Future Role of Immunotherapy in the Management of Advanced Prostate Cancer

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STUDIES ON PROSTATIC CANCER

II. THE EFFECTS OF CASTRATION ON ADVANCED CARCINOMA OF THE PROSTATE GLAND

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CHICAGO

The thesis of this work may be briefly summarized. In many instances a malignant prostatic tumor is an overgrowth of adult epithelial cells. All known types of adult prostatic epithelium undergo atrophy when androgenic hormones are greatly reduced in amount or inactivated. In this paper evidence is presented that significant improvement often occurs in the clinical condition of patients with far advanced cancer of the prostate after they have been subjected to castration. Conversely, the symptoms are aggravated when androgens are injected. We believe that this work provides a new concept of prostatic carcinoma.

The evidence that prostatic carcinoma is often composed of an adult type of epithelium derives from a study of such tissue with respect to the phosphatase which manifests optimum activity at p_H 5. An important advance in the technic of investigation of the prostate gland was made by Kutscher and Wolbergs,[1] who found that this enzyme is present in large amounts in adult human and monkey prostate glands; indeed, this phosphatase is present in prostate tissue in larger amounts than any phosphatase in any other tissue. Gutman and Gutman[2] found that the enzyme is present in small amounts in infancy and childhood and is increased during puberty to the high values found in the adult. These

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From the Department of Surgery, University of Chicago.

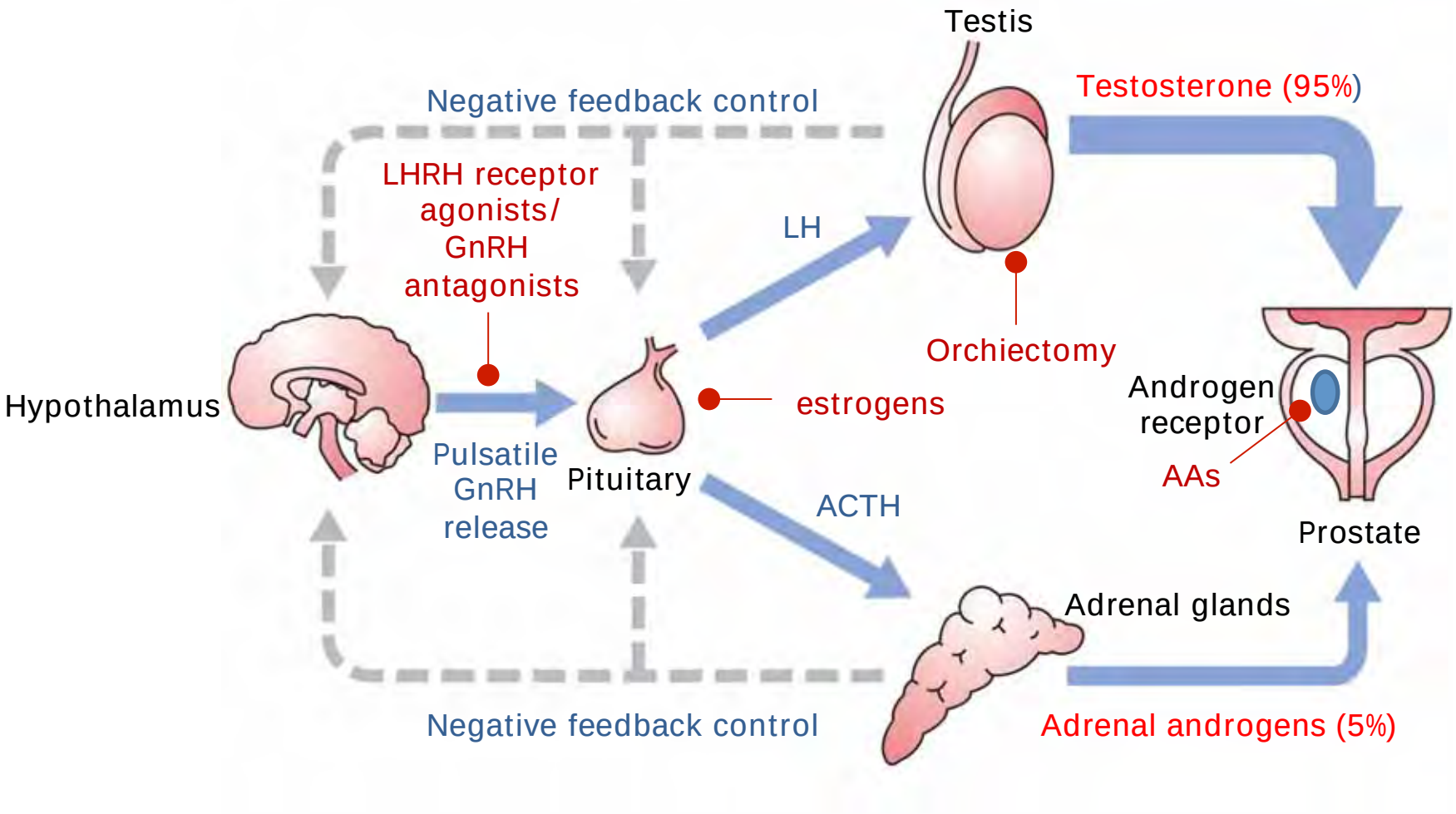
Dr. Hodges is a Fellow of the Douglas Smith Foundation for Medical Research of the University of Chicago.

This investigation was supported by a grant from the Committee for Research in Problems of Sex of the National Research Council.

1. Kutscher, W., and Wolbergs, H.: Prostataphosphatase, Ztschr. f. physiol. Chem. **236**:237, 1935.

2. Gutman, A. B., and Gutman, E. B.: "Acid" Phosphatase and Functional Activity of the Prostate (Man) and Preputial Glands (Rat), Proc. Soc. Exper. Biol. & Med. **39**:529 (Dec.) 1938.

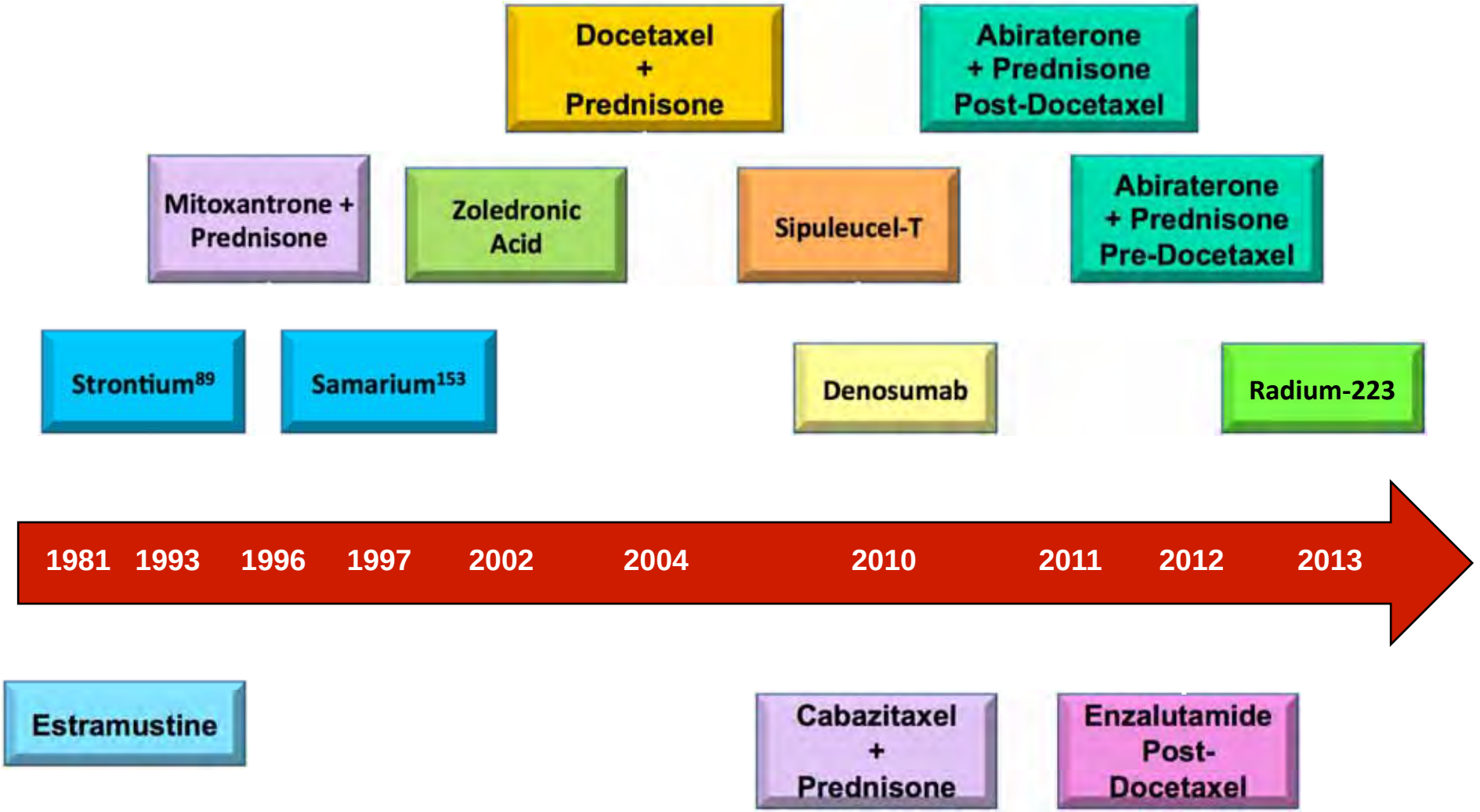
Hormonal control of androgen pathways and sites of action of PCa therapies



ACTH, adrenocorticotrophic hormone; FSH, follicle-stimulating hormone; LH, luteinising hormone

Drudge-Coates. Int J Urol Nurs 2009;3:85-92

Chronology of FDA Approvals, CRPC



Agents with OS Benefit in mCRPC

Drug[1-3]	Trial	Comparator	Primary Endpoint	FDA Approval
Chemotherapy-naïve				
Abiraterone acetate + prednisone	COU-AA-302	Placebo + prednisone	OS benefit 5.2 months*	Dec 2012
Sipuleucel-T	IMPACT	Placebo	OS benefit 4.1 months	Apr 2010
Radium-223	ALSYMPCA	Placebo	OS benefit 3.6 months	May 2013
Enzalutamide	PREVAIL	Placebo	OS benefit 2.2 months (interim analysis)	N/A
Post-chemotherapy				
Abiraterone acetate + prednisone	COU-AA-301	Placebo + prednisone	OS benefit 4.6 months	Apr 2011
Enzalutamide	AFFIRM	Placebo	OS benefit 4.8 months	Aug 2012
Cabazitaxel + prednisone	TROPIC	Mitoxantrone + prednisone	OS benefit 2.4 months	June 2010
Docetaxel + prednisone	TAX327	Mitoxantrone + prednisone	OS benefit 2.4 months	May 2004

*P=0.0151. Did not meet the prespecified value for statistical significance.

1. Ryan CJ et al. *N Engl J Med*. 2013;368:138-148. 2. El-Amm J et al. *Ther Adv Med Oncol*. 2013;5:25-40. 3. Medivation Press Release. October 2013. http://investors.medivation.com/releasedetail.cfm?ReleaseID=798880. Accessed November 4, 2013. 4. TAXOTERE [package insert].

Adapted from Gomella

VOLUME 31 · NUMBER 15 · MAY 20 2013

JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

Advancing Precision Medicine for Prostate Cancer Through Genomics

Sameek Roychowdhury and Arul M. Chinnaiyan

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Published online ahead of print at www.jco.org on April 15, 2013.

Supported by American Cancer Society Mentored Scholar Research Grant No. MRSG-12-194-01, a Landon Foundation American Association for Cancer Research Innovator Award for Personalized Cancer Medicine, and a Prostate Cancer Foundation Young Investigator Award (S.R.) and by the Prostate Cancer Foundation, National Institutes of Health Early Detection Research Network Grants No. U01CA111275 and R01CA132874-01A1, Prostate Specialized Program of Research Excellence Grant No. P50CA69568, and by a Doris Duke Charitable Foundation Clinical Scientist Award (A.M.C.).

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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ABSTRACT

Prostate cancer is the most common type of cancer in men and the second leading cause of cancer death in men in the United States. The recent surge of high-throughput sequencing of cancer genomes has supported an expanding molecular classification of prostate cancer. Translation of these basic science studies into clinically valuable biomarkers for diagnosis and prognosis and biomarkers that are predictive for therapy is critical to the development of precision medicine in prostate cancer. We review potential applications aimed at improving screening specificity in prostate cancer and differentiating aggressive versus indolent prostate cancers. Furthermore, we review predictive biomarker candidates involving *ETS* gene rearrangements, *PTEN* inactivation, and androgen receptor signaling. These and other putative biomarkers may signify aberrant oncogene pathway activation and provide a rationale for matching patients with molecularly targeted therapies in clinical trials. Lastly, we advocate innovations for clinical trial design to incorporate tumor biopsy and molecular characterization to develop biomarkers and understand mechanisms of resistance.

J Clin Oncol 31:1866-1873. © 2013 by American Society of Clinical Oncology

INTRODUCTION

Prostate cancer is the most common nonskin cancer and the second leading cause of cancer death in men in the United States.[1,2] Although there has been sig-

Genomic results have the potential to be translated clinically as diagnostic, prognostic, or predictive biomarkers. Diagnostic biomarkers facilitate obtaining an accurate cancer diagnosis as part of screening or confirmatory testing. Prognostic bio-

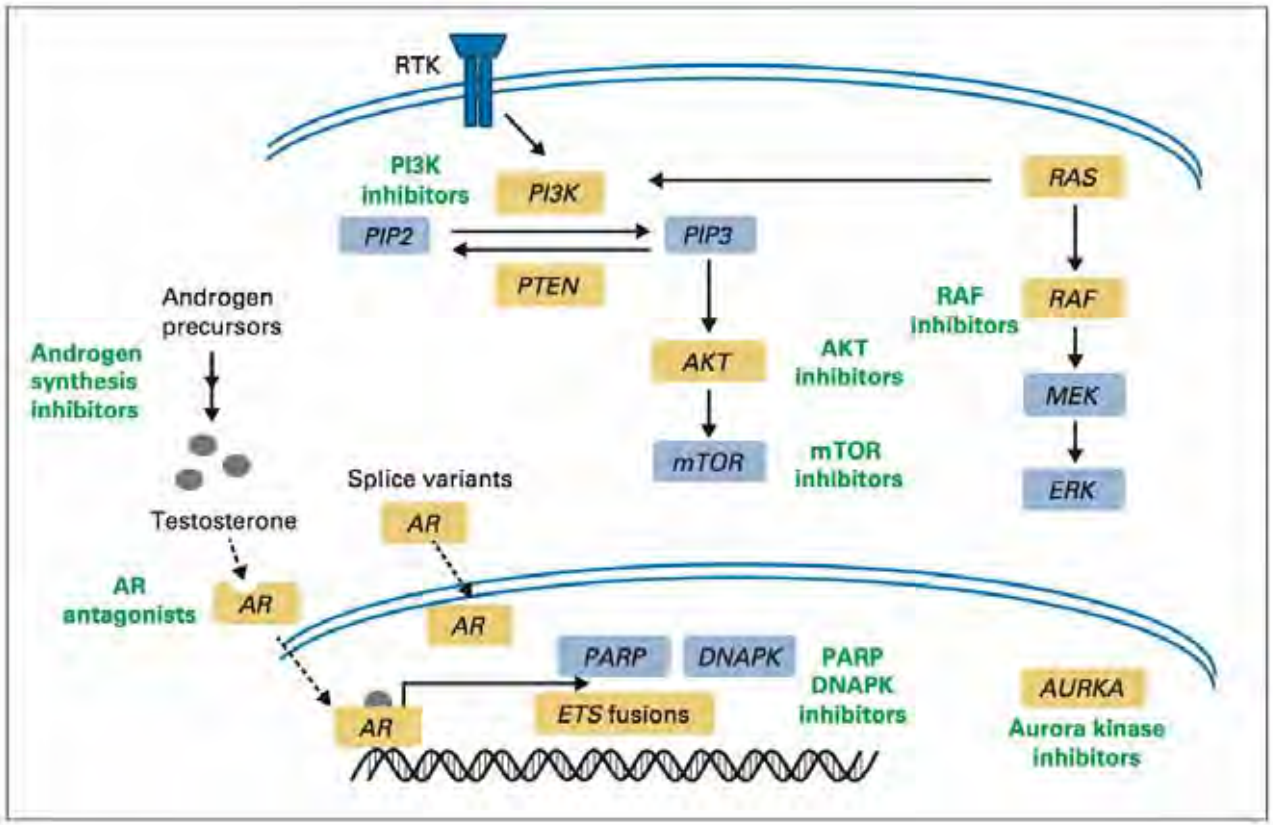


Fig 1. Pathway-guided treatment in prostate cancer. This diagram highlights pathways for targeting in prostate cancer, including the phosphatidylinositide 3-kinase (PI3K) pathway, *ETS* rearrangements, and androgen signaling. Green indicates putative treatment hypotheses for relevant pathways. Each of these pathways can be driven by genomic aberrations, such as point mutations, copy number alterations, and rearrangements. The diagram also highlights less common driving mutations involving *RAS*, *RAF*, and *AKT* oncogenes. Furthermore, there is potential for cooperation between pathways because these are not necessarily mutually exclusive. Genes highlighted in gold have known genomic alterations. AR, androgen receptor; mTOR, mammalian target of rapamycin, PARP, poly (ADP-ribose) polymerase; RTK, receptor tyrosine kinase.

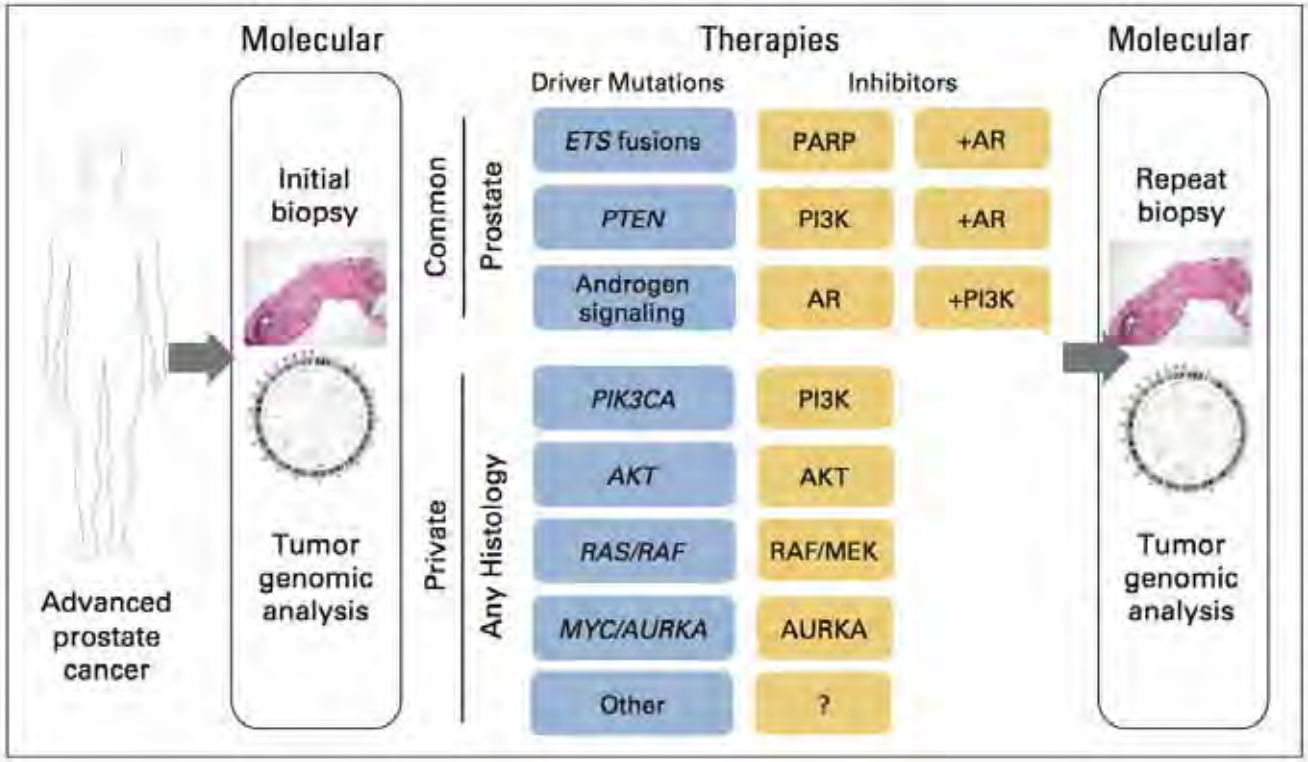
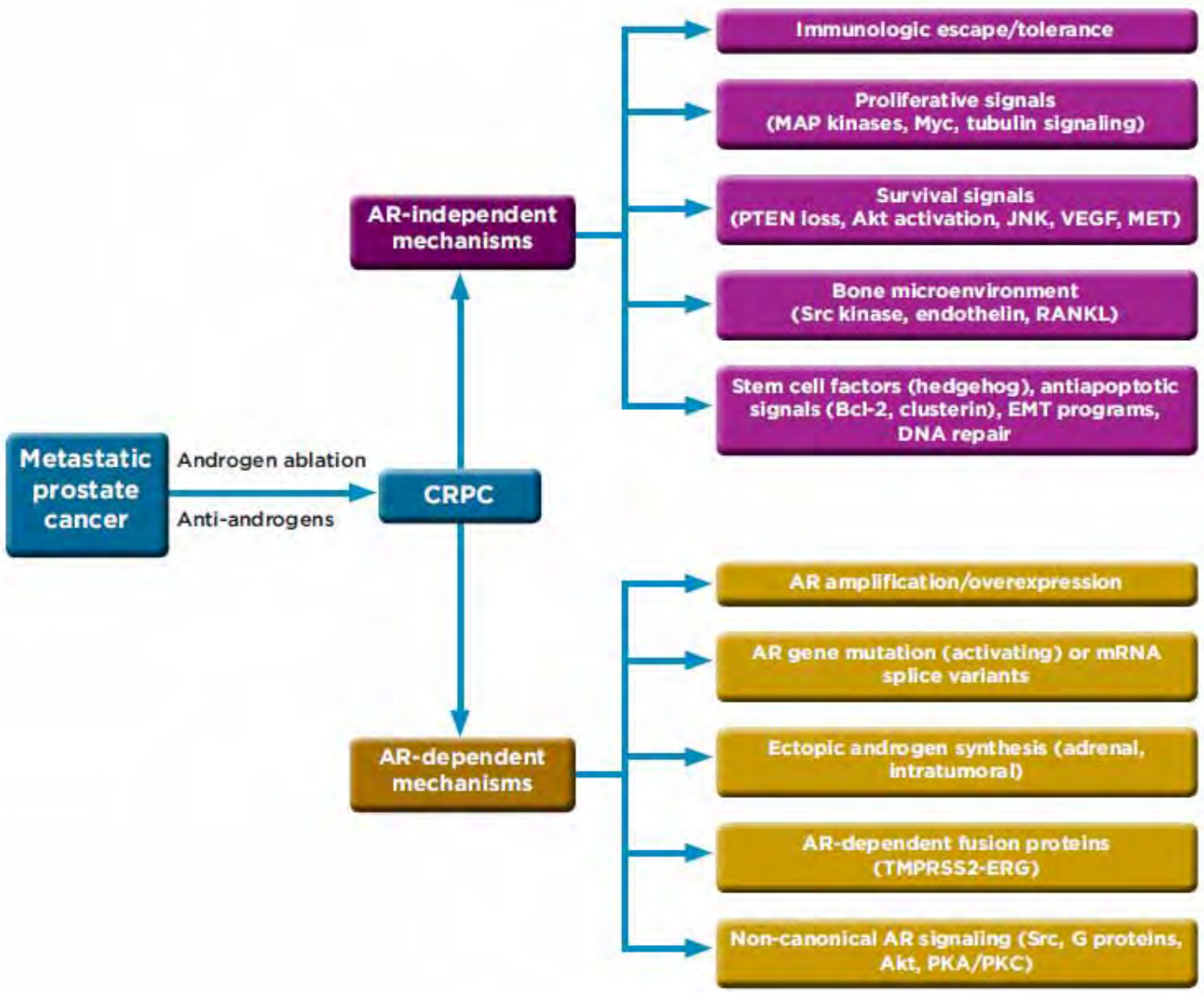


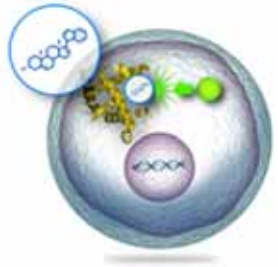
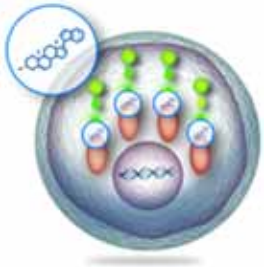
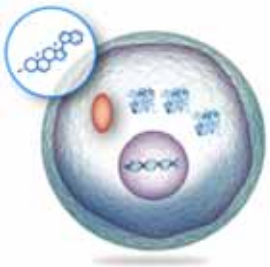
Fig 2. Translating genomics for prostate cancer trials. This diagram outlines a path to genomics-driven trials in prostate cancer. Patients with advanced prostate cancer would undergo a fresh tumor biopsy for assessment of their current disease and molecular stratification to trials, including random assignment within those groups. Because of the prevalence of phosphatidylinositide 3-kinase (PI3K) pathway activation, *ETS* rearrangements, and androgen signaling, genomic enrichment of patients for these common disease subsets may follow traditional trial structures including combination treatments. However, for rare or private molecular disease subsets, these patients may be better suited to studies based on molecular aberrations and that include multiple histologies. For all studies, repeat biopsy for genomic assessment will be valuable for evaluating mechanisms of resistance, including tumor subclone selection. AR, androgen receptor; PARP, poly (ADP-ribose) polymerase.

Biologic Mechanisms Driving CRPC



Antonarakis and Armstrong, Clin Oncol News 2011

Galeterone: Selective, Multi-targeted, Small Molecule for Treatment of CRPC

	CYP17 Lyase Inhibitor	AR Antagonist	AR Degrader
	 **Inhibits androgen synthesis**	 **Blocks androgen binding**	 **Decreases AR levels**
Abiraterone	✓		
Enzalutamide		✓	
Galeterone	✓	✓	✓
	• No mandatory steroids • Fasting not required • Preclinical activity in mutation T878A	• Not a $GABA_A$ antagonist • No seizures • Preclinical activity in mutation F876L	• Active in C-terminal loss AR splice variants

In-licensed from the University of Maryland, Baltimore.

Galeterone in Four Castrate Resistant Prostate Cancer (CRPC) Populations: Results from ARMOR2

M-E Taplin[1], KN Chi[2], F Chu[3], J Cochran[4], WJ Edenfield[5], M Eisenberger[6], U Emmenegger[7], EI Heath[8], A Hussain[6], A Koletsky[9], D Lipsitz[10], L Nordquist[11], R Pili[12], M Rettig[13], O Sartor[14], ND Shore[15], R Dhillon[16], J Roberts[16], B Montgomery[17]

[1]Boston, MA/US, [2]Vancouver/CA, [3]San Bernardino, CA/US, [4]Dallas, TX/US, [5]Greenville, SC/US, [6]Baltimore, MD/US, [7]Toronto/CA, [8]Detroit, MI/US, [9]Boca Raton, FL/US, [10]Concord, NC/US, [11]Omaha, NE/US, [12]Buffalo, NY/US, [13]Los Angeles, CA/US, [14]New Orleans, LA/US, [15]Myrtle Beach, SC/US, [16]Cambridge, MA/US, [17]Seattle, WA/US

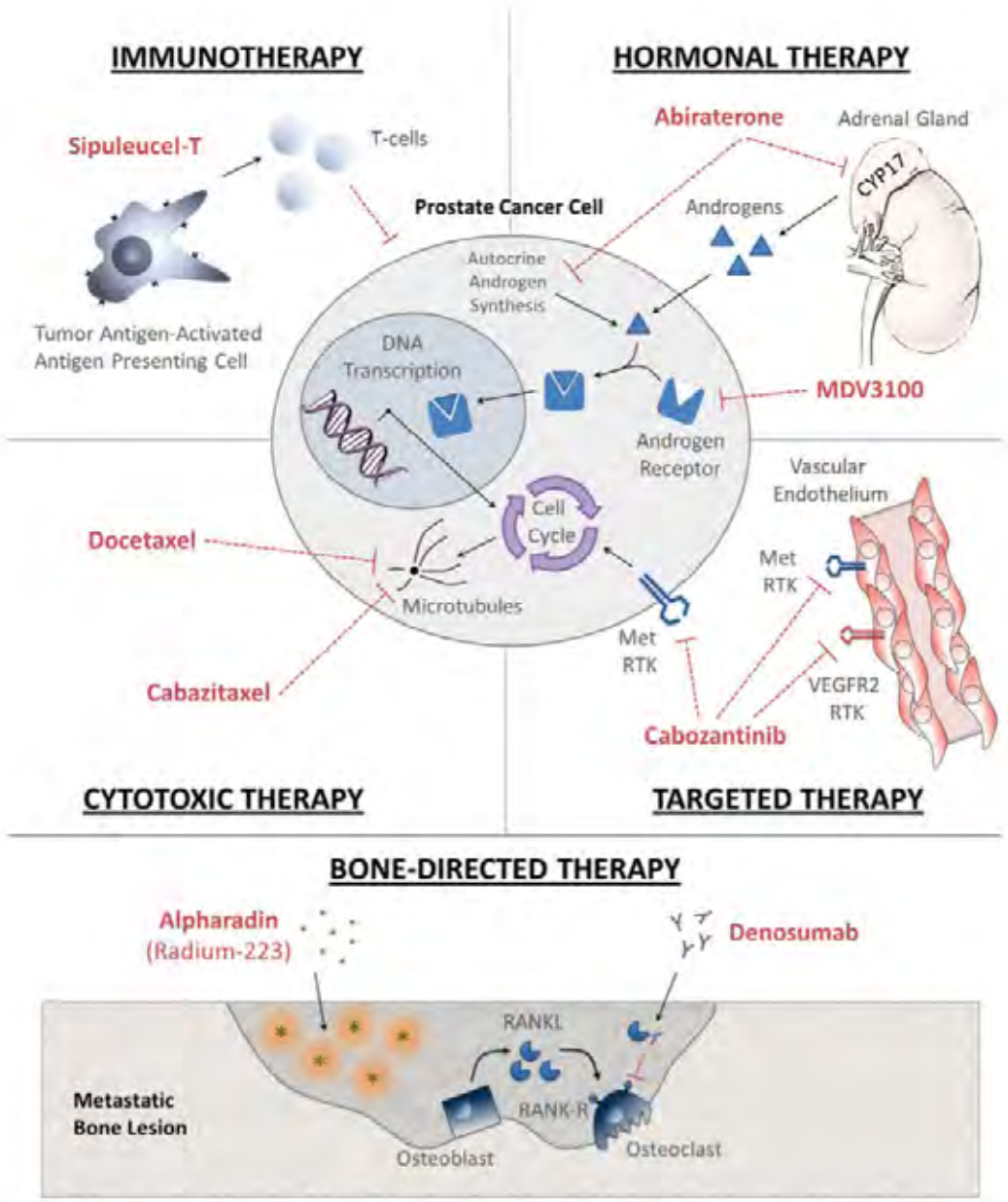
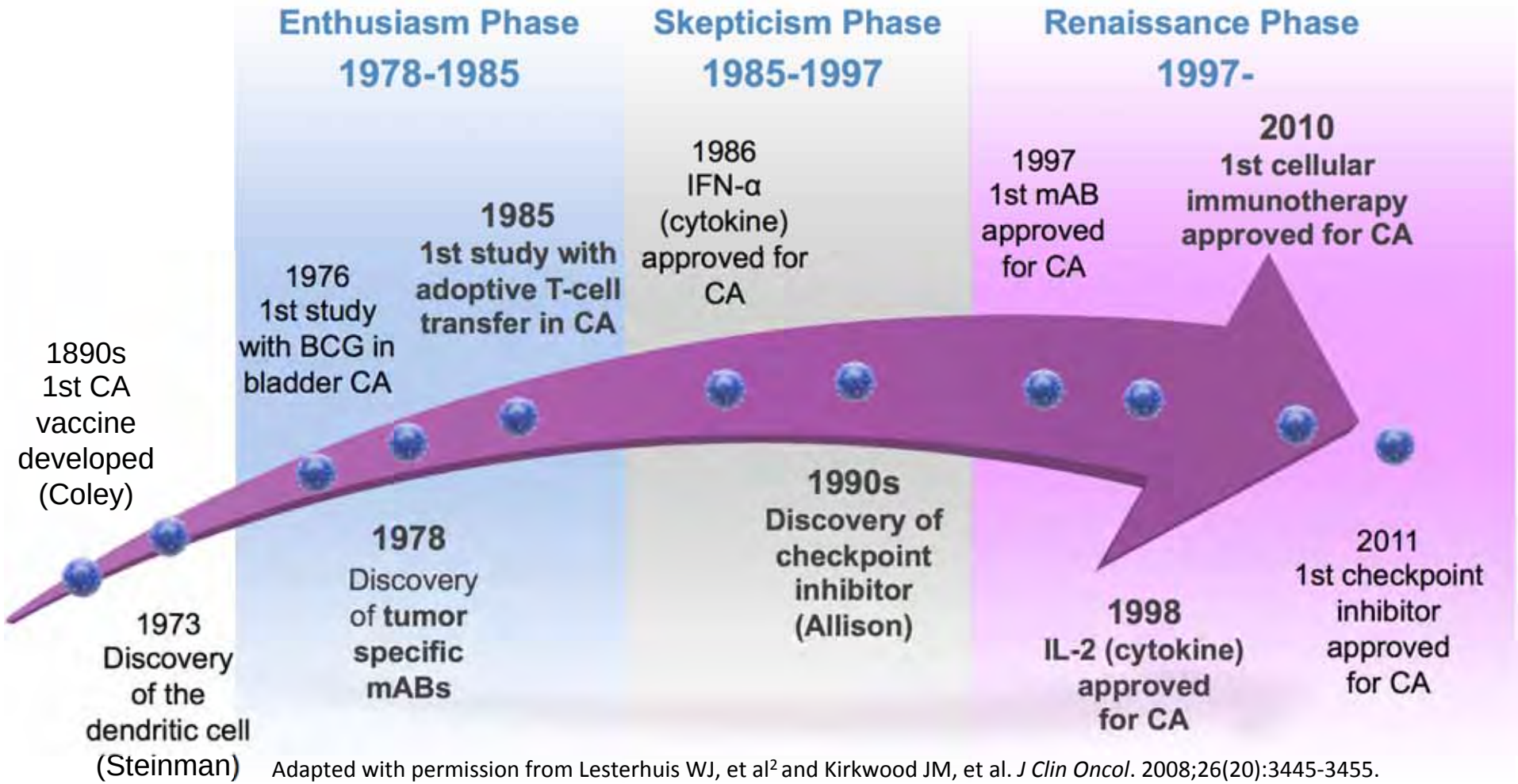


FIGURE 2. Mechanisms of Action of Novel Therapies for Castration-Resistant Prostate Cancer. CYP17 indicates a cytochrome p450 complex involved in adrenal steroidal synthesis; Met RTK, Met receptor tyrosine kinase; VEGFR2, vascular endothelial growth factor receptor 2; RANKL, receptor activator of nuclear factor kappa-B ligand; RANK, receptor activator of nuclear factor kappa-B.

Breakthrough of the Year 2013

The Renaissance of Immunotherapy



Adapted with permission from Lesterhuis WJ, et al[2] and Kirkwood JM, et al. *J Clin Oncol*. 2008;26(20):3445-3455.

BCG, Bacille Calmette-Guerin; mABs, monoclonal antibodies; CA, cancer; IFN-α, interferon alpha; IL-2, interleukin-2

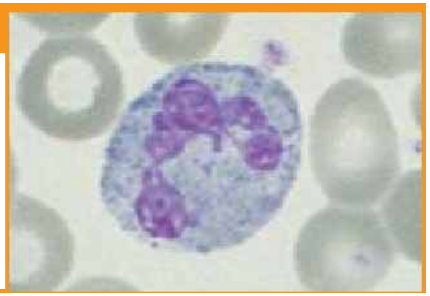
1. Kirkwood JM, et al. *CA Cancer J Clin*. 2012;62(5):309-335.
2. Lesterhuis WJ, et al. *Nat Rev Drug Discov*. 2011;10(8):591-600.
3. Krummel MF, et al. *J Exp Med*. 1995;182(2):459-465.
4. Cheson BD, et al. *N Engl J Med*. 2008;359(6):613-626.

The Immune System: Innate – Adaptive

CHARACTERISTICS	INNATE	ADAPTIVE
Specificity	Non-Specific	Specific
Antigens	Not Needed	Required
Memory	None	Generated
Time Course	Immediate	Slowly Developing
Duration	Transient	Lifelong
Cell Types	MØ, DC, NK, Neutrophil	T Cells, B Cells

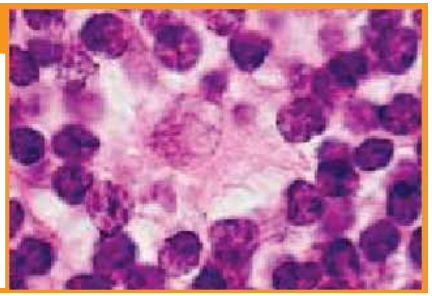
Cells of the Innate Immune System

Neutrophil



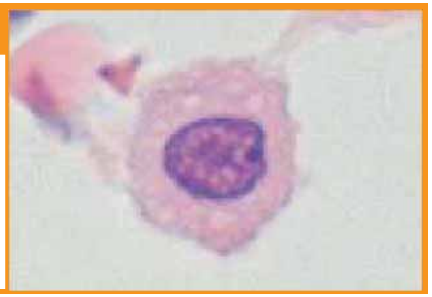
Phagocytosis and debris clean up
Secrete chemokines that call in other innate immune cells

Dendritic Cell



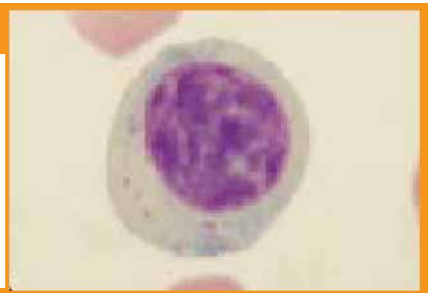
Potent antigen presenting cells (APC)
Uptake and process antigen
Both “class I” and “class II” pathways
Will stimulate both CTL and T helper (Th) cells

Macrophage



Phagocytosis and cleaning up debris, secrete cytokines
Type 1 can turn on adaptive immunity
Type 2 will limit adaptive immunity

Natural Killer Cell



Can directly kill tumor without docking to MHC
Secrete high levels of IFN-gamma (critical cytokine)
Antibodies can activate them via FC receptor (ADCC

THE TUMOR MICROENVIRONMENT

The multicellular composition of the tumor microenvironment plays an important role in how tumors can inhibit the antitumor immune response

The role of the tumor microenvironment in disrupting the cancer immunity cycle

- The tumor microenvironment plays an important role in disrupting the last stage of the cancer immunity cycle
- Tumors can create an immunosuppressive microenvironment by upregulating inhibitory molecules, such as programmed death-ligand 1 (PD-L1), on tumor cells and tumor-infiltrating immune cells[1,2,4-6]
- This ability to inhibit antitumor immune response makes the multicellular composition of the tumor microenvironment an important consideration for cancer research[4,6]
- The tumor microenvironment includes tumor cells (malignant cells that are both aided by and influence the makeup of the tumor microenvironment to ensure growth and survival), tumor-infiltrating immune cells (such as lymphoid and myeloid cells, which are key players in the cancer immunity cycle), and stromal cells (tumor-associated fibroblasts and endothelial cells that contribute to the tumor's structural integrity)[1,4,7,8]

T cells

Antigen-specific immune cells that carry out cell-mediated adaptive immune responses following activation by dendritic cells. Includes CD8 T cells (cytotoxic T cells) and CD4 T cells[9,10]

B cells

Antigen-specific immune cells that produce antibodies during an immune response[10]

Natural killer (NK) cells

Cytotoxic lymphocytes that recognize and kill stressed or malignant cells independent of antigen specificity (unlike T and B cells)[9]

Dendritic cells (DCs)

Antigen-presenting cells that capture and process cancer antigens to initiate an immune response[1]

Macrophages

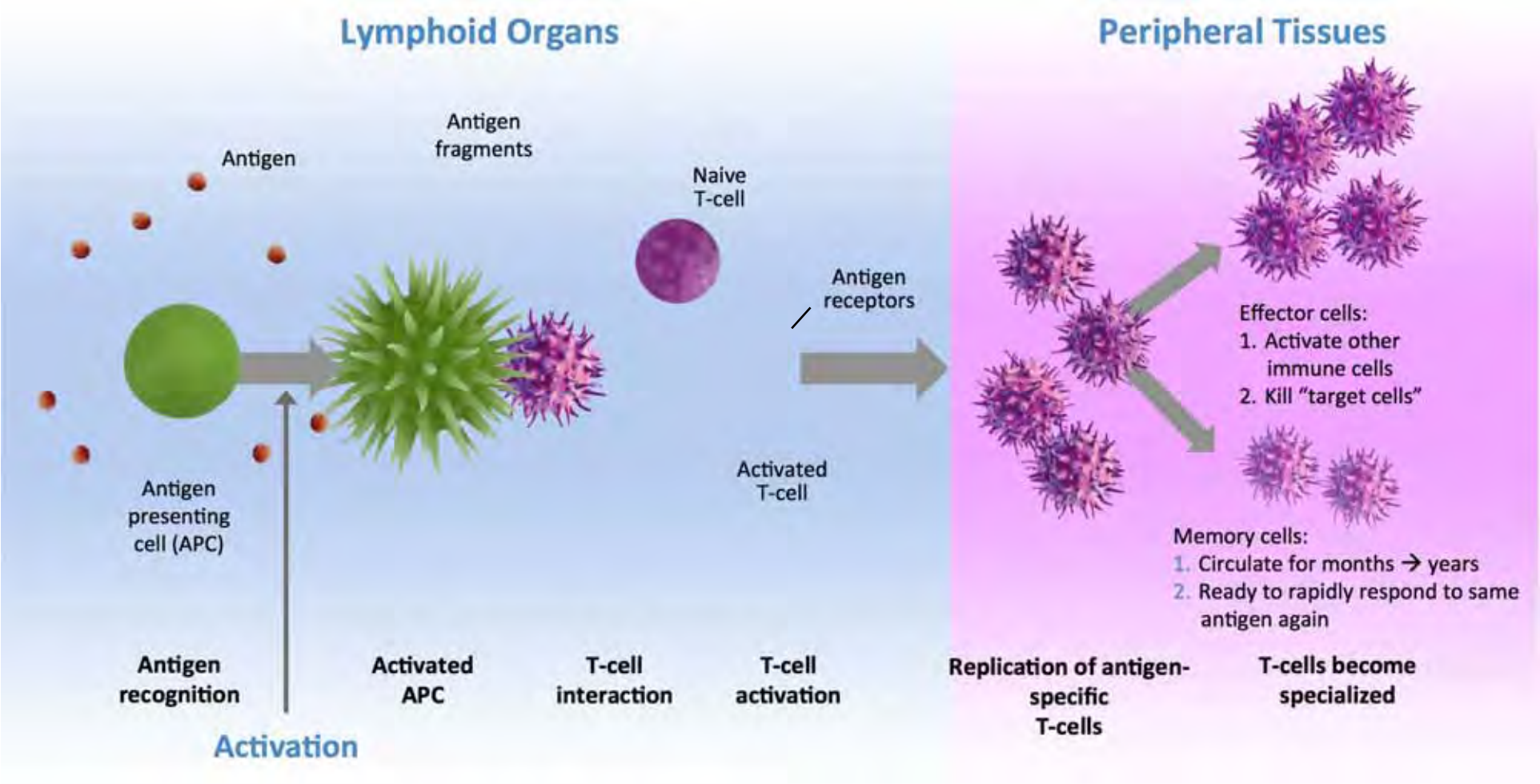
Type of phagocyte that detects pathogens, secretes cytokines, and presents antigens. Includes M1 and M2 macrophages[8,9]

- M1 macrophages develop in response to bacterial antigens and/or pro-inflammatory cytokines, such as interferon gamma. They promote inflammation and antitumor responses through the production of antitumor molecules[8,11]
- M2 macrophages develop in response to cytokines. They reduce anti-inflammatory cytokine production and produce factors that can promote tumor growth[8,11]

Myeloid-derived suppressor cells (MDSCs)

Immature myeloid cells, including DC and macrophage precursors, which have potent immunosuppressive activity on T-cell function[12]

Initiation of Immune Response: Key Cells



Adapted from Abbas AK, et al.

Abbas AK, et al. *Basic Immunology*. 3rd ed. 2011.

General Approaches for Cancer Immunotherapy

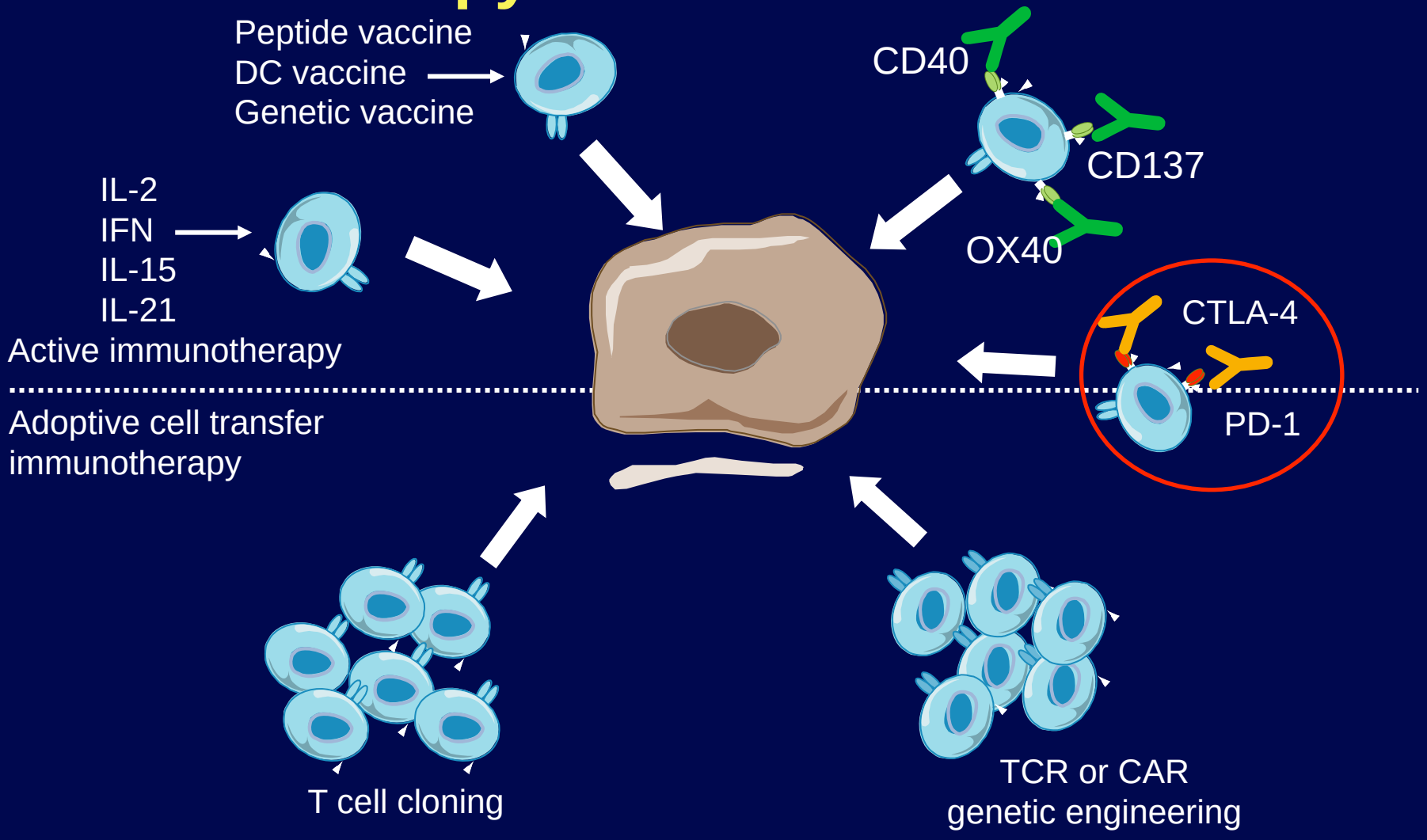
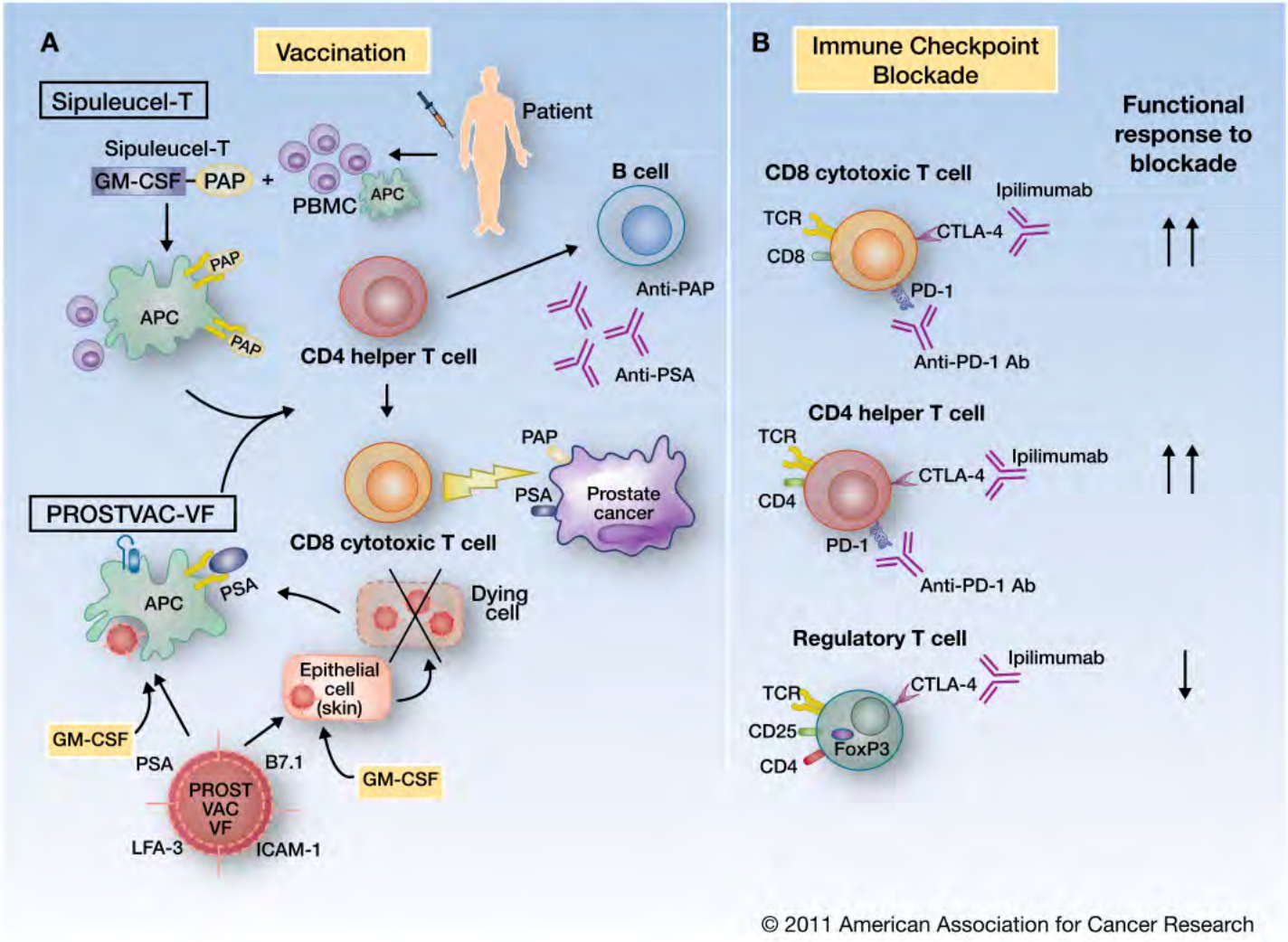
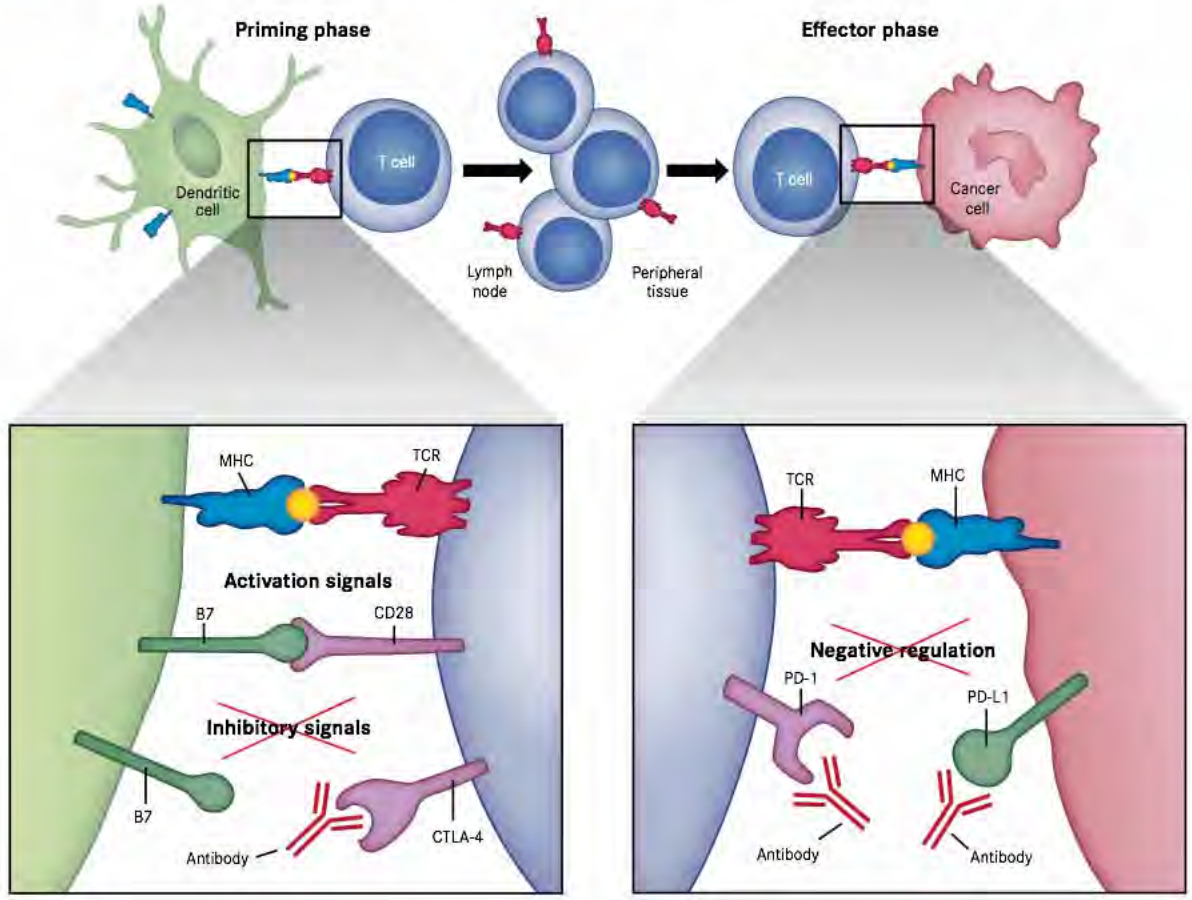


Figure. Immunotherapeutic Approaches That Augment Antitumor Immunity Against Prostate Cancer Include Vaccination (A) and Immune Checkpoint Blockade (B)[28]



APC indicates antigen-presenting cell; CD, cluster of differentiation; CTLA, cytotoxic T-lymphocyte antigen; GM-CSF, granulocyte-macrophage colony-stimulating factor; ICAM, intracellular adhesion molecule; LFA, leukocyte function antigen; PAP, prostatic acid phosphatase; PBMC, peripheral blood mononuclear cells; PD, programmed death; PSA, prostate-specific antigen; TCR, T-cell receptor.

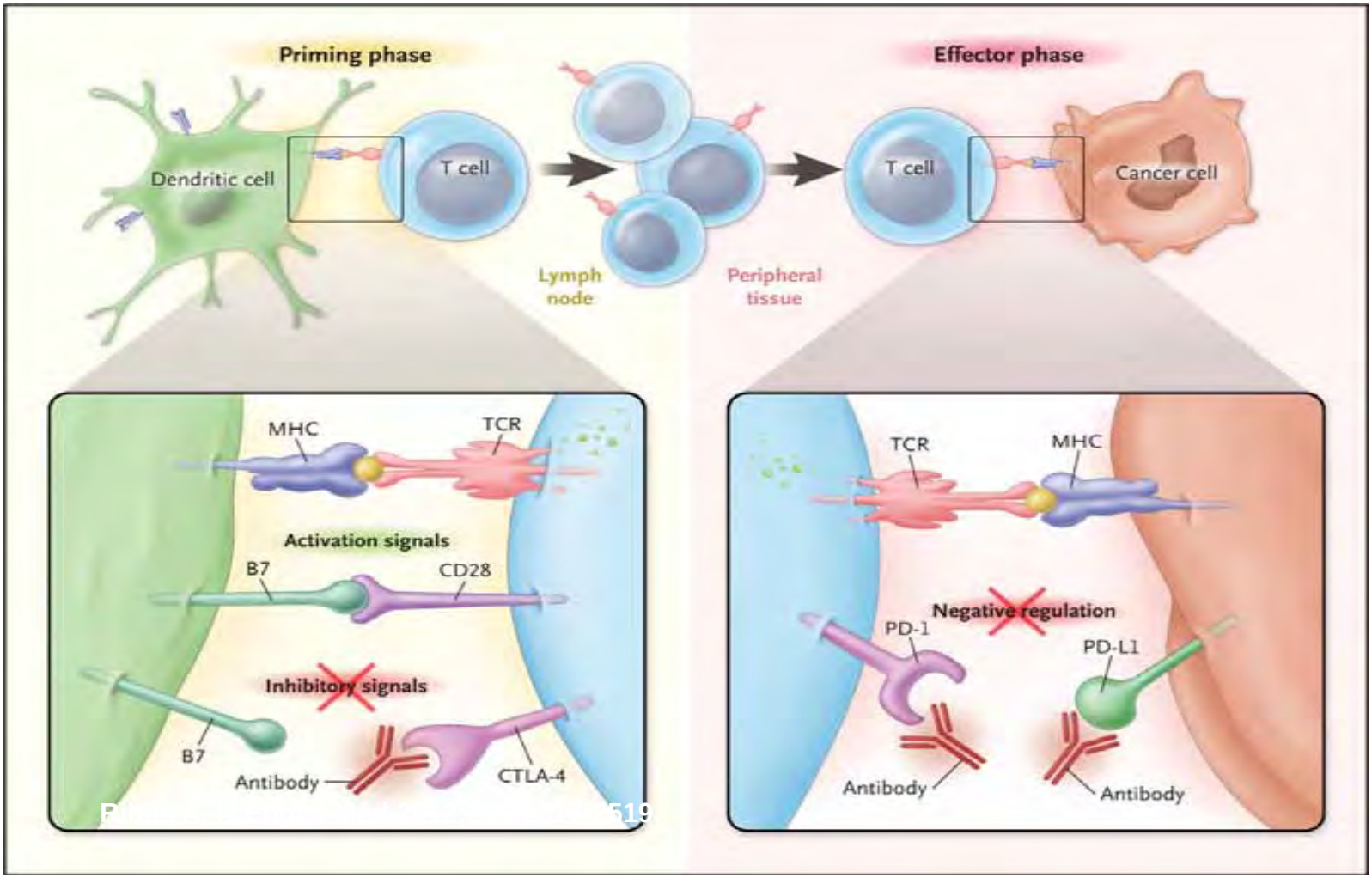
Figure 2. Targeting the Immune Checkpoints for Cancer Immunotherapy[28]



CD28 indicates cluster of differentiation 28; CTLA-4, cytotoxic T-lymphocyte antigen-4; MHC, major histocompatibility complex; PD-1, programmed death-1; PD-L1, programmed death ligand-1; TCR, T-cell receptor.

Activation of T cells is a 2-step process that requires recognition of specific antigens presented by MHC on the surface of cancer cells through their "primed" T-cell receptor, as well as a co-regulatory signal delivered by the B7 family of receptors (the so-called immune checkpoints). The 2 checkpoints that deliver inhibitor signals, CTLA-4 and PD-1, function at different points in T-cell function. CTLA-4 is upregulated shortly after activation and negatively regulates T-cell activation during the "priming" phase of T-cell response within the lymph nodes by binding to B7 molecules on the surface of antigen-presenting cells. Conversely, when these B7 molecules bind to CD28 instead, they generate the opposite, activating signals. PD-1 is expressed on T cells later on in the immune response, during the effector phase of T-cell response. When PD-1 binds to either of its ligands (PD-L1 or PD-L2), which are primarily expressed within inflamed tissues and the tumor microenvironment, it results in inhibition of T-cell activity. Blockade of CTLA-4 or PD-1/PD-L1 with antibodies results in the preferential activation of T cells with specificity for cancer cells.

Releasing the Power of T-Cells: CTLA-4 and PD-1 Blockade



THE ROLE OF THE PD-L1 PATHWAY UNDER NORMAL CONDITIONS

Maintaining immune homeostasis and protecting normal cells from collateral damage

PD-L1 and PD-L2 downregulate cytotoxic T-cell activity to maintain immune homeostasis

- PD-L1 and PD-L2 bind to specific receptors on T cells. When bound to their receptors, cytotoxic T-cell activity is downregulated, thereby protecting normal cells from collateral damage[13,14]

- **PD-L2 binds primarily**

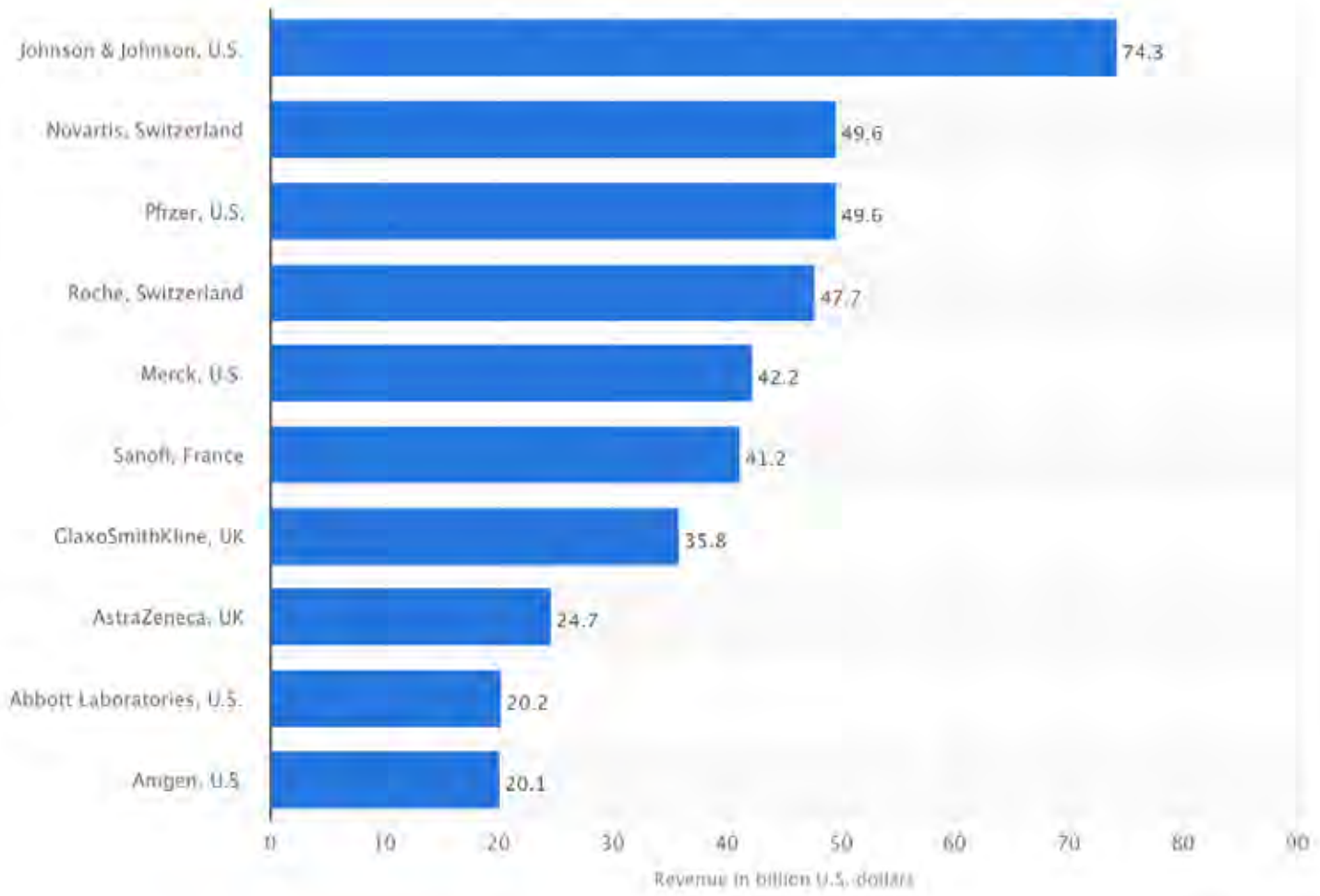
PD-L1 and PD-L2 downregulate cytotoxic T-cell activity to maintain immune homeostasis

- PD-L1 and PD-L2 bind to specific receptors on T cells. When bound to their receptors, cytotoxic T-cell activity is downregulated, thereby protecting normal cells from collateral damage[13,14]

2015 ranking of the global top 10 biotech and pharmaceutical companies based on revenue (in billion U.S. dollars)

This statistic shows the 2015 ranking of the global top 10 biotech and pharmaceutical companies worldwide, based on revenue. The values are based on the 2015 Financial Times Global 500 list. U.S. pharmaceutical company Johnson & Johnson was ranked first, with a total revenue of approximately 74.3 billion U.S. dollars.

Show more



Biotech Craze

- Kite (June 2014) $2.2B
- June (Dec 2014) $2.4B
- NantKwest (Aug 2015) $2.6B
- 2014 $4.9B raised

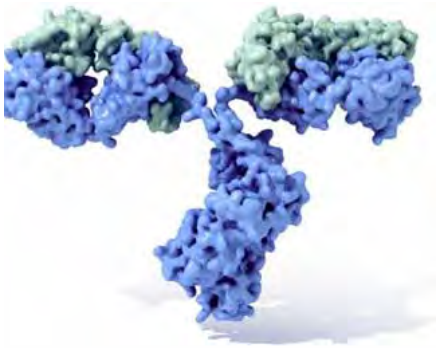
Evolution of Breakthrough Therapeutic Modalities in Cancer

ADCC

Leapfrogging Immunotherapy

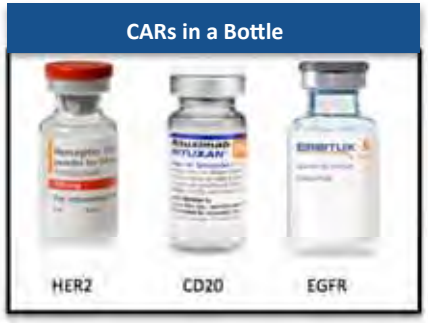
Innate Immunotherapy

mAbs



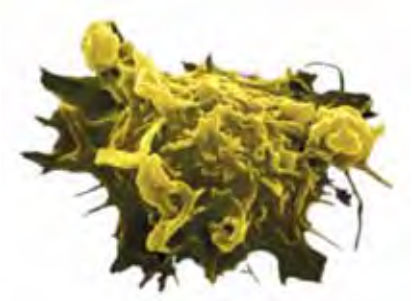
Antibody

- Binds directly to antigens
- Often dependent on patient immune system for effect



Adaptive Immunotherapy

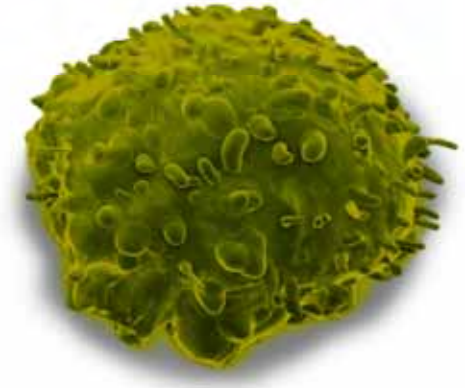
CAR-T Therapy



T-Cell

- Learned (Adaptive)
- Requires switching on
- Delayed killing

NK Therapy

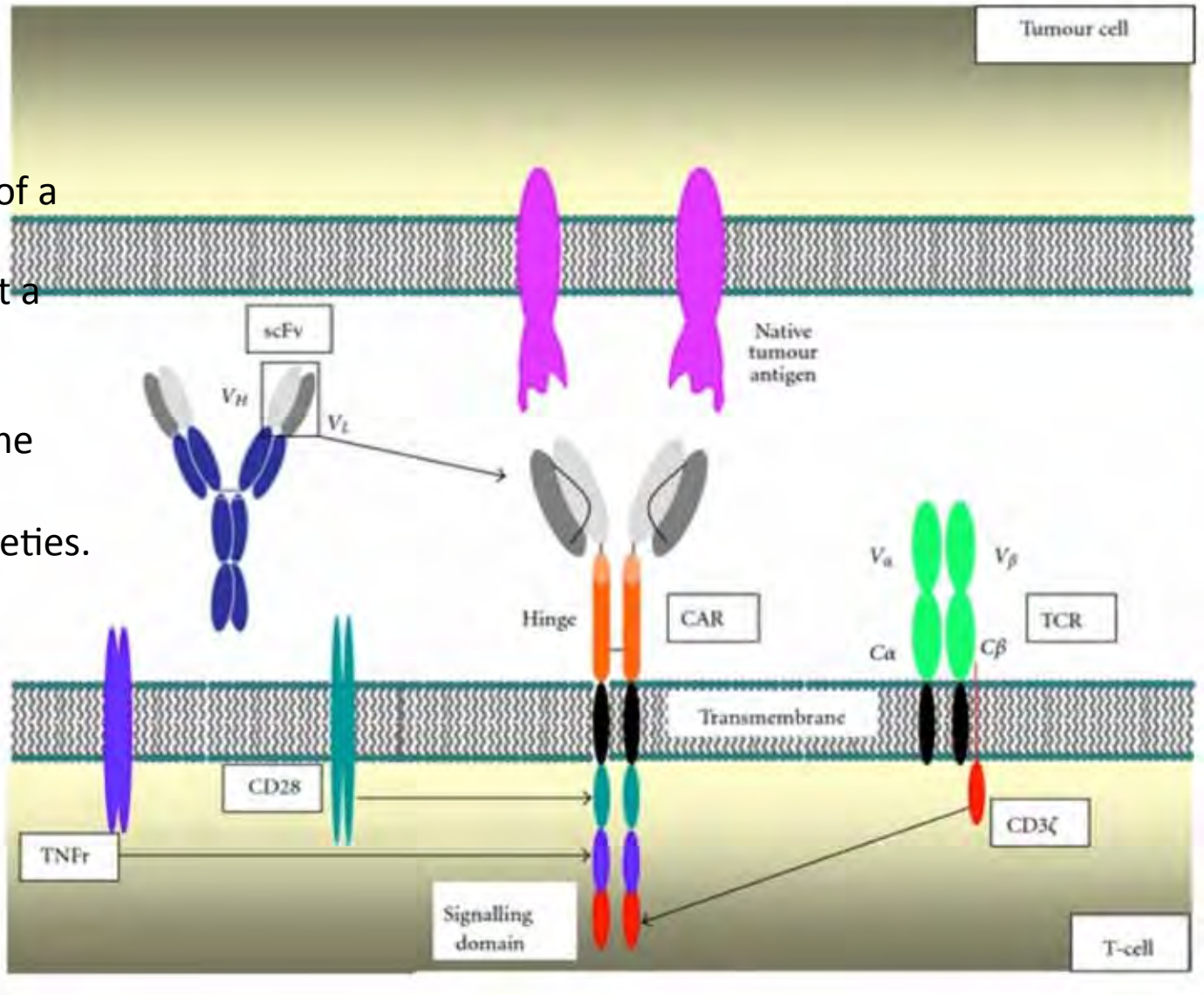


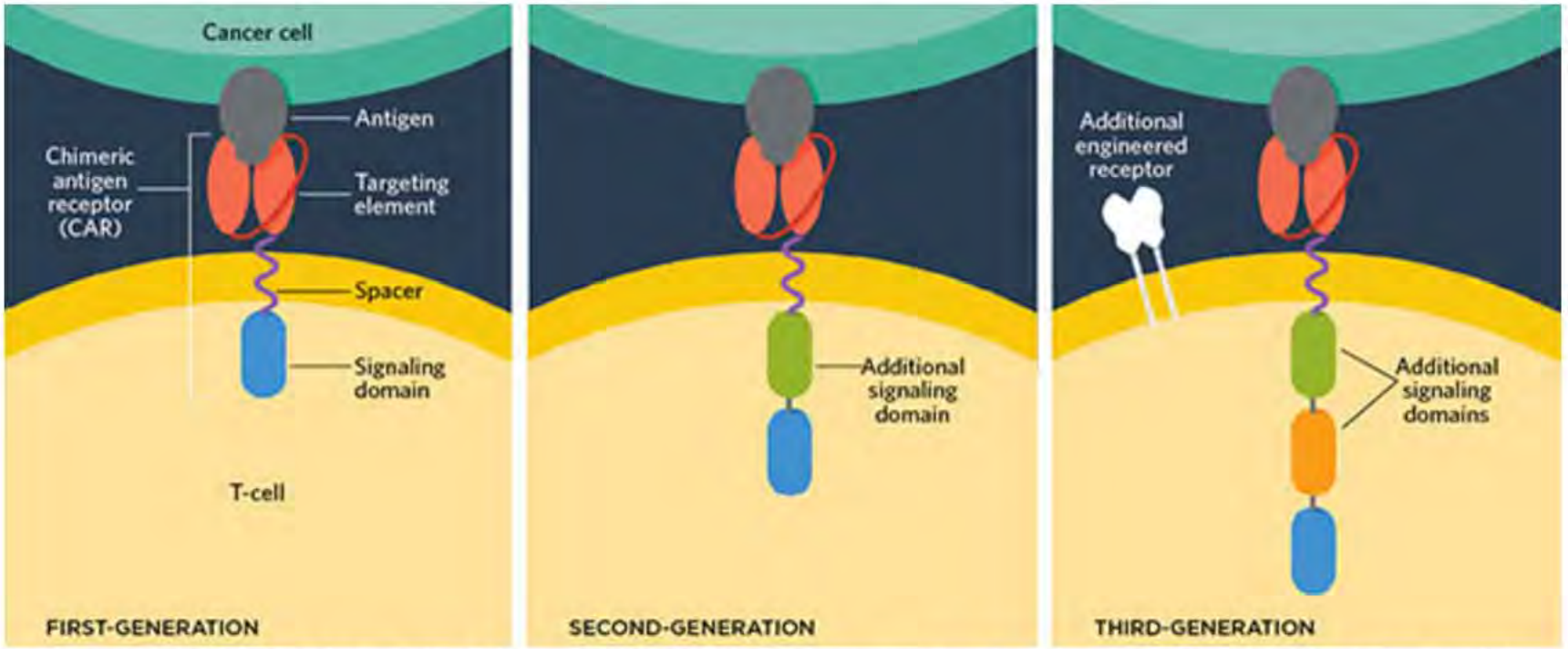
NK Cell

- Innate
- Always switched on
- Multiple modes of killing
  - Innate direct killing
  - Antibody-mediated killing
  - Tumor-targeted killing

Building a CAR

Structurally CARs consist of a single chain antibody Fragment directed against a tumor-associated antigen fused to an extracellular spacer and transmembrane domain followed by T cell cytoplasmic signaling moieties.





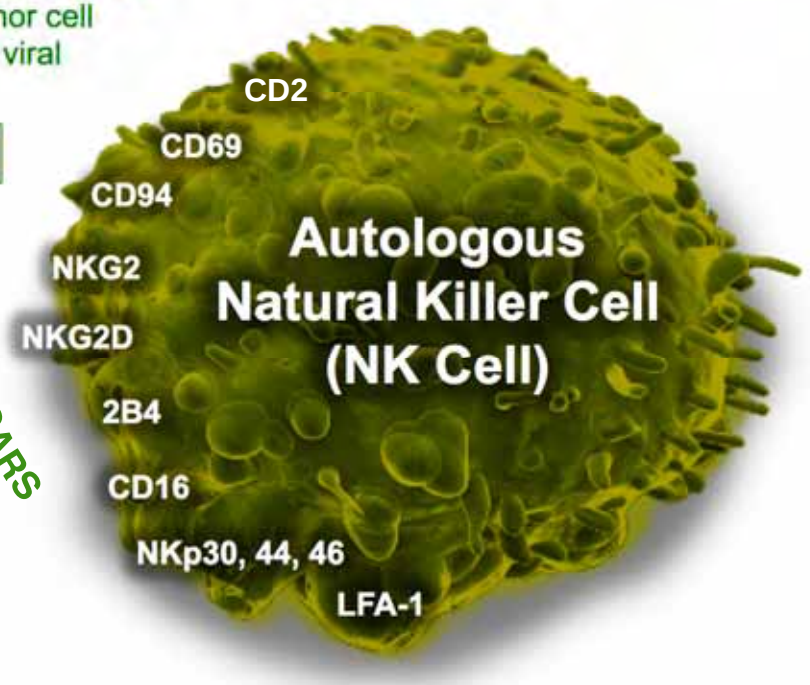
NEW AND IMPROVED CARs: Zelig Eshhar and Steven Rosenberg constructed the first CAR T cells using a modular design, including a specific cancer-targeting antibody outside the cell, a transmembrane component, and an intracellular costimulatory signaling domain that amplifies the activation of the CAR T cells. Second- and third-generation CAR T-cell technologies have added additional costimulatory domains within the cells, as well as additional receptors to improve targeting of the T-cell attack and minimize side effects.

A Living Killing Machine:
NK Cell Innate Immune Protector

1 **Adhesion & Targeting Receptors**
Targets and binds to tumor cell & tumor cell matrix, and viral infected cells

Innate Direct Killing

Innate CARs



NantKwest Unique NK Cell:
Activated Natural Killer (The aNK Cell)

1 Adhesion & Targeting Receptors
Targets and binds to tumor cell & tumor cell matrix, and viral infected cells

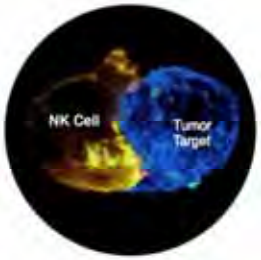
Innate Direct Killing

7 ~~Inhibitory Receptors (KIRS)~~
~~Turns off cell killing~~

Antibody Mediated Killing

6 Binds to Antibodies
Activates cell death (ADCC)

2 Activation Receptors
Triggers release of killing mechanism

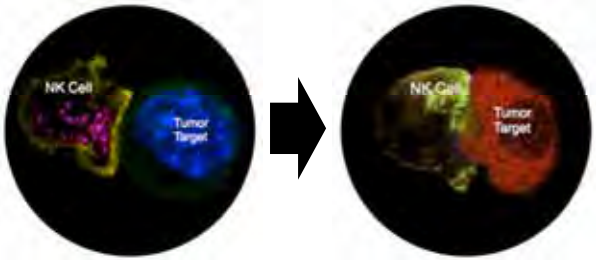


3 Release of Chemokines
Attracts killer T-Cells

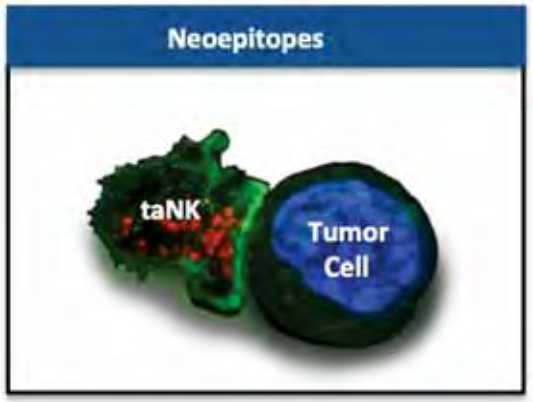
4 Release of Cytokines
Induces apoptosis

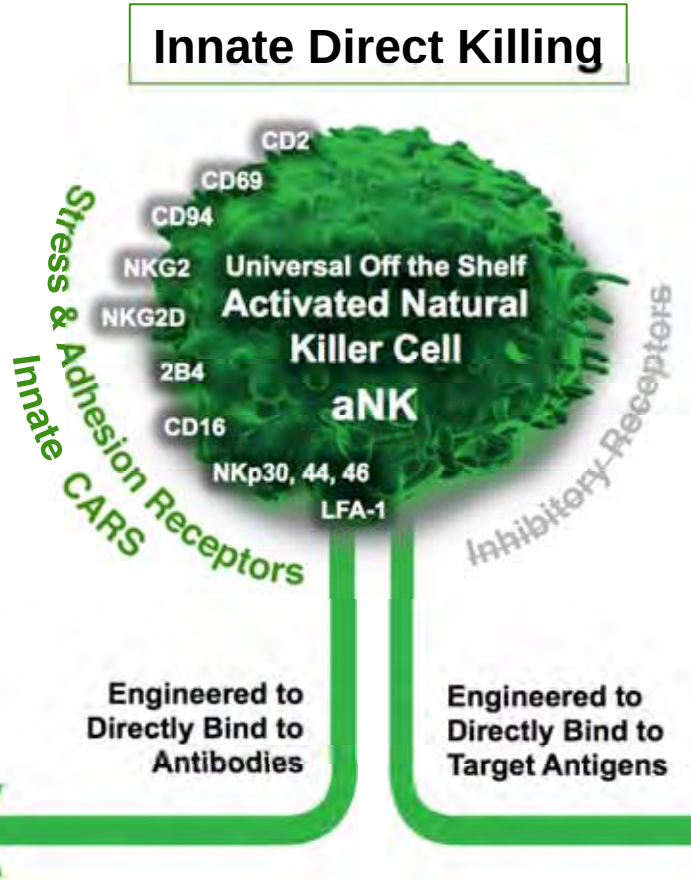
Targeted Killing

5 Release of Perforin & Granzyme
Direct cell killing & targeted killing

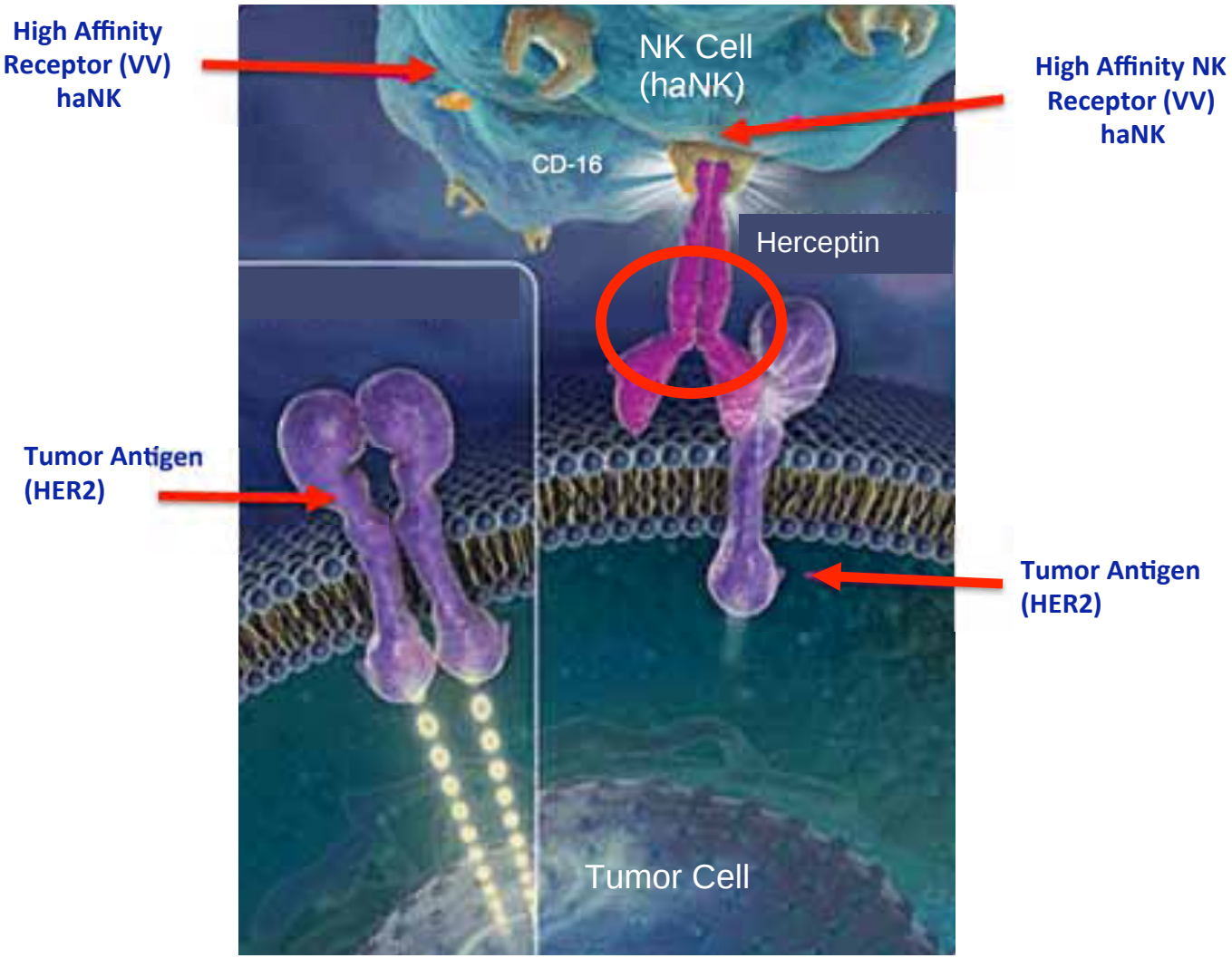


A Next Generation Immuno Therapy Platform:
A Living Drug - Delivered in a Blood Bag with Multiple Modes of Killing





haNK Enhanced Antibody Killing (ADCC)



NK vs CAR-T Cells: Key Differentiators

	NK	CAR-T Cells
Cell Production	Off-the-shelf product	Autologous (patient-derived) invasive procedure leukapheresis
Transduction Characteristics	GMP Master cell bank	Variable CAR transfection & expression
MOA	Multiple MOAs - targeting and killing through CAR-dependent and innate mechanisms	Targeting and killing CAR-dependent
Anti-Solid Tumor Activity	No requirement for additional co-stimulation	Require co-stimulators (CD80, CD86) not present in many solid tumors
Safety	On-target / off-tumor effects less likely due to short half-life and lack of IL-6 production	Cytokine release syndrome Prolonged bone-marrow suppression Cardiotoxicity and encephalitis risks
COGS	**Low:** large scale bioreactor manufacturing for many patients	**High:** requires individual patient processing