City of Hope®

Advances and Innovations in Endoscopic Oncology and Multidisciplinary Gastrointestinal Cancer Care

Leveraging Endoscopic Ablation and Immunotherapy

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Disclosures

- Consultant/Advisor for Dracen Pharmaceuticals, Elevar Therapeutics, Incyte, Mirati Therapeutics
- Grant/Research Support from Dracen Pharmaceuticals, GSK, Merck, Nektar Therapeutics, Novartis, Sirnaomics, Takeda
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This presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their product(s) and/or other business interests.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

This presentation has been peer-reviewed and no conflicts were noted.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:

Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

This presentation is dedicated solely to research or other issues that do not contain a direct patient care component.

Unleashing the power of the immune system to defeat cancer

Immunotherapy — a medical treatment that mobilizes the body's own natural defense system to fight diseases — is revolutionizing the way we treat cancer. There are several different immunotherapy approaches that treat a variety of cancers. Some are approved for use; others are being tested in clinical trials.

FIVE TYPES OF CANCER IMMUNOTHERAPY

Cellular therapy

The transfer of human cells to replace diseased cells with healthy, functional ones. Stem cell transplant and chimeric antigen receptor (CAR) T-cell therapy are examples of cellular therapies.

Immunomodulators

Medications that regulate and boost parts of the immune system. Checkpoint inhibitors and cytokines are immunomodulators.

Oncolytic virus therapy

Lab-modified viruses that infect and kill cancer cells without harming normal cells. Some of the viruses are found in nature, while others are modified in a lab.

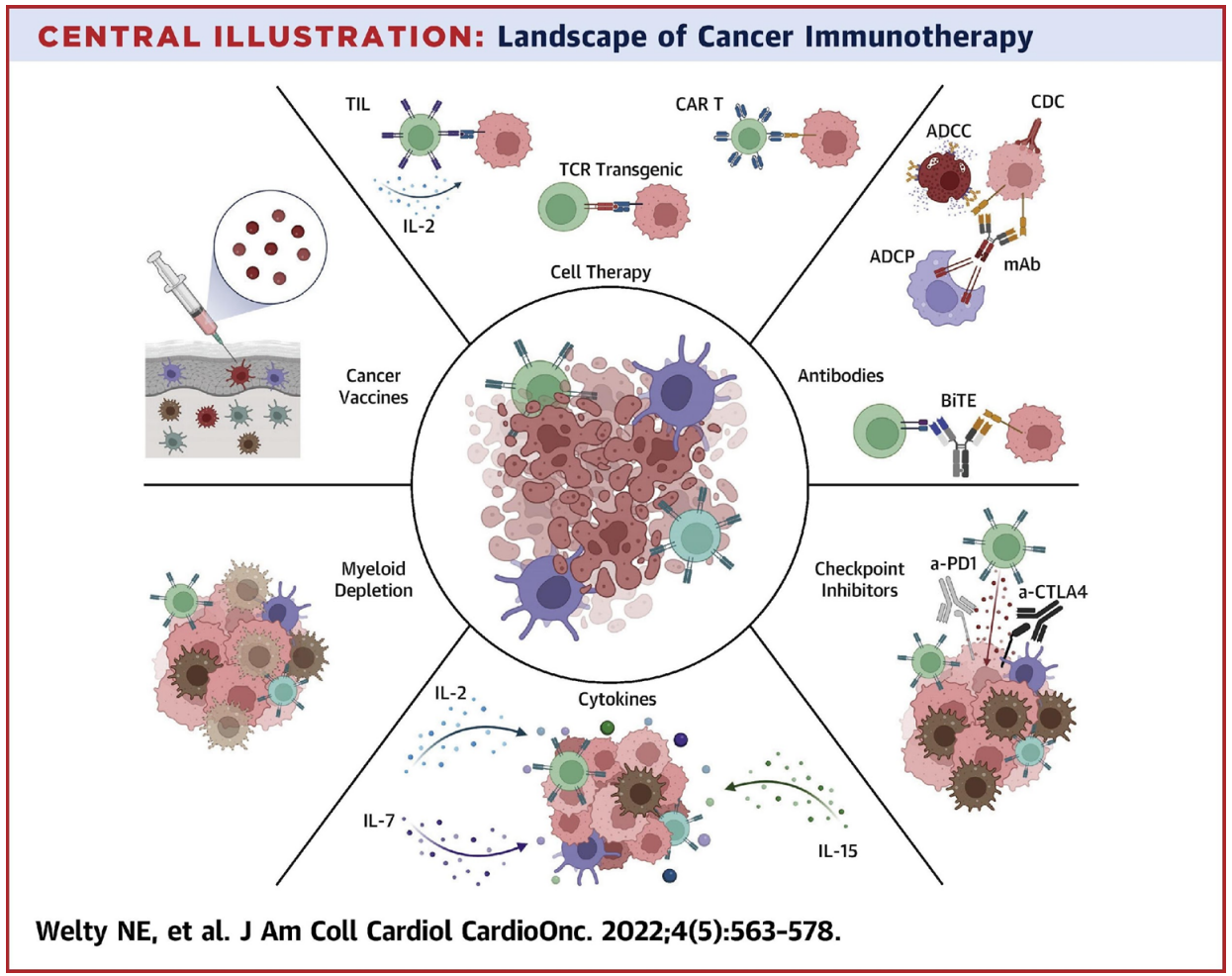
Monoclonal antibodies

Man-made proteins that attack a specific part of a cancer cell. Some monoclonal antibodies are described as targeted therapies.

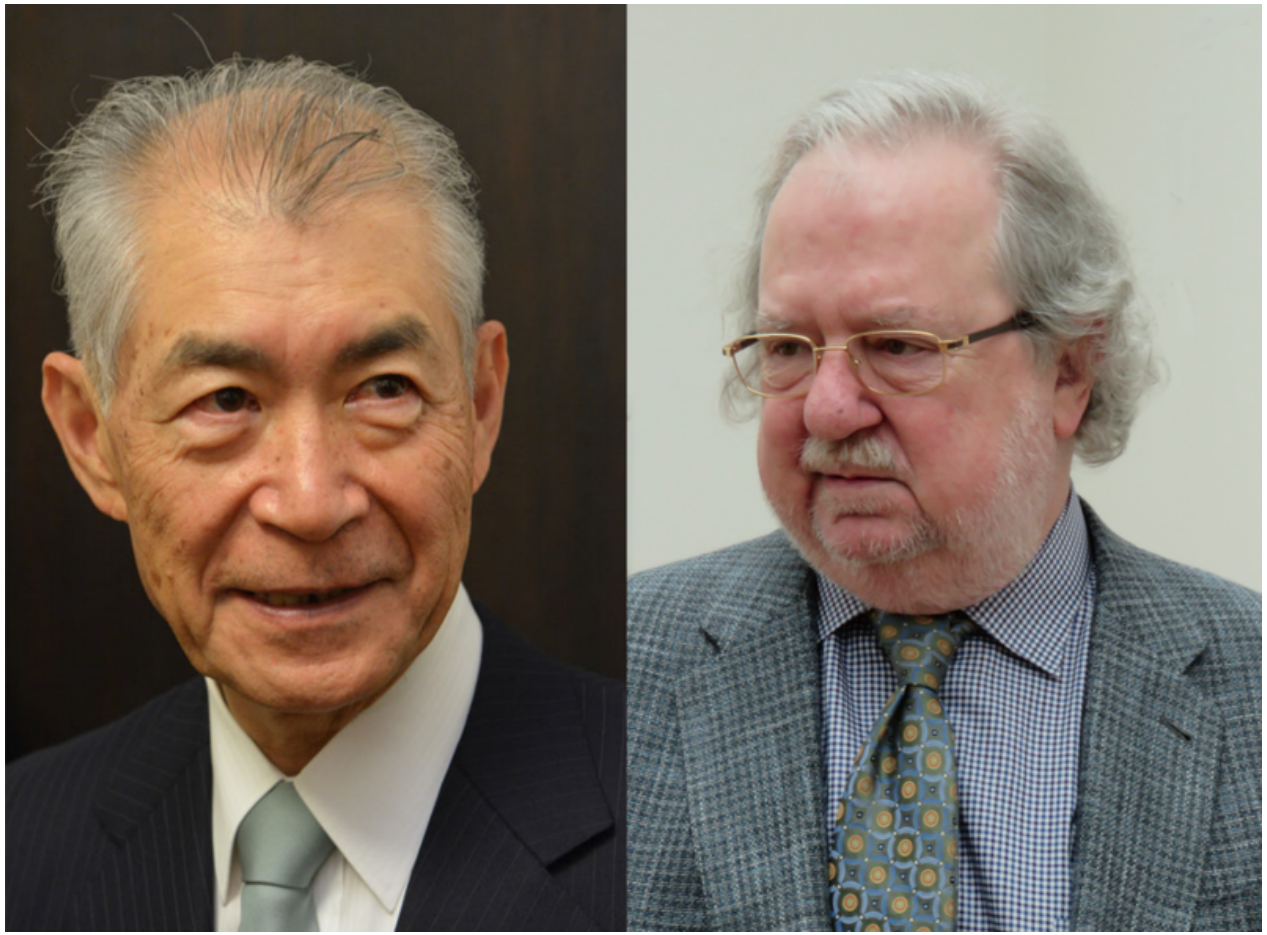
Cancer treatment vaccines

Medicines that train the Immune system to recognize and destroy cancer cells. Unlike cancer prevention vaccines, these are designed for people who already have cancer.

Development of Immunotherapies for Cancer

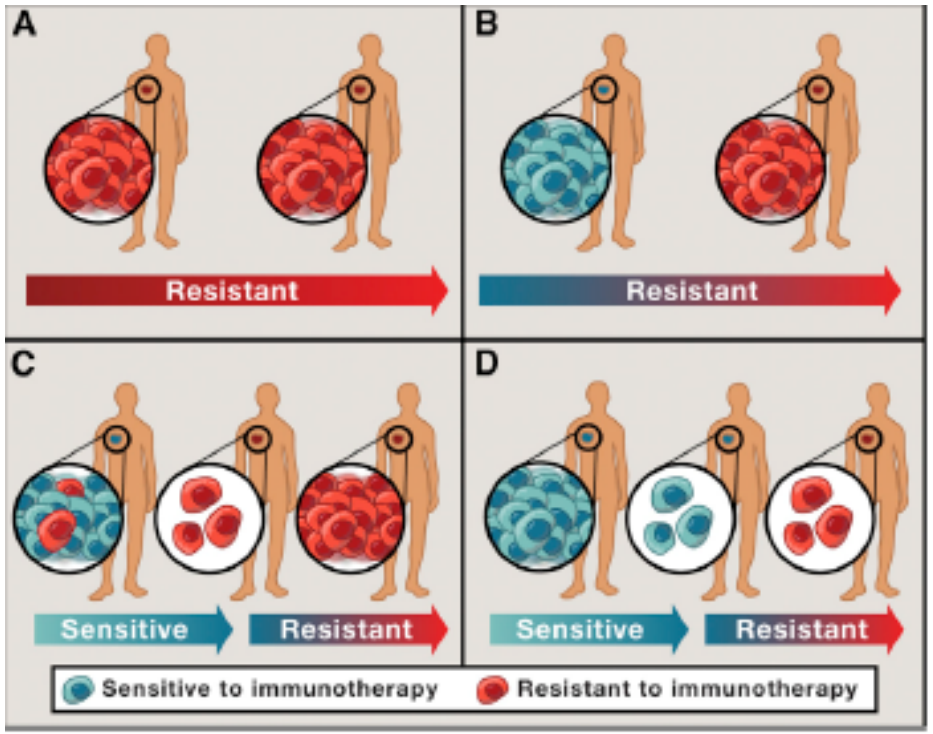


Nobel Prize in Physiology and Medicine 2018



Tasuku Honjo Jim Allison

Resistance to Cancer Immunotherapies



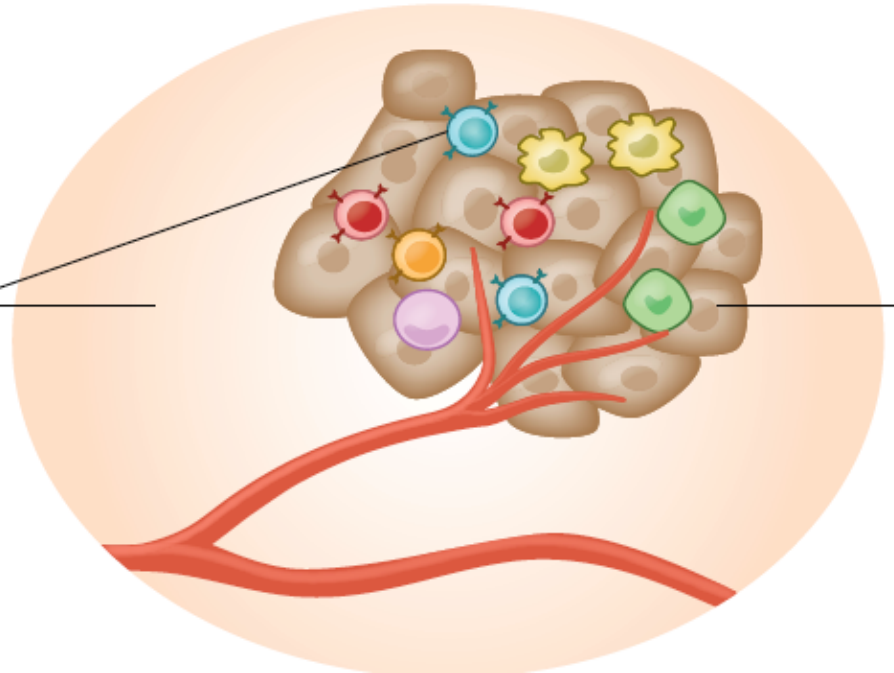
	Mechanism	Examples
umor cell ntrinsic	absence of antigenic proteins	low mutational burden lack of viral antigens lack of cancer-testis antigens overlapping surface proteins
	absence of antigen presentation	deletion in TAP deletion in B2M silenced HLA
	genetic T cell exclusion	MAPK oncogenic signaling stabilized b-catenin mesenchymal transcriptome oncogenic PD-L1 expression
	insensibility to T cells	mutations in interferon gamma pathway signaling
umor cell extrinsic	absence of T cells	lack of T cells with tumor antigen-specific TCRs
	inhibitory immune checkpoints	VISTA, LAG-3, TIM-3
	immunosuppressive cells	TAMs, Tregs

Padmanee Sharma et al Cell 2017

Mechanisms of Immunotherapy Resistance

Tumor cell extrinsic

- Microbiome
- PD-L1 expression on immune cells
- Tumoral and peripheral immune cell composition

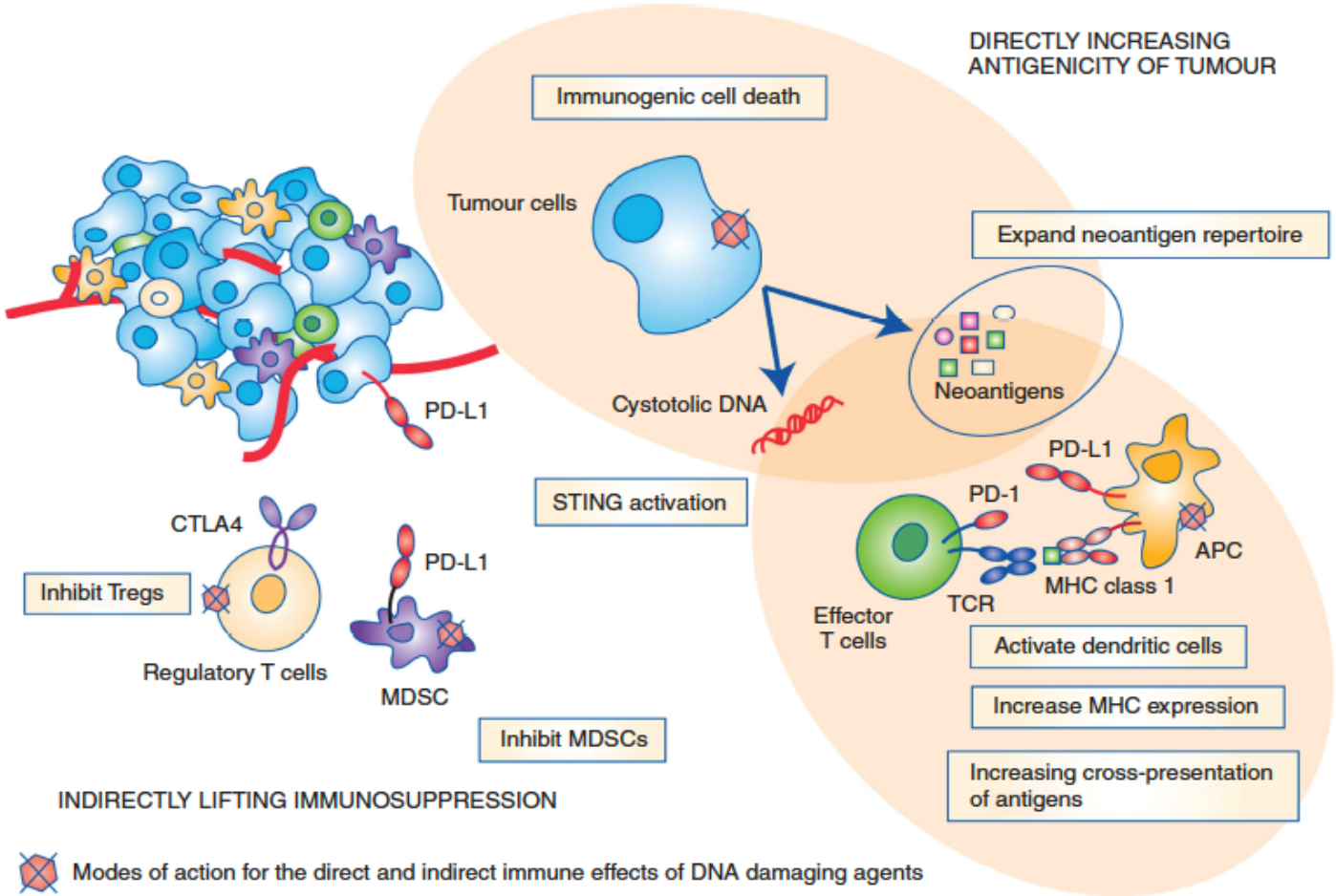


Tumor cell intrinsic

- PD-L1 expression
- Mutational burden
- Neoantigen expression
- Epigenetic variations
- Type II interferon signaling
- Antigen presentation pathways

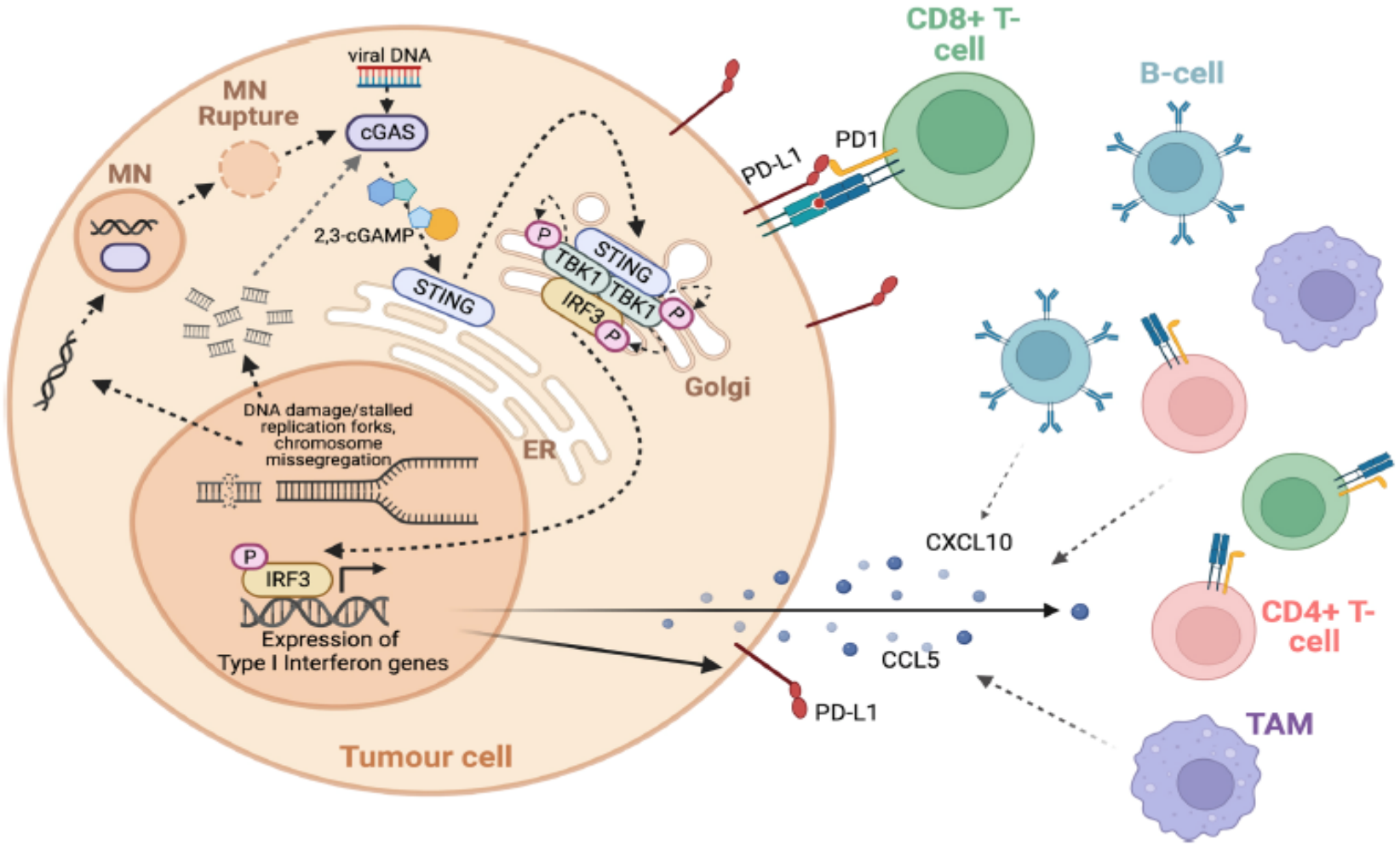
Bagchi et al Annu Rev Pathol Mech Dis 2021

DNA damaging strategies can overcome immunotherapy resistance



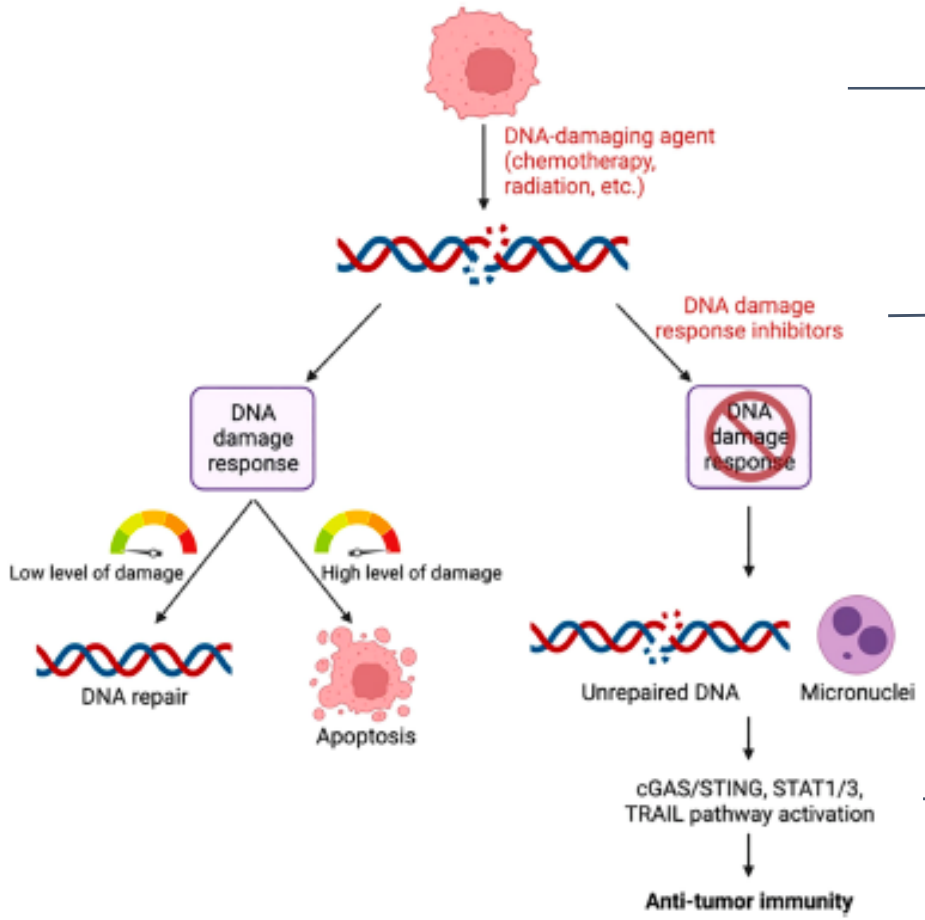
Brown et al British J Cancer 2018

Mechanism of immune activation by DNA damage



Barros et al DNA Repair 2022

How can DNA damaging strategies improve response to immune therapies?



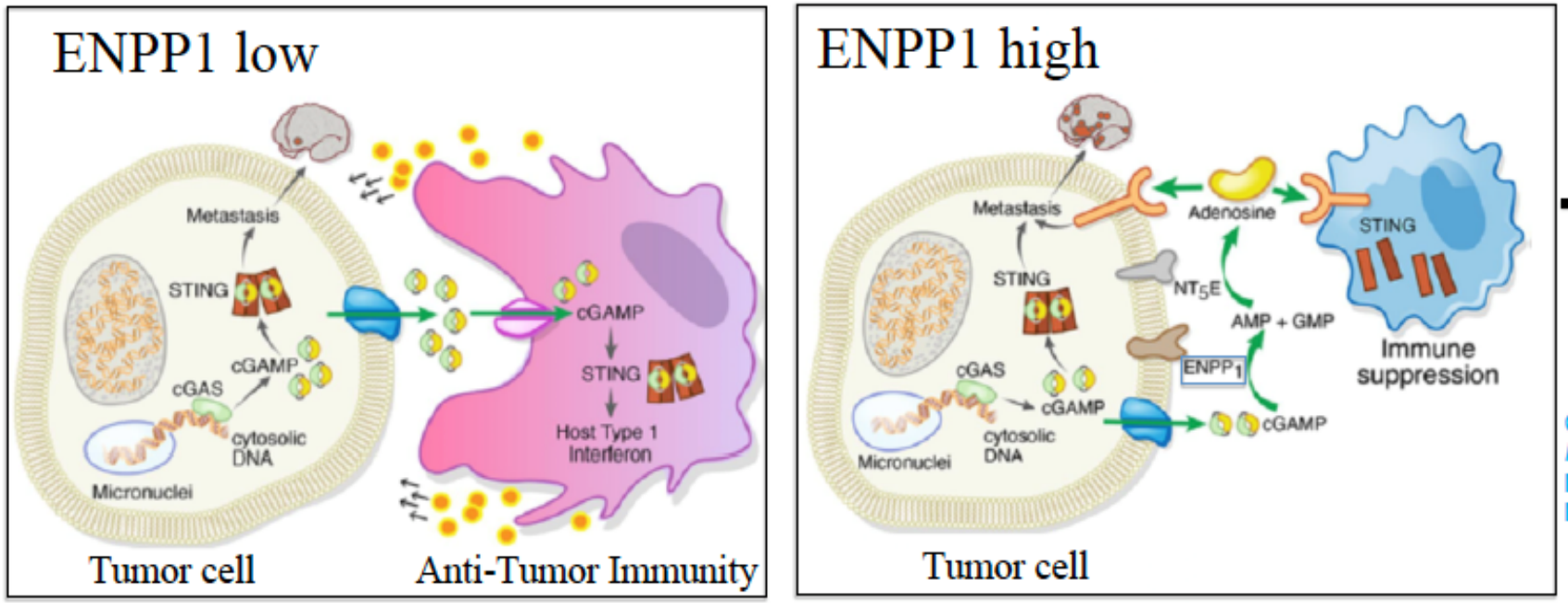
Ablation

PARP inhibitor

ENPP1 inhibitor

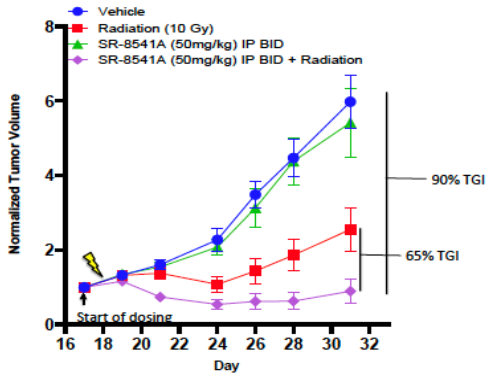
Carlsen et al Front Oncol 2022

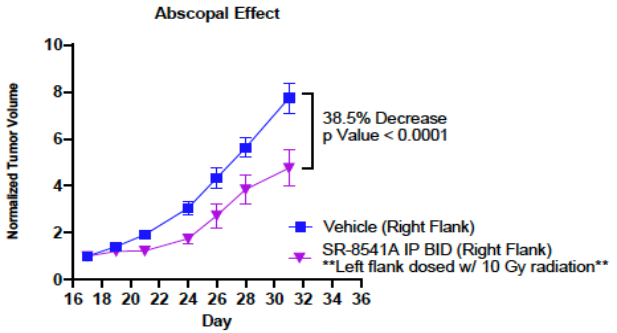
ENPP1 inhibitors enhance immune infiltration in cold tumors



- Reduced immune infiltration
- Increased metastasis
- Tumors resistant to immuno- and chemo-therapy

Cancer Discov. 2020 Dec 28:CD-20-0387.
Nature Cancer volume 1, pages184–196(2020)
Nat Commun. 2018 Oct 24;9(1):4424.
Nat Chem Biol. 2014 Dec;10(12):1043-8





Immune Modulation with Endoscopic Ablations

- The ***increased release of these neoantigens*** would lead to increased danger signals, which would initiate the process of enhancing cancer immunity
- Cell death caused by cryoablation with cell contents remaining intact, which induces the ***release of intracellular DNA, RNA and heat shock proteins (HSP)***
- HSP70 completes antigen presentation by chaperoning antigen to dendritic cells(DC) and ***promoting the expression of major histocompatibility complex class 1 (MHC 1)***
- ***Programmed cell death 1 ligand 1 (PD-L1) expression*** in target tumor tissues and programmed death 1 ***(PD-1) expression*** in specific CD8+ and CD4+T lymphocytes are increased

Chen et al Front Immunol 2023

Possible ideas to explore immune modulation from endoscopic ablations

- **Study the systemic immune modulation from localized endoscopic ablations using state-of-the-art techniques in humans**
  - **Cytokine panels**
  - **Single cell sequencing**

- **Study the effect of endoscopic ablations pre-clinically in combinations**
  - **DNA damage response inhibitors (1)**
  - **Innate immune activators esp. ENPP1 inhibitors (2)**
  - **Checkpoint inhibitors singly or in combination with 1 and/or 2**

- **Study the interactions of endoscopic ablations with human microbiome in the gut**

- **Develop endoscopic ablation strategies as adjuncts to cancer vaccines**