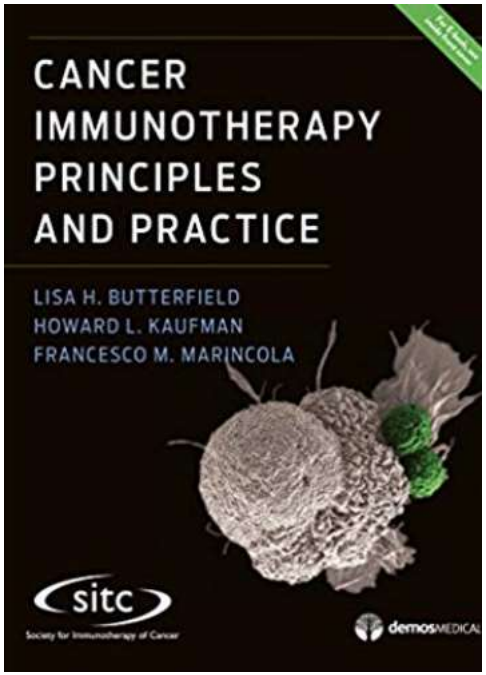
Introduction to immune function in cancer patients



Speaker: 洪家燕

2019.11.2

Introduction to textbook

- Section I: Basic principles of tumor immunology
  - Principles of immunity and its intersection with cancer biology
- Section II: Cancer immunotherapy targets and classes
  - Wide array of approaches to clinical immunotherapy
- Section III: Immune function in cancer patients
  - Presence of cancer can impact and deregulate immune functions in patients.
  - Current understanding of immune function at the tumor site, and immune function throughout the human system as generally measured in the blood.
  - Specific cell types and molecules that have protumor and antitumor effects.
- Section IV: Disease-specific treatments and outcomes

Chapter 26, 30

Ch. 26: Tumor-Infiltrating Immune Cells of Myeloid Origin
Ch. 30: Assessment of Antitumor Immunity in Blood and LymphNodes

- Chapter 26
  - Examination of tumor infiltrates and focuses on the function and impact of myeloid cells from pathology

BCC Research

Tumor Infiltrating Lymphocytes (TILs) Open New Era in Cancer Treatment

Adoptive Transfer of Autologous Lymphocytes Find Success in Common Epithelial Cancers

Email | Print Friendly | Share

July 24, 2018 08:00 ET | Source: BCC Research

WELLESLEY, Mass., July 24, 2018 (GLOBE NEWSWIRE) -- Adoptive cell therapies (ACTs), and recently the infusion of autologous or redirected tumor-specific T-cells, have the potential to drastically impact the treatment of a variety of cancers, especially common epithelial cancers.

The **BCC Research** report Adoptive Transfer of Autologous Lymphocytes Targeting Somatically Mutated Genes: *Success in Common Epithelial Cancers with Low Mutation Rates, Gastrointestinal, Bile Duct and Breast Cancers* provides an essential briefing on this revolutionary cancer therapy. The report summarizes the current state of clinical research and trials and explains the impact of ACTs on the treatment of several metastasized malignancies, while and raising important concerns about the scalability and compatibility of TILs treatments.

https://globenewswire.com/news-release/2018/07/24/1541045/0/en/Tumor-Infiltrating-Lymphocytes-TILs-Open-New-Era-in-Cancer-Treatment.html

Chapter 26, 30

Ch. 26: Tumor-Infiltrating Immune Cells of Myeloid Origin
Ch. 30: Assessment of Antitumor Immunity in Blood and LymphNodes

- Chapter 30
  - How to measures of immune function from blood samples

nature
International journal of science

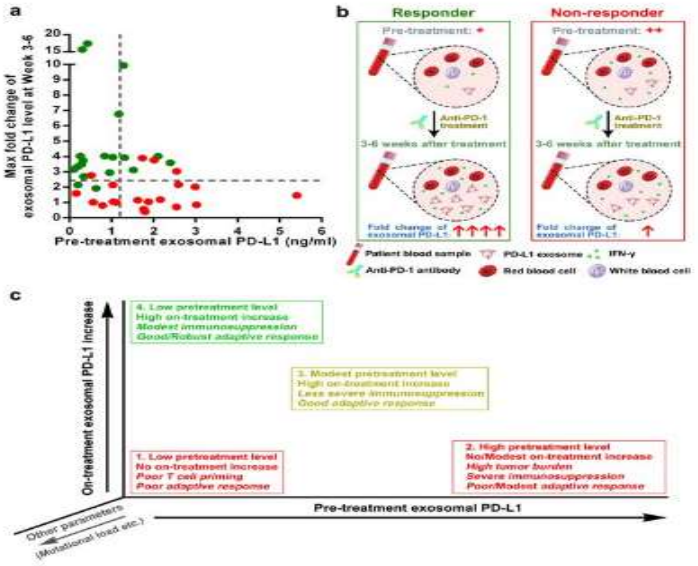
Letter | Published: 08 August 2018

Exosomal PD-L1 contributes to immunosuppression and is associated with anti-PD-1 response

Gang Chen, Alexander C. Huang, [...] Wei Guo

Nature **560**, 382–386 (2018) | Download Citation

Extended Data Fig. 10: Circulating exosomal PD-L1 is a potential rationale-based and clinically accessible predictor for clinical outcomes of anti-PD-1 therapy.

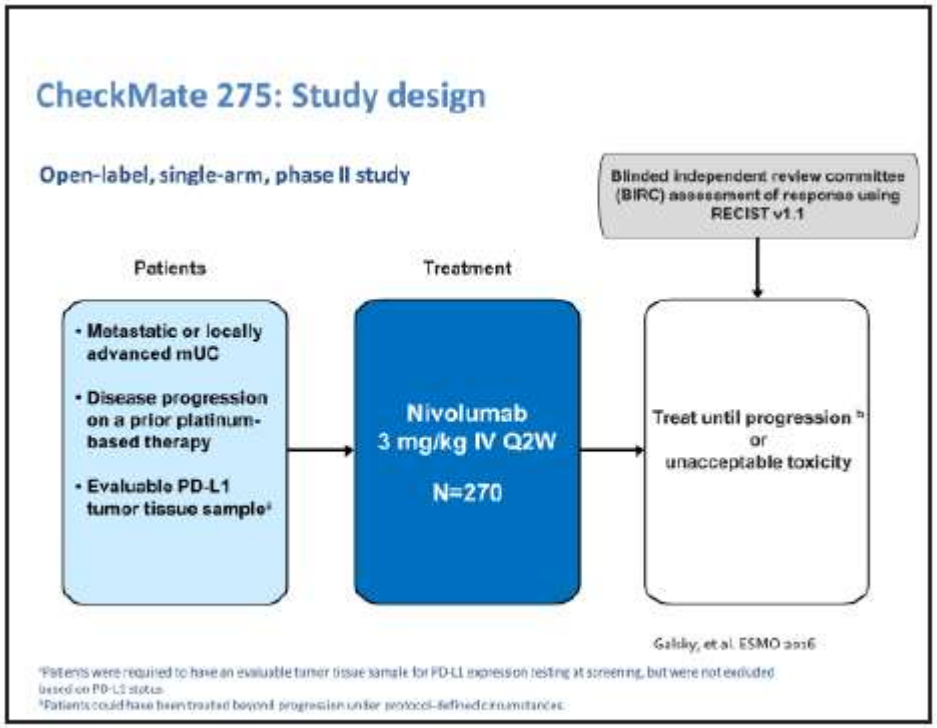


Chen, Gang et al. Nature 2018;560:382-386

Chapter 27

Ch. 27 : Intratumoral Gene Signatures and Host Genetic Variations Associated with Immune Responsiveness

- Genetic signature of the tumor, impact of host genetic on the ability to raise effective antitumor immunity. The transcriptional signature of response provide mechanistic insights to further improve antitumor responses.



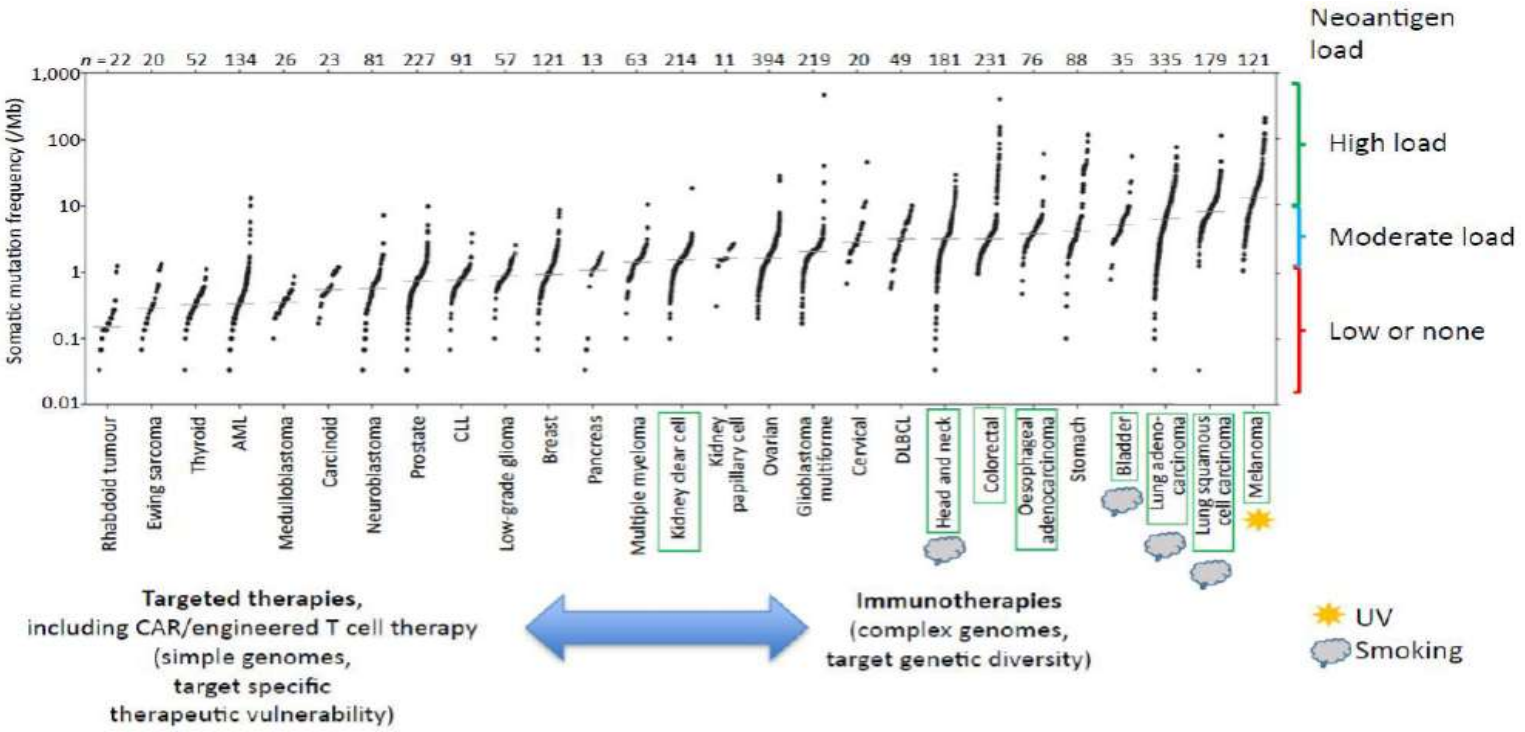
Multiparameter immune gene expression profiling in the Checkmate 275 study (nivolumab) found IFN-γ signature correlated with better response to nivolumab (high IFN-γ signature: CR/Prin 20/59 patients; medium or low IFN-γ signature: CR/PR in 18/118 patients; (p=0.0003).

Chapter 28, 29

Ch. 28: Impact of Somatic Mutations on the Local and Systemic Antitumor Immune Response

Ch. 29: Tumor Antigen Profiling

- Somatic mutations can impact the development of an immune response
- Tumor-specific mutation load and neoantigens



Trends Immunol. 2018 Jul;39(7):536-548

Chapter 31, 32, 33

Ch. 31: Regulatory T Cell Biology and Its Application in Cancer
Ch. 32: Systemic Measures of Immune Function in Cancer Patients: Suppressive Cellular Mechanisms
Ch. 33: Circulating Mediators of Tumor-Induced Immune Suppression

- Regulatory T cells suppress antitumor immunity
- Types of suppressive cells: MDSCs
- Mediators of immune suppression: exosomes

Therapeutic induction of MDSCs

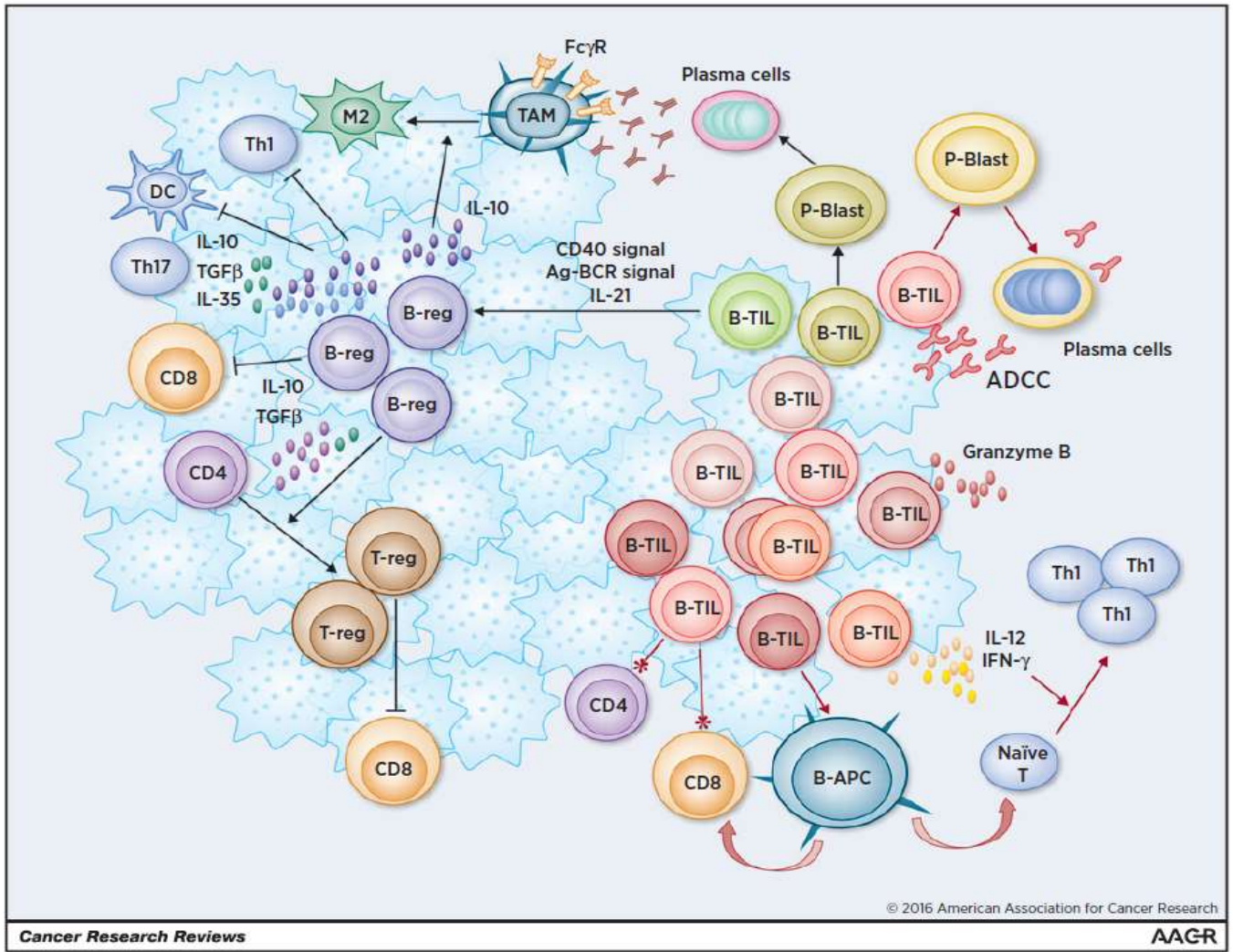
Source of MDSCs	Type of immune pathology tested	Effect of MDSCs	Refs
Activated following $CD8^+$ T cell-induced acute enterocolitis	Inflammatory bowel disease (mice)	Inhibition of antigen-specific $CD8^+$ T cells	18
Generated *in vitro* from mouse embryonic stem cells	Graft-versus-host disease (mice)	Prevention of disease following adoptive transfer of MDSCs	19
Induced by perioperative treatment with CD28-specific antibodies	Kidney allograft transplant (mice)	Maintenance of graft tolerance	20
Induced by endotoxin	Skin allograft transplant (mice)	Prolongation of graft survival following adoptive transfer of MDSCs	21

https://www.nature.com/nri/posters/mdscs/nri1005_mdscs_poster.pdf

Chapter 34

Ch. 34: The Multifaceted Roles of B Cells and Plasma Cells in Antitumor Immunity

- Presentation of B cells and humoral immunity in cancer have important pro and antitumor effects. Associate with autoimmunity and transplantation.



Distinct subsets of B cells helps in tumor microenvironment in both pro- (black) and antitumorigenic manner (red)

Tsou, Peiling et al. Cancer Res;76:11-5

Chapter 35

Ch. 35 : Systems Immunology Approaches to Cancer Immunotherapy

- Systemic biology approaches for dealing with the complexity of immune-cancer interactions.

What does systems biology mean to you?

The study of biological systems (i.e. cells, tissues, organisms) through experimental and computational approaches, viewed as an *integrated, interacting, complex network* of genes, proteins and biochemical reactions

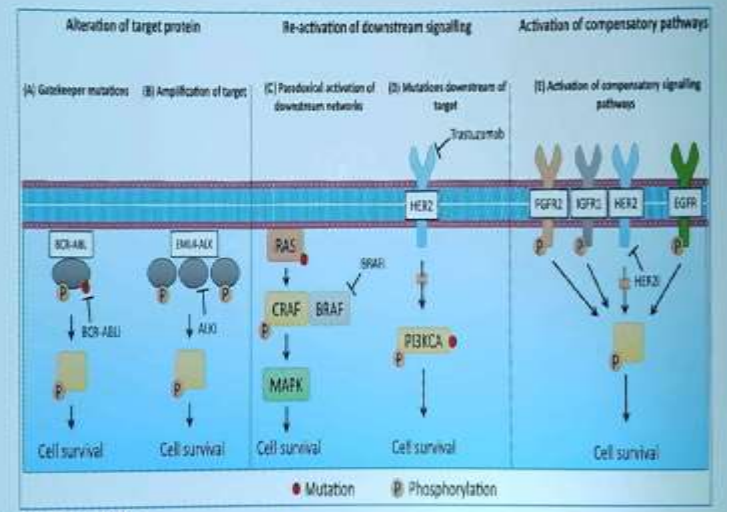
Today's session is devoted to communicating advances in how we study cancer cells as integrated networks

Emerging themes:

- Single cell analysis
- Microfluidics
- Tumor heterogeneity
- Machine learning
- Dynamics of drug responses
- Precision medicine

Cancer systems biology

- Has advanced fundamental knowledge of signal transduction
- Has driven therapeutic design
- Has helped elucidate resistance mechanisms



Harrison & Huang. Essays in Biochemistry, 2018. 30072489

Chapter 36 Metabolism

Ch. 36: Tumor Microenvironment Metabolism as a Primordial Checkpoint in Antitumor T Cell Immunity

Ch. 37: Age-Related Immune Function Changes as They Relate to Cancer Immunotherapy

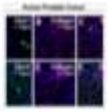
- Effects of cancer on metabolism and how cancer metabolism and immune metabolism intersect. Identifying new areas for therapeutic intervention
- Impact of aging

Cancer metabolism refers to the alterations in cellular metabolism pathways that are evident in cancer cells compared with most normal tissue cells. Metabolic alterations in cancer cells are numerous and include aerobic glycolysis, reduced oxidative phosphorylation and the increased generation of biosynthetic intermediates needed for cell growth and proliferation.

Latest Research and Reviews

Reviews | 13 August 2018

Fructose and prostate cancer: toward an integrated view of cancer cell metabolism

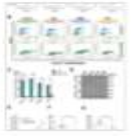


Daniela Carreño, Néstor Corro [...] Alejandro S. Godoy

Prostate Cancer and Prostatic Diseases, 1–10

Research | 14 August 2018 | OPEN

Sensitivity of Colorectal Cancer to Arginine Deprivation Therapy is Shaped by Differential Expression of Urea Cycle Enzymes



Constantinos Alexandrou, Saif Sattar Al-Aqbi [...] Alessandro Rufini

Scientific Reports **8**, 12096

Reviews | 10 August 2018

Nutrient scavenging in cancer

This Review discusses nutrient scavenging, a process by which cancer cells use macromolecules from their environment to fuel cell metabolism and growth even when nutrients are limiting.

Brendan T. Finicle, Vaishali Jayashankar & Aimee L. Edinger

Nature Reviews Cancer, 1–15

Chapter 37 Aging

Ch. 36: Tumor Microenvironment Metabolism as a Primordial Checkpoint in Antitumor T Cell Immunity

Ch. 37 : Age-Related Immune Function Changes as They Relate to Cancer Immunotherapy

- Immune competence with increasing age also plays a role in tumor escape.
  - Data from immunosuppressed patients :
    - Certain tumor types are much more common than in age-matched healthy controls.
  - Data from the small number of animal :
    - The results of cancer immunotherapy protocols in older mice are different, usually worse, than when using the same protocols in younger animals.

➢ **Hypothesis: Immunotherapy relying on checkpoint blockade may be less effective in older patients.**

- Clinical trials:
  - **Anti- CTLA-4 antibodies: in advanced melanoma, response rates and, toxicity profiles** in older patients are **similar to those of the young.**
  - **PD-1- based treatments:** There is also some evidence that **the same** may hold true.
  - However, **response rates** to these single-agent therapies **are generally low**
  - ➢ It remains possible that **immunosenescence may be contributing to non-responsiveness in the elderly**, whereas a different mechanism would explain the lack of response in the young.

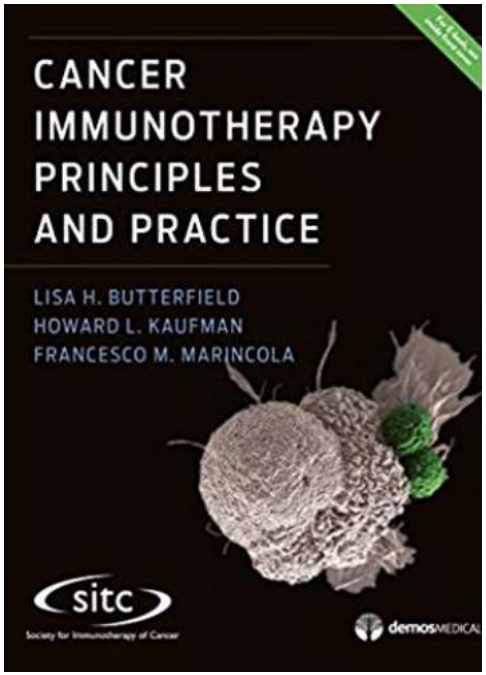
Chapter 38

Ch. 38: Clinical Measures: Imagine, Pseudoprogression and Metabolism

- Imaging approaches can be used to understand antitumor immunity and the impact of immunotherapy

	irRECIST	iRECIST
CR	Complete resolution of non-nodal lesions and < 10 mm short-axis for lymph nodes. No confirmation necessary	Complete resolution of non-nodal lesions and < 10 mm short-axis for lymph nodes. No new lesions
PR	≥30% decrease in tumour burden	≥30% decrease in tumour burden
SD	Does not meet criteria for irCR/irPR/irPD	Does not meet criteria for iCR/iPR/iUPD/iCPD
PD	≥20% increase in tumour burden relative to nadir and a minimum absolute increase of 5 mm; new lesions. Confirmation of PD via a subsequent scan ≥ 4 weeks later to detect delayed responses is required	iUPD—presence of new measurable/non-measurable lesions, or ≥ 20% increase in tumour burden relative to nadir iCPD-confirmation of IUPD with >/= 5 mm increase in size of target or new target lesions, increase in non-target or new non-target or increase in number of new lesions.

Introduction to principles of cancer immunotherapy



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Introduction to textbook

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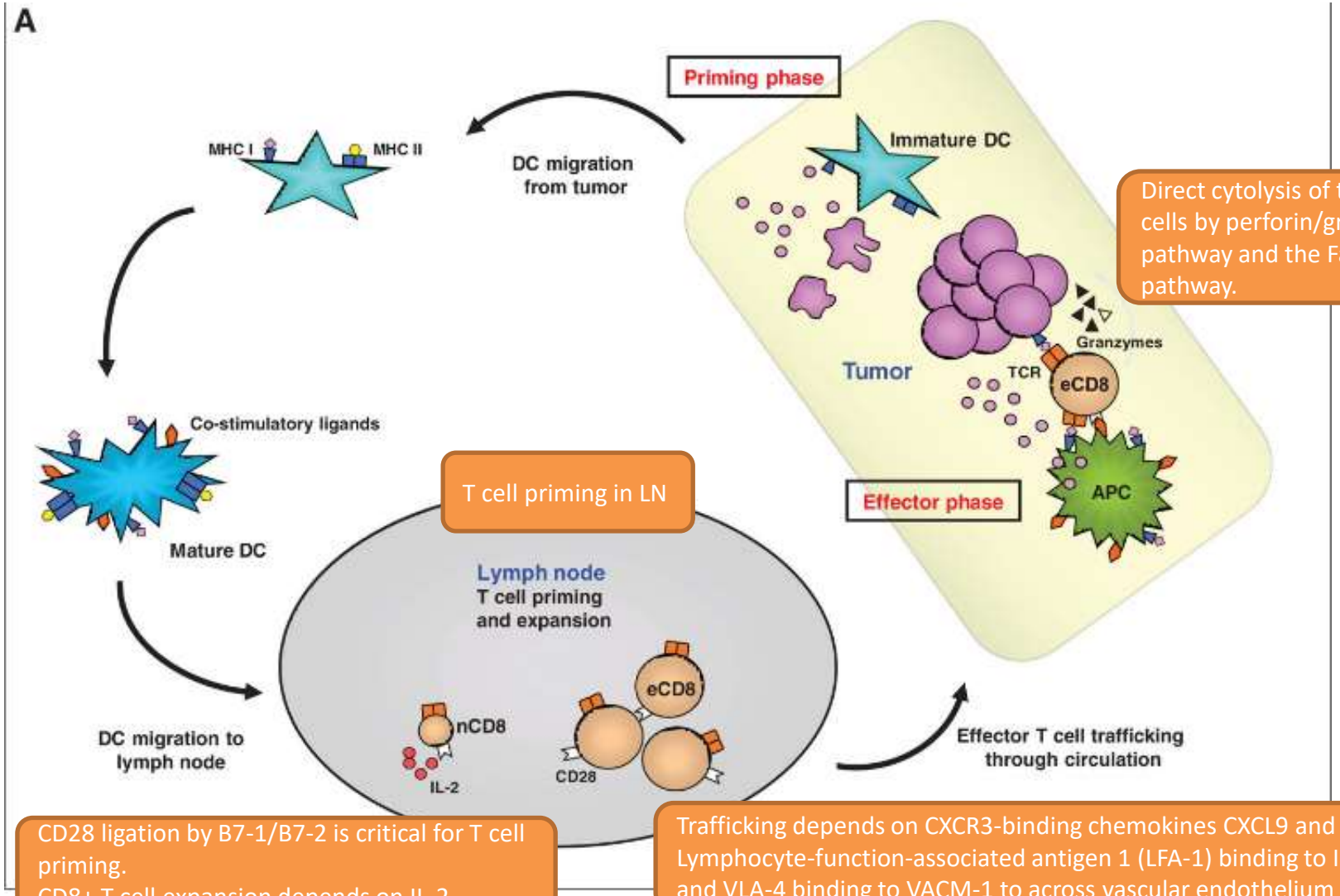
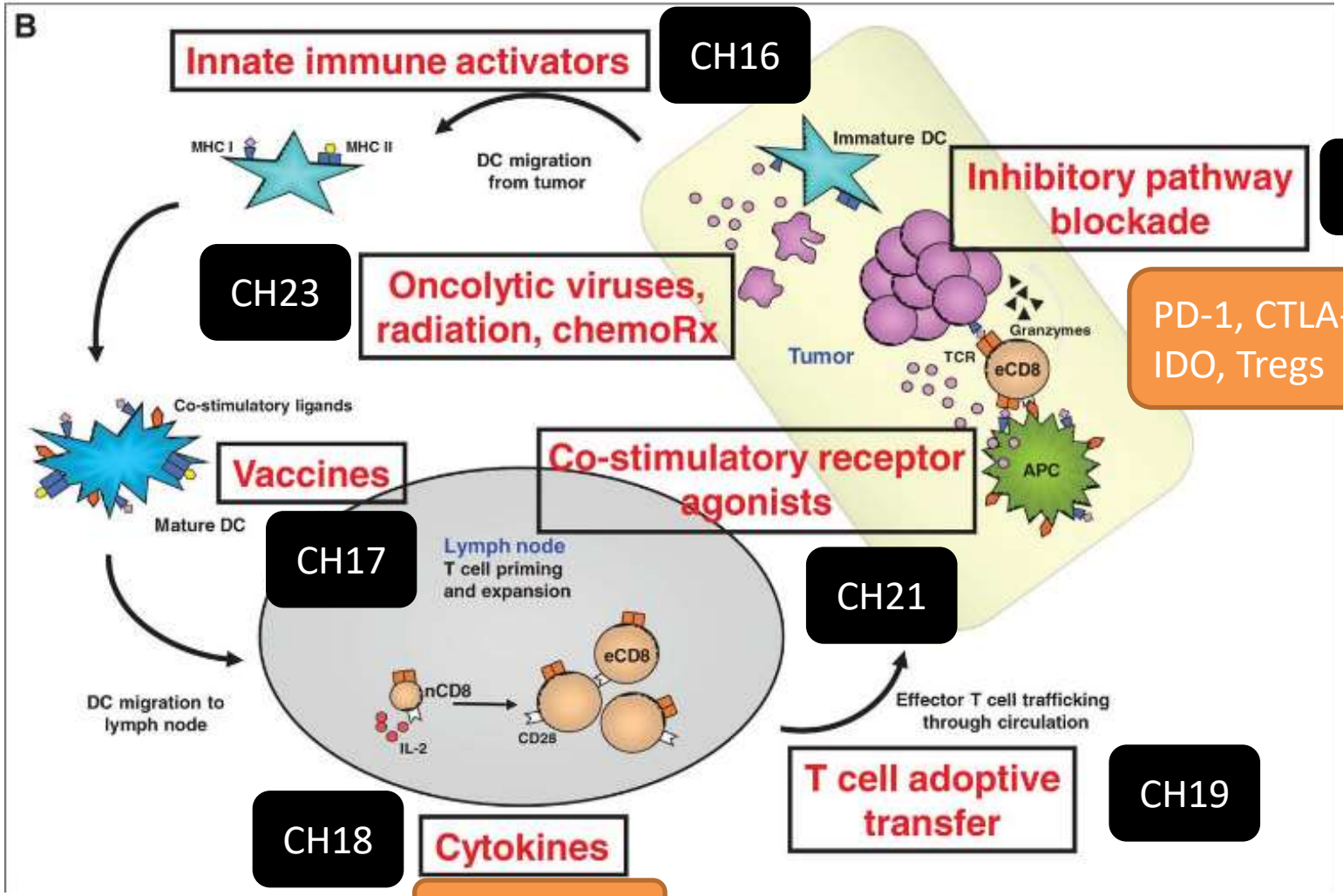
  - Events in anti-tumor immunity have pointed to therapeutic opportunities
  - Vaccines, adoptive T cell therapy, cytokines, and co-stimulatory ab can expand T cells
  - Innate immune activators can provoke a new immune response
  - Blockade of negative regulatory pathways can restore T cell function and modulate tumor microenvironment
  - Expanded efforts exploring predictive and pharmacodynamics biomarkers are identifying new candidate interventions
- Section III: Immune function in cancer patients
- Section IV: Disease-specific treatments and outcomes

Key steps involved in the generation of antitumor T cell responses



Categories of therapeutic intervention designed to amplify or overcome blocks in each stage of antitumor immunity



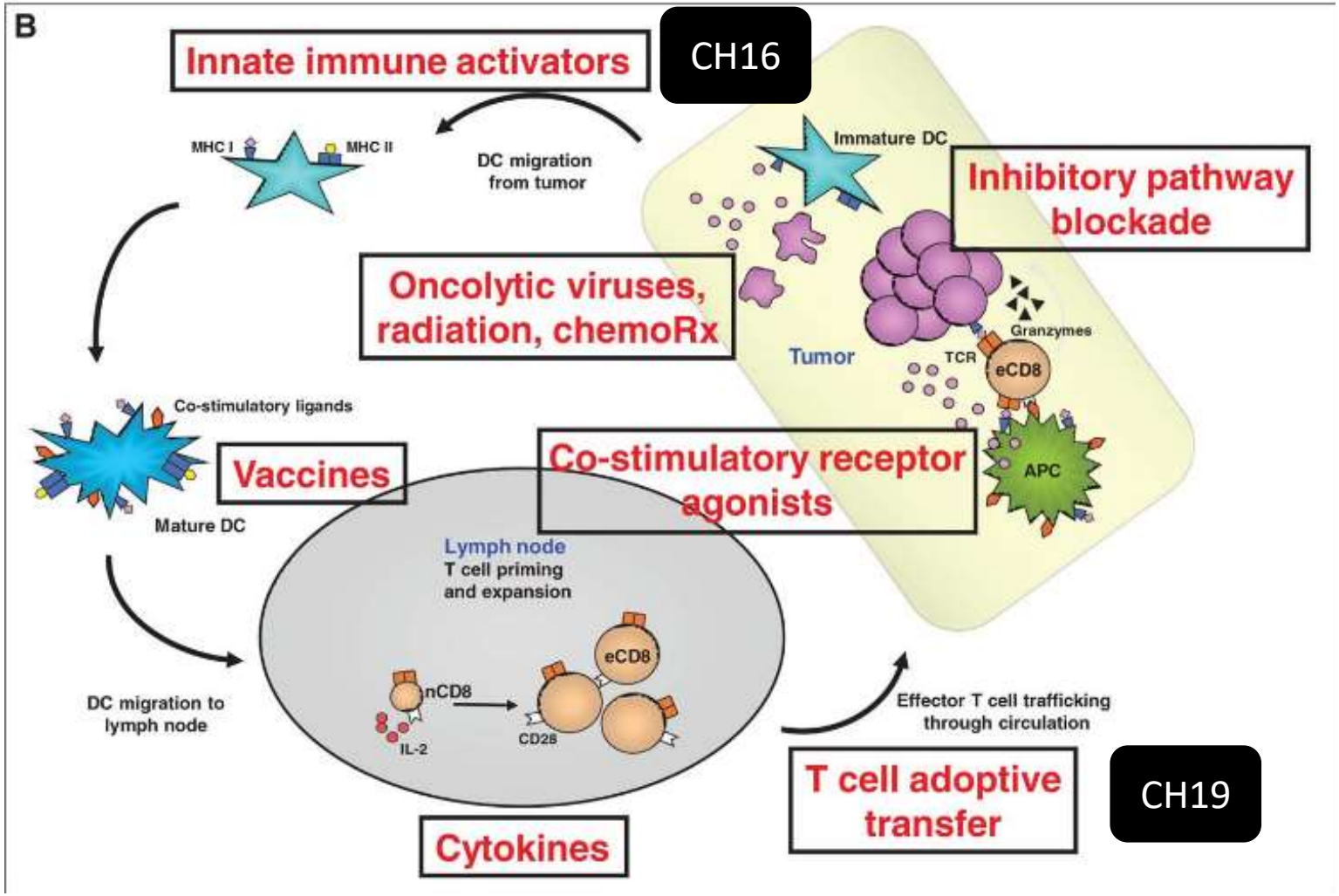
Chapter 16

CH 16-1、16-2

Manipulating Innate Immune Pathways as Cancer Immunotherapy

- Increasing antitumor T cells is through interventions that prime immune responses from within the tumor microenvironment.
- Intratumoral application of innate immune activators can induce cytokines and local inflammation within the tumor, activate APCs to initiate T cell priming against tumor-associated antigens.
- Imiquimod is a FDA-approved TLR7 agonist for topical treatment of basal cell carcinoma
- Clinical trials are ongoing with stimulators of TLR3, TLR4, and TLR9 and also STING agonists: innate immune activators
  - Priming new T cell responses
  - Establish local inflammation and promote new T cell entry

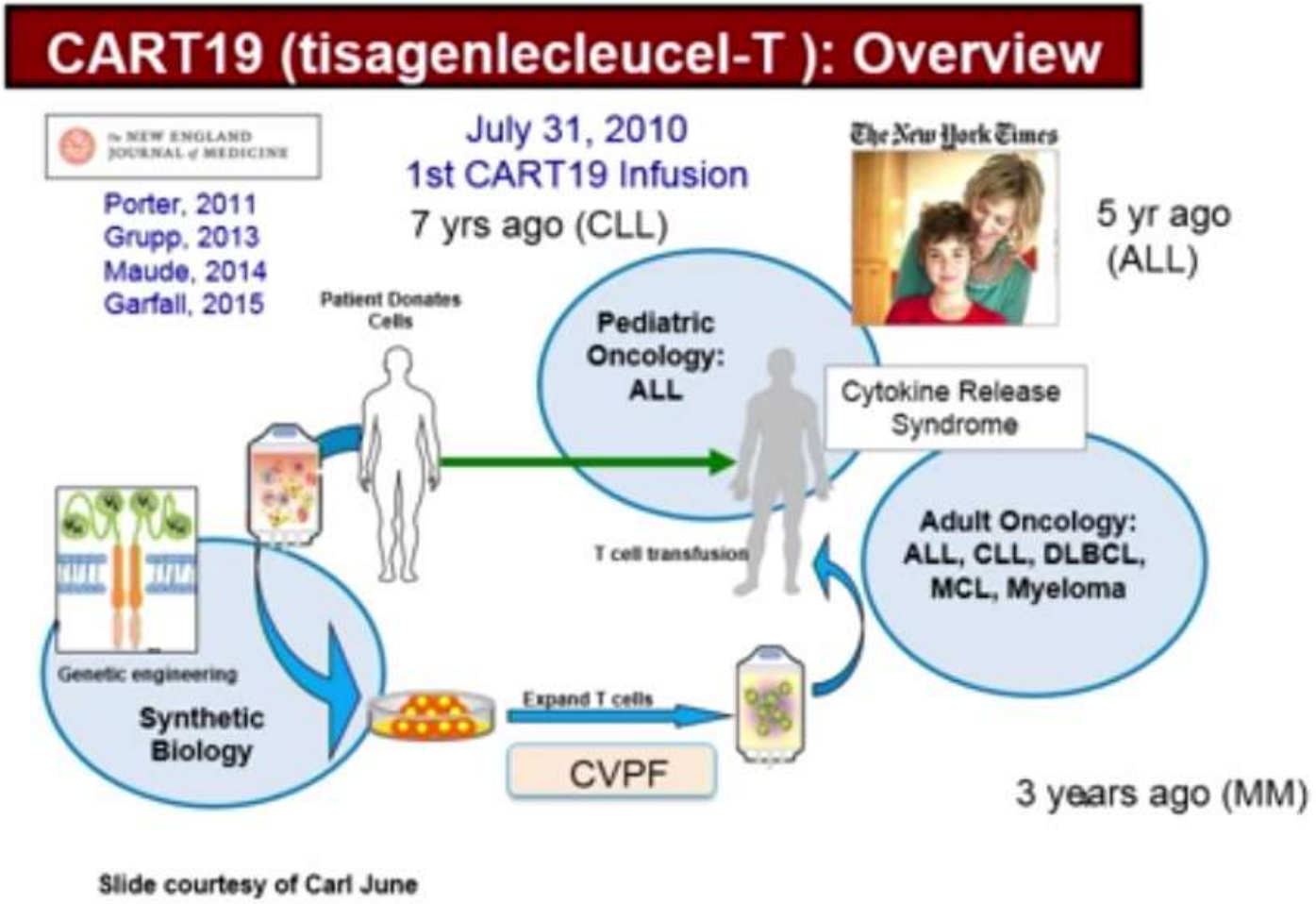
Categories of therapeutic intervention designed to amplify or overcome blocks in each stage of antitumor immunity



Chapter 19

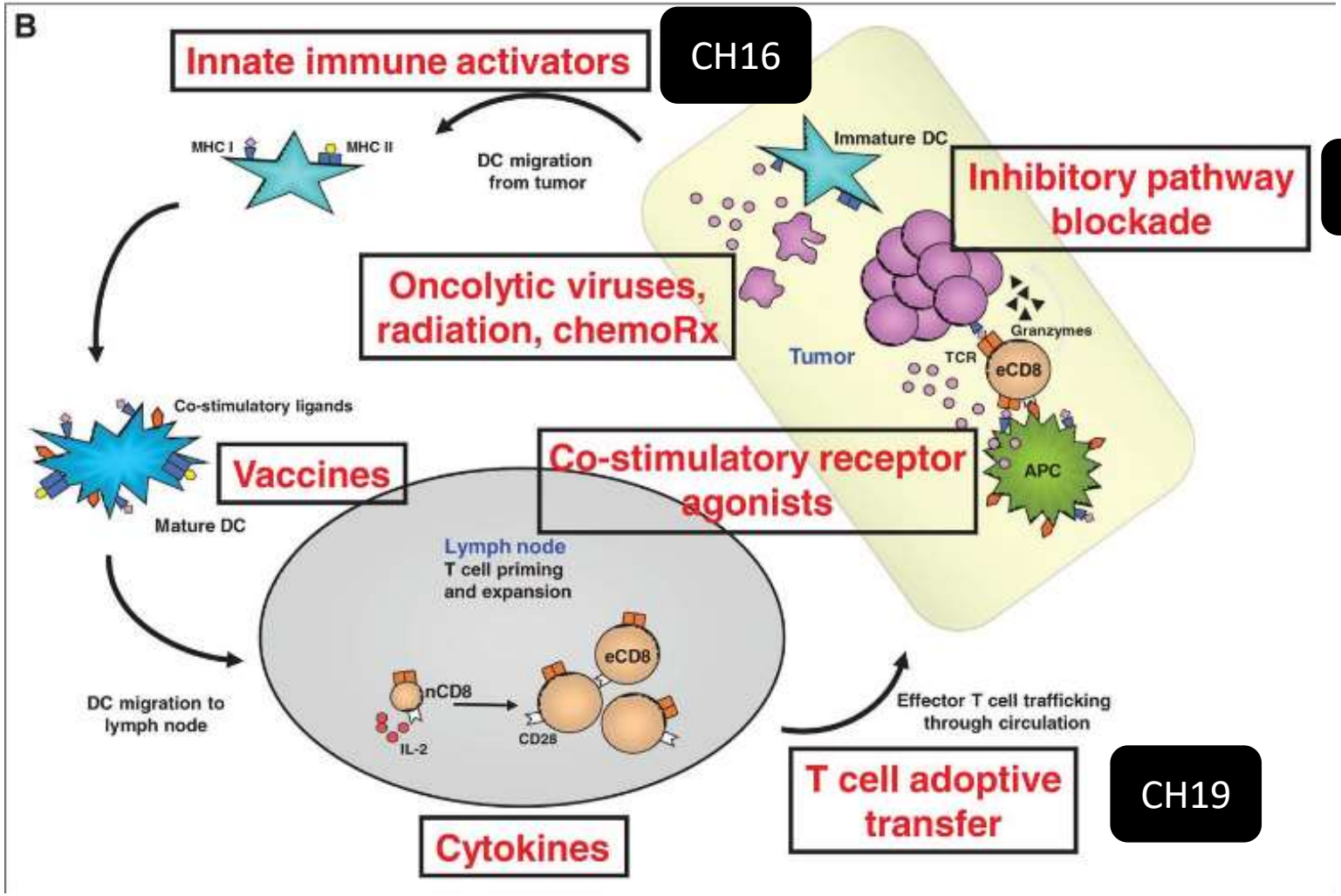
CH 19-1 、19-2

Adoptive T Cell Transfer



Slide courtesy of Carl June

Categories of therapeutic intervention designed to amplify or overcome blocks in each stage of antitumor immunity



Chapter 20

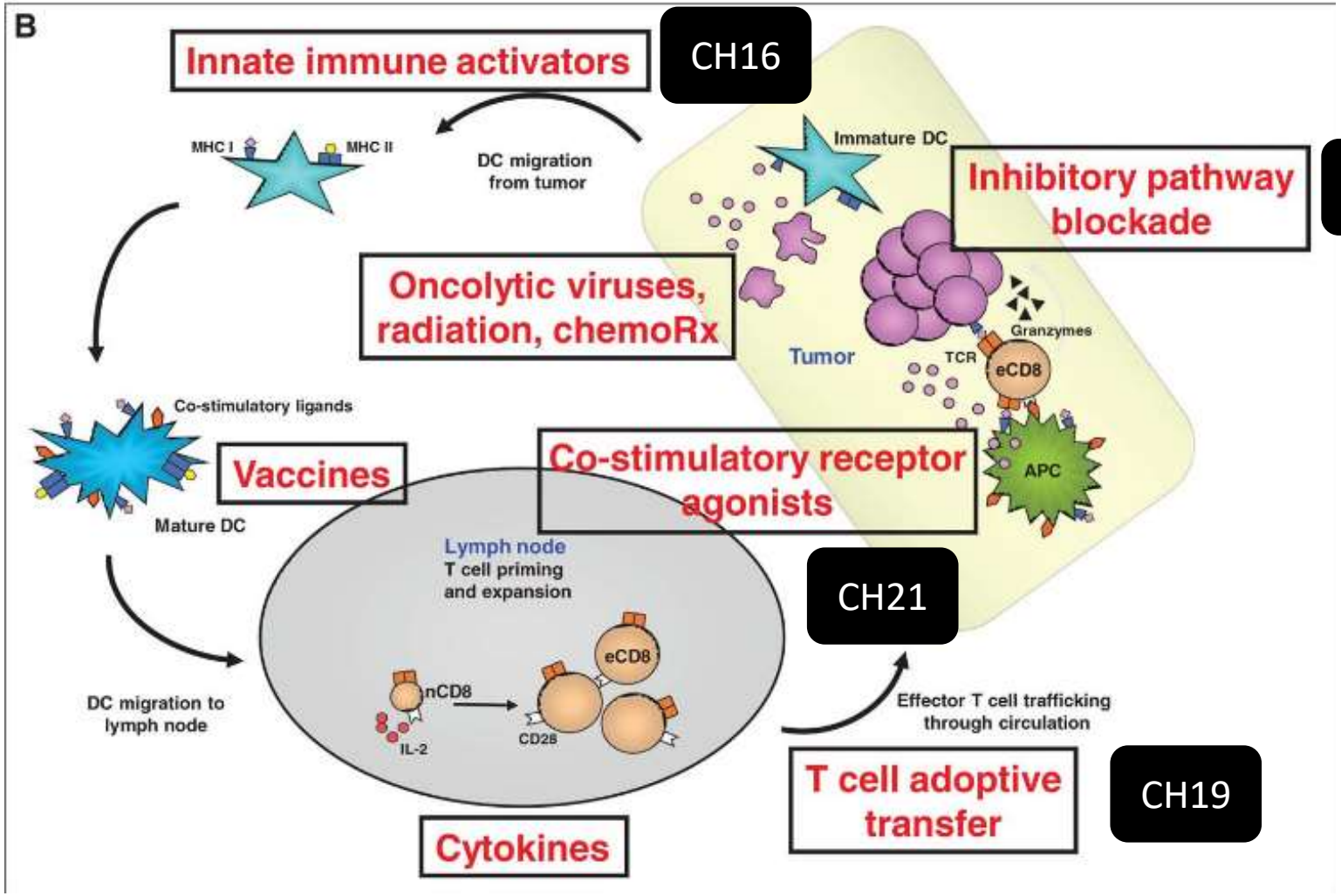
CH 20

Immunotherapy Based on Blocking T Cell Inhibitory Pathways

- Even if effector T cells migrate into tumor sites, negative regulatory pathways quickly impair T cell function as negative feedback mechanism
- Abs blocking PDL-1/PD-1 interactions approved by FDA for multiple cancers types.
- Inhibitors of IDO have entering phase III trials in multiple cancer types
  - At this time, it is unclear if there is a path forward for IDO inhibitors in melanoma; after the results of the phase III trial with epacadostat which did not meet the primary endpoint of PFS, and OS, several other trials with indoximod and BMS-986205 were suspended or placed on hold.

https://oncology.medicinematters.com/melanoma/ido-inhibitors/ido-inhibitors-in-melanoma--a-path-forward-/16410630

Categories of therapeutic intervention designed to amplify or overcome blocks in each stage of antitumor immunity



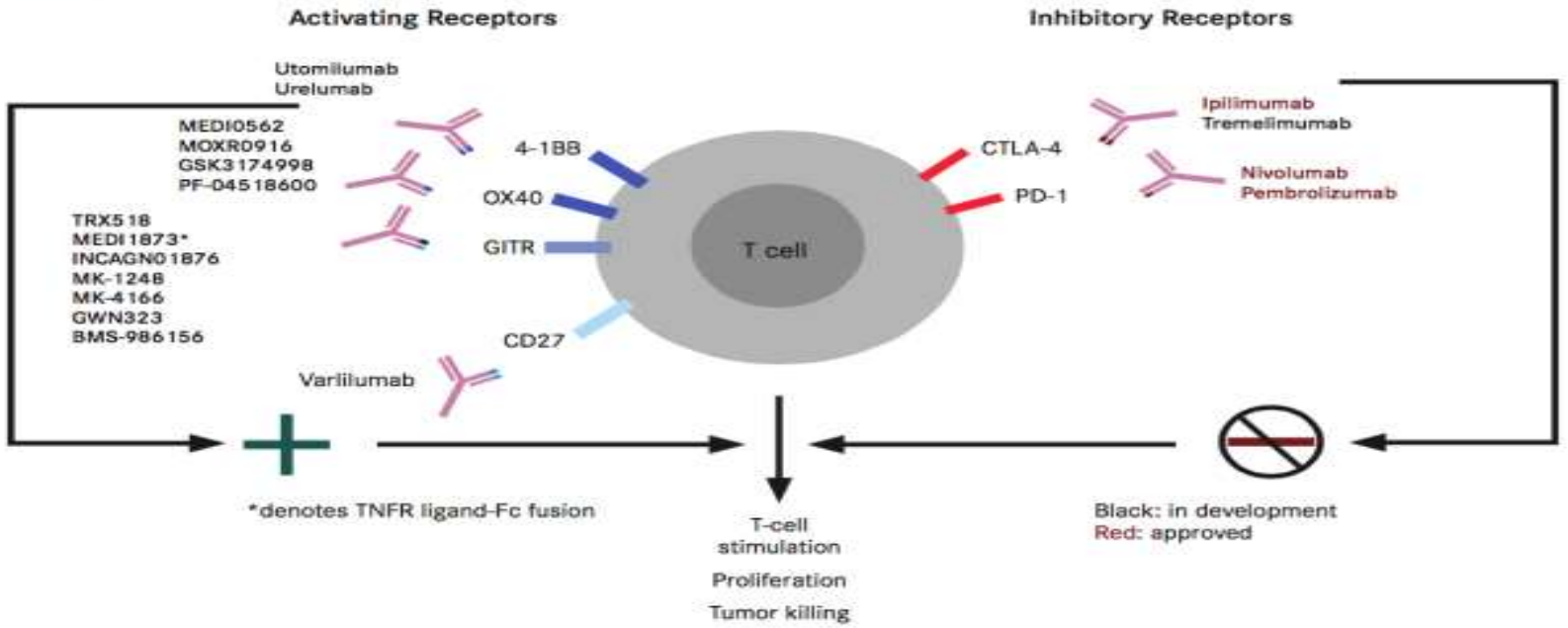
Chapter 21

CH 21

Agonistic Antibodies to Co-Stimulatory Molecules

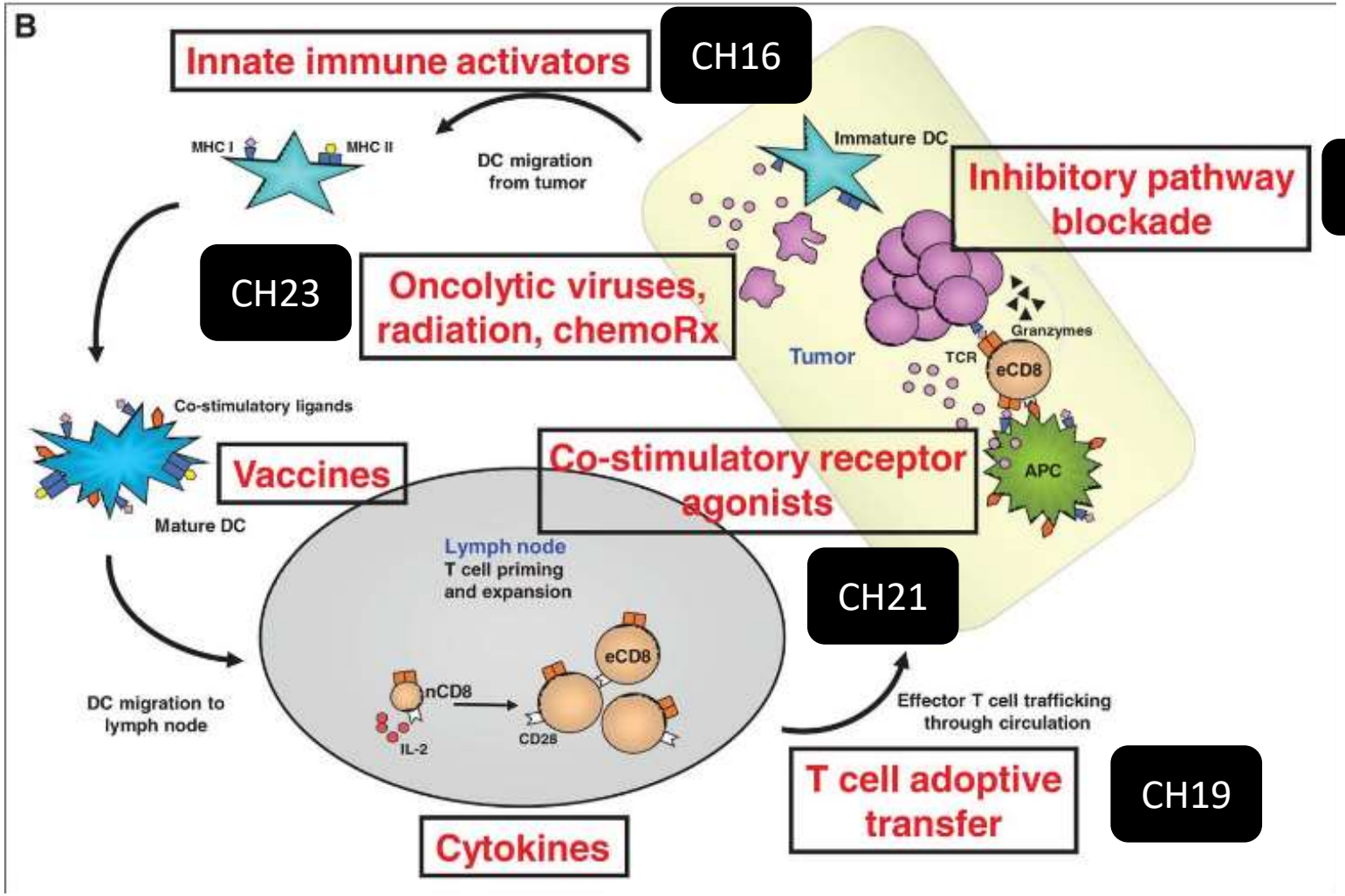
- TNF-super family (TNF-SF) mebmers 4-1BB and OX40, and agonists Abs against these targets are in early-phase clinical trials

FIGURE. Immunotherapies Targeting T-Cell Receptors (currently approved or in development).



AJHO. 2017;13(11):4-15

Categories of therapeutic intervention designed to amplify or overcome blocks in each stage of antitumor immunity

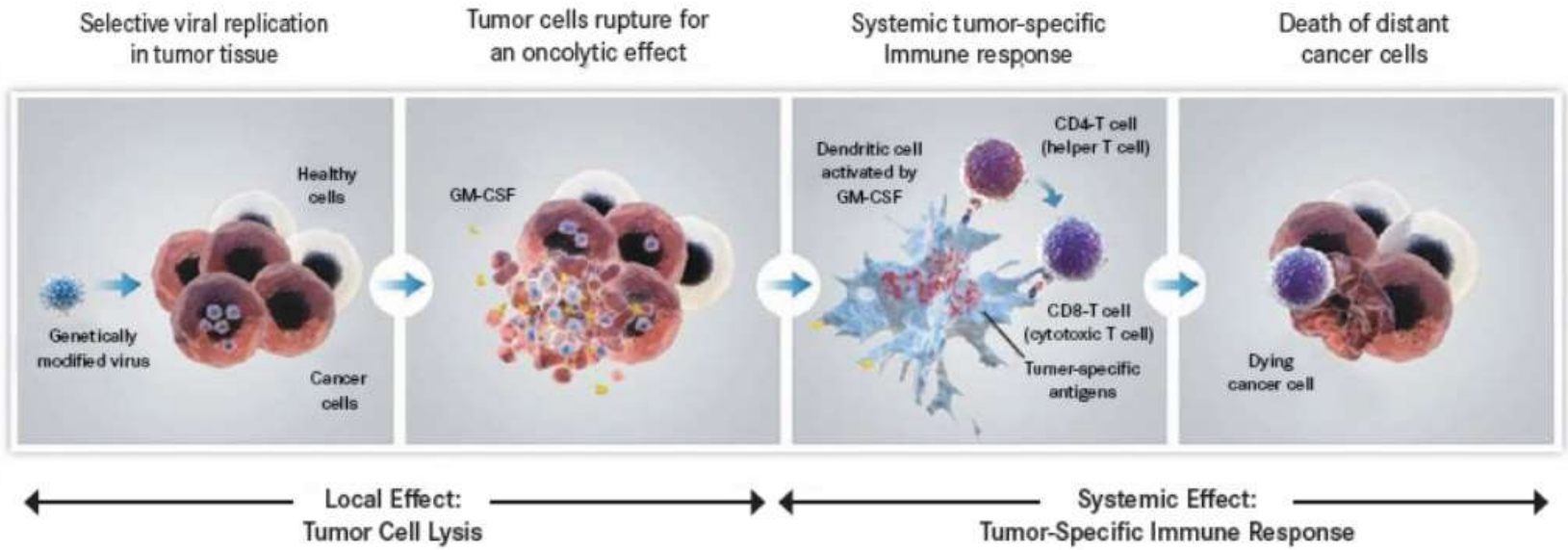


Chapter 23

CH 23-1 ~ 23-2
Oncolytic Viruses

- Intratumoral injection of oncolytic virus, such as T-VEC that is FDA approval for melanoma, prime T cell responses from

FIGURE 1. Talimogene laherparepvec (T-VEC) is a viral oncolytic immunotherapy designed to produce both local and systemic effect resulting in tumor lysis and death.



* Reproduced with permission from Amgen.
GM-CSF indicates granulocyte-macrophage colony-stimulating factor.

https://www.gotoper.com/publications/ajho/2016/2016apr/an-update-on-talimogene-laherparepvec

Chapter 24

CH 24

Principles of Combination Immunotherapies

- FDA approved only CTLA-4 Ab ipilimumab with anti-PD-1 Ab nivolumab in metastatic melanoma
- Additional combinations are in clinical development

- TIM-3 has critical roles in tumor-induced immune suppression. Blockade of TIM-3, alone or in combination with PD-1 pathway blockade, has shown anti-tumor efficacy in several preclinical cancer models. TIM-3/PD-1 pathway co-blockade to activate immune response and control tumor growth could reflect the combined effects on modulating not only the functional phenotype of dysfunctional effector T cells, but also inhibiting the suppressive activity of various suppressor cells.

https://www.pharmaweek.com/Combination-Immunotherapy


THANKS FOR YOUR
ATTENTION