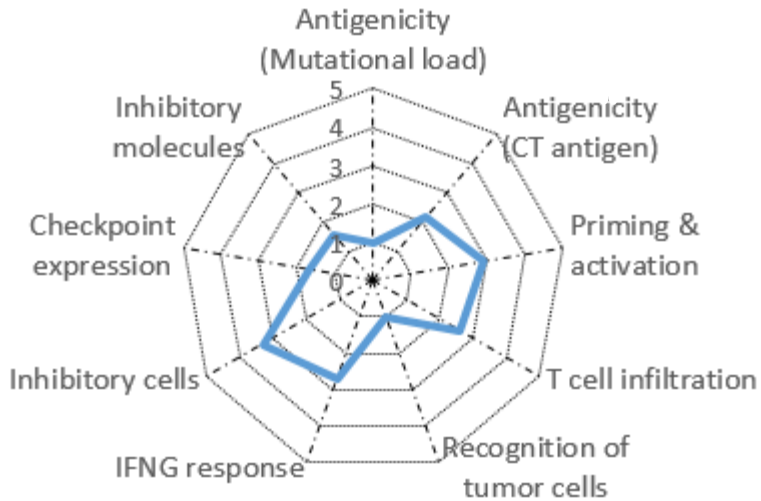
Tregs ++
MDSC +



➤ Agents that unleash counter regulations may be beneficial :

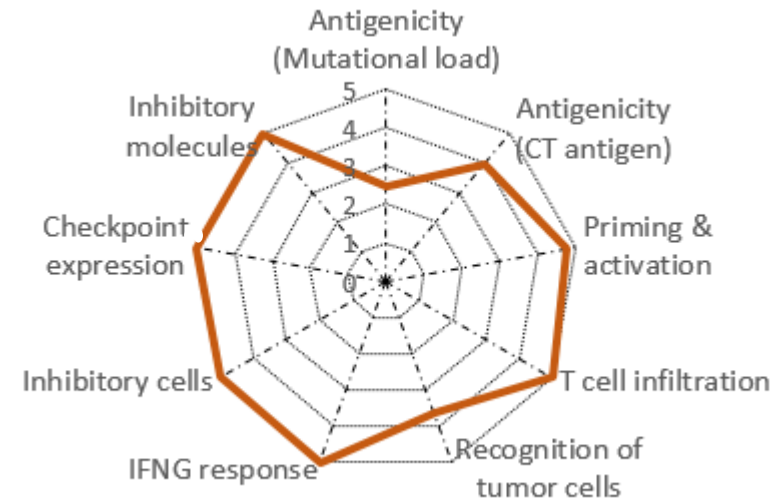
- ✓ Deprivation of Treg/MDSC
- ✓ Anti-PD1/PDL1
- ✓ Anti-TIM3

Non-T cell-inflamed



- ✓ Induce immunogenic cell death
- ✓ Neoantigen vaccine
- ✓ Anti-CTLA4
- ✓ IFN α , CD40-agonist, microbiota
- ✓ Epigenetic therapy
- ✓ CAR-T cell therapy

T cell-inflamed



- ✓ Deprivation of Treg/MDSC
- ✓ Anti-PD1/PDL1
- ✓ IDO/arginase inhibitor
- ✓ Control of glucose metabolism

Optimal cancer control

Lessons and Take Home Messages

Immunogram for the cancer-immunity cycle

- can **visualize** the landscape of **cancer-immunity** interaction in each patient.
- can translate cumbersome **omics data** into easily comprehensible “**report cards**” of immune status for clinicians.
- can be used as an **integrated biomarker**.
- may thus become a valuable resource for **personalized immunotherapy**.