HIV Management 2016

THE NEW YORK COURSE

Brave New World of Cancer Therapeutics (Back to the Future)

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City of Hope National Medical Center

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FACULTY DISCLOSURE

I have no conflict of interests to disclose.

There is a relationship between Mind and Body

MIND / BODY RELATIONSHIP

We have had Western medicines for less than 100 years, but doctors (healers, “medicine men”, etc.) have been present for THOUSANDS of years

If they were not effective, we (ie the doctors) might not even be here today

Tate, London

Sir Luke Fildes, *The Doctor* (1891)

Re-introduce The Oldest Advance In Medicines.

It's called talking. Right or wrong, many older people today feel that doctors just don't spend as much time talking with their patients as they used to. Things seem more rushed and hurried.

But talking, especially about medicines, is more important than ever before. Your older patients may be taking several different medicines and seeing more than one doctor. And many older people are treating themselves with over-the-counter drugs.

Unfortunately, an older person's response to medicines is less predictable than a younger person's. They can experience altered drug actions and adverse drug reactions.

So, if they don't tell you first, ask them what they're taking and if the medicines are causing any problems. Take a complete medications history including both prescription *and* non-prescription medicines.

Make it a point to tell them what they need to know — the medicine's name, how and when to take it, precautions, and possible side effects. Give them written or printed information they can take home, and encourage them to write down what you tell them.

Good, clear communication about medicines can increase compliance, prevent problems, and lead to better health.

So re-introduce the oldest advance in medicines. Make talking a crucial part of your practice. It isn't a thing of the past. It's the way to a healthier future.

Before they take it, talk about it.

National Council on
Patient Information and Education.
666 Eleventh St. N.W. Suite 810
Washington, D.C. 20001

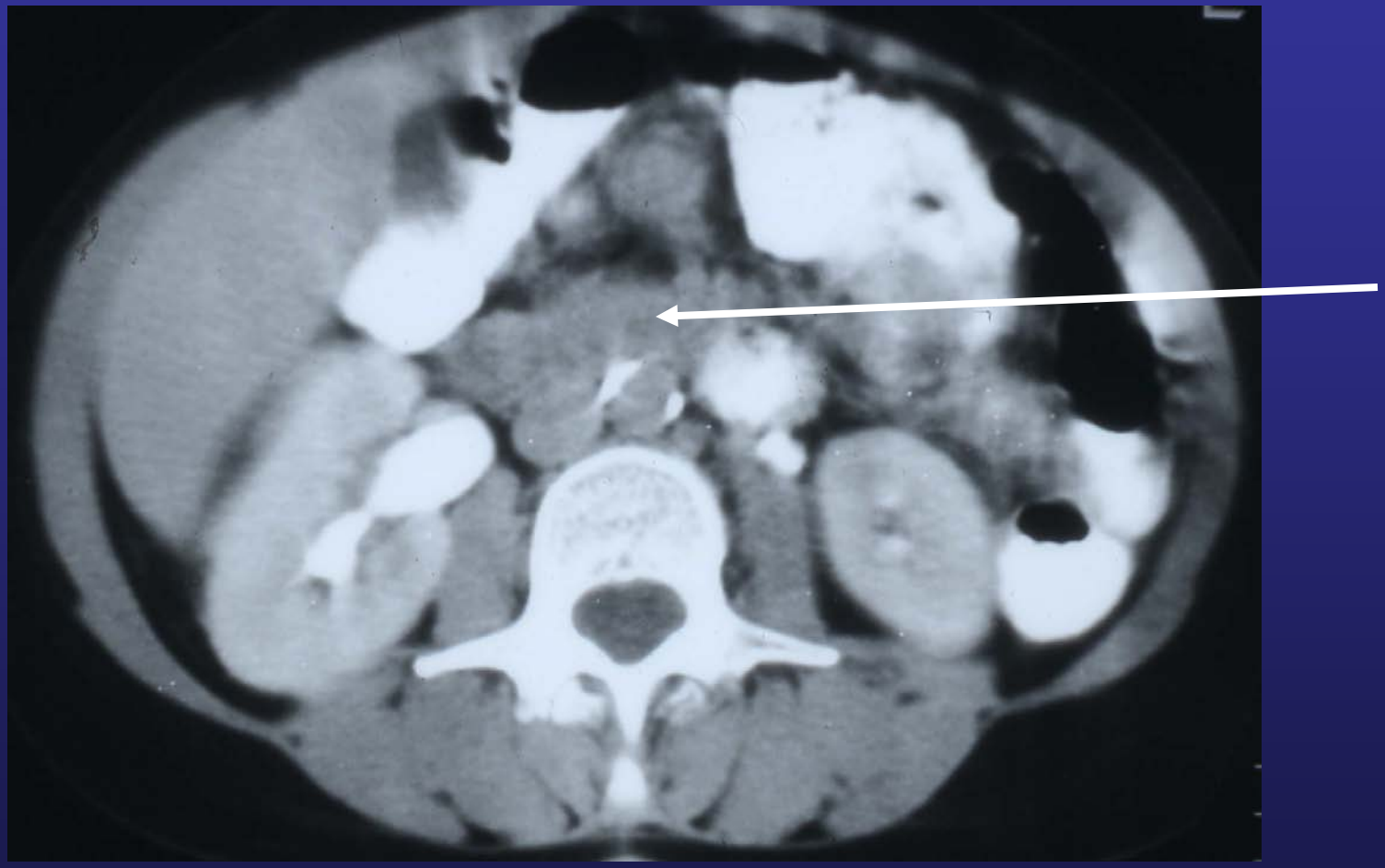
“…One of the essential qualities of the clinician is interest in humanity, FOR THE SECRET OF THE CARE OF THE PATIENT IS IN CARING FOR THE PATIENT.”

F.W. Peabody
Doctor and Patient
Harvard University Press
Cambridge, Mass, 1928

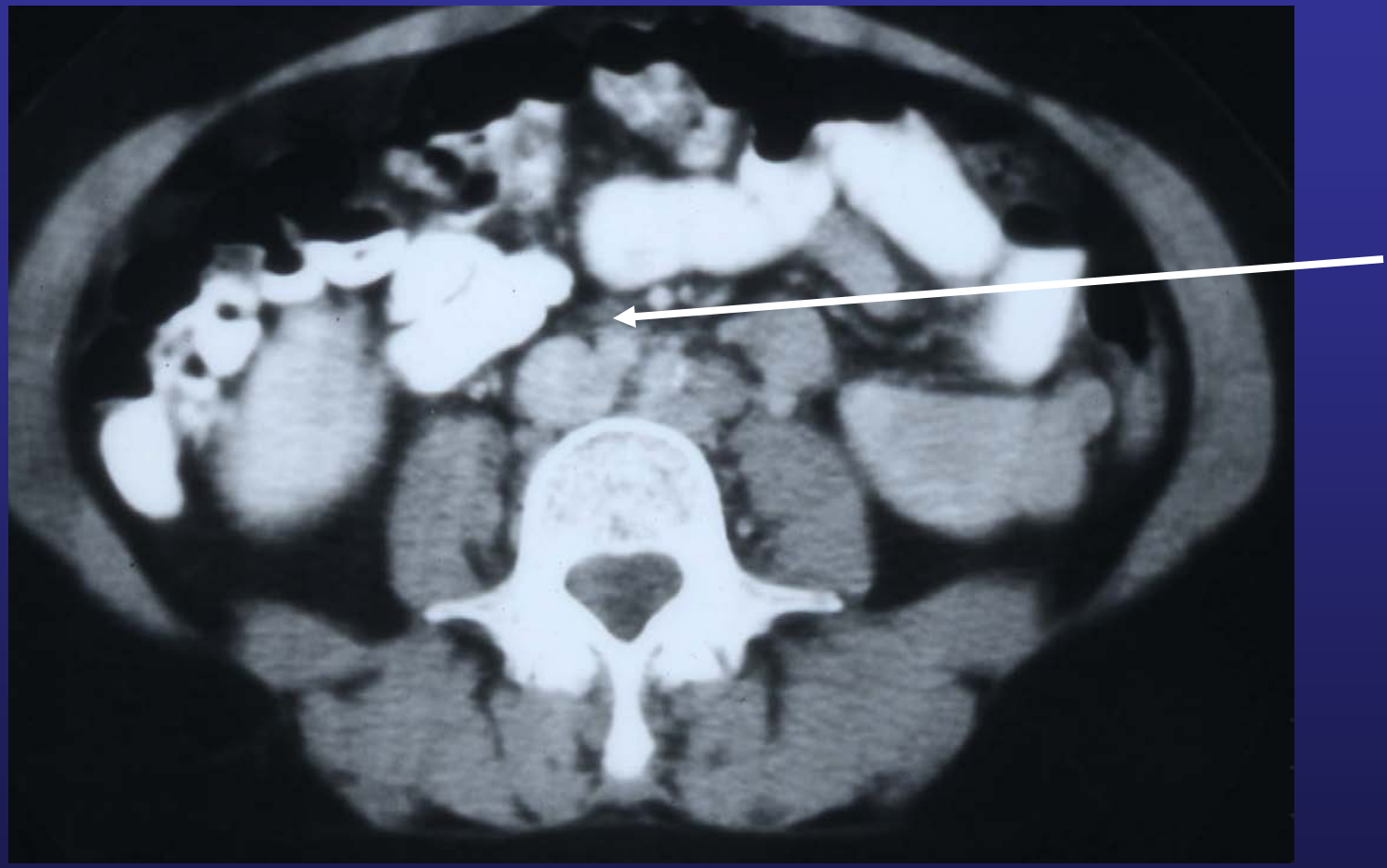
Can human caring / kindness / attention really work??

(Even in cancer or AIDS?)

Indolent Lymphoma (Follicular, grade 1)
March, 1989



Indolent Lymphoma (Follicular, grade 1)
June, 1990



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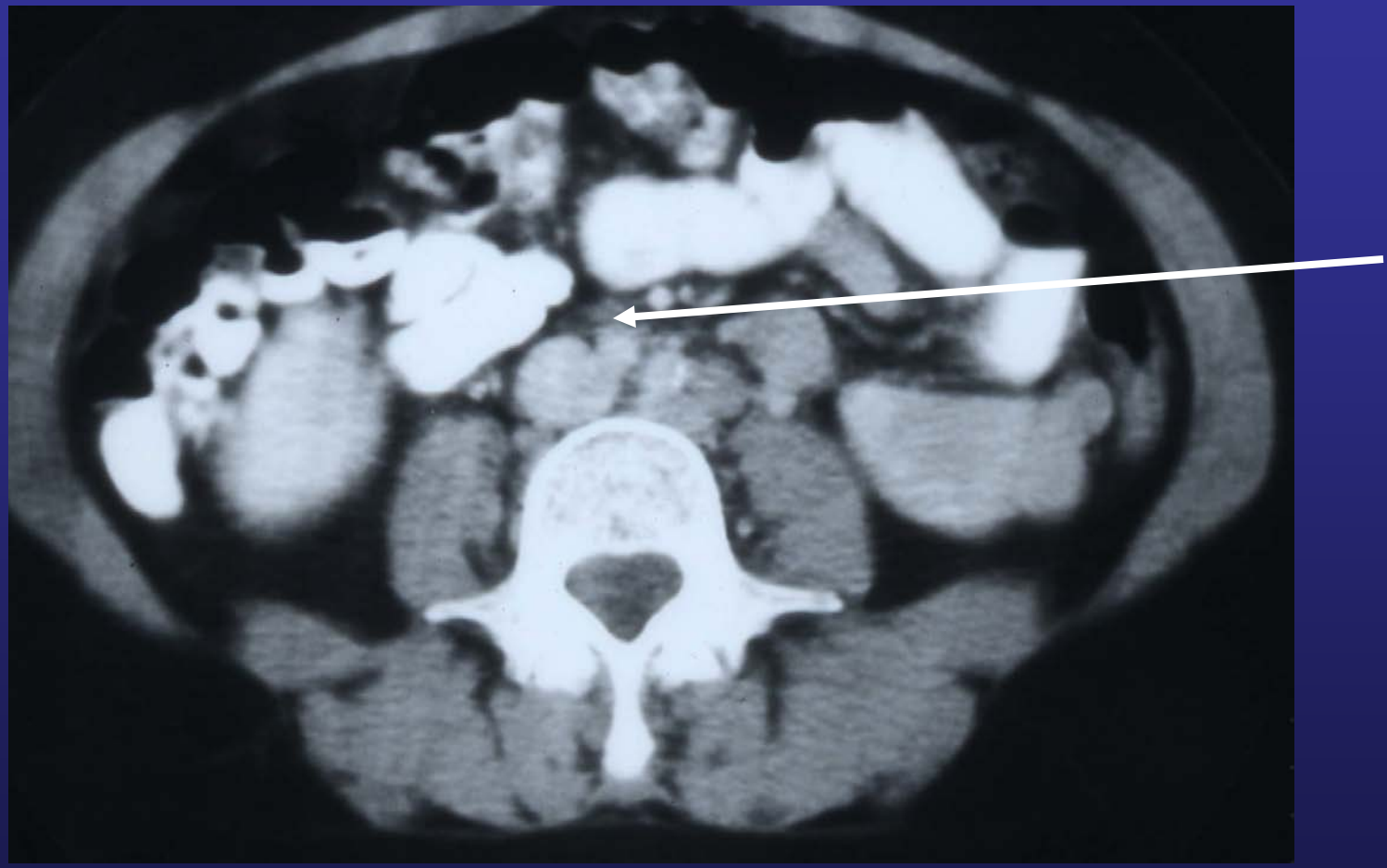


NO THERAPY GIVEN

Natural History of Low-Grade, Indolent Lymphoma

Spontaneous regression in 20-30%

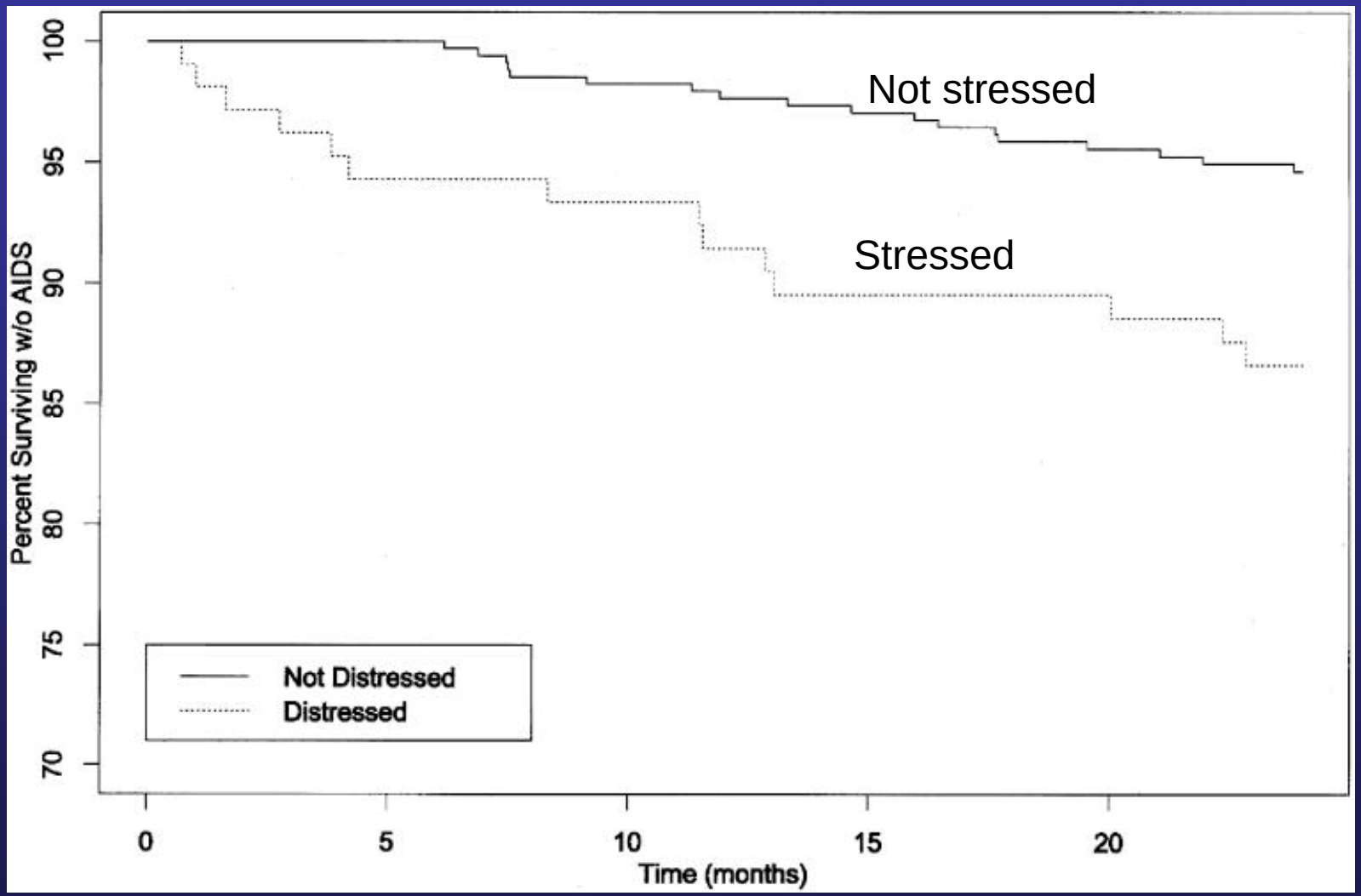
- Median duration = 15 mos (range 4+ to 72+ mos)

Ref: Horning and Rosenberg: NEJM 311, 1471, 1984.

What about HIV/AIDS??

Effect of Psychological Distress on Progression to AIDS in 451 HIV+ IDU's (ALIVE Study)

% NOT Progressing to AIDS



MULTIVARIATE ANALYSIS: Stress; CD4<200; Thrush

Ref: Golub ET, et al: J AIDS 2003; 32:429-34.

Potential Biologic Mechanisms for “Mind-Body” Connection

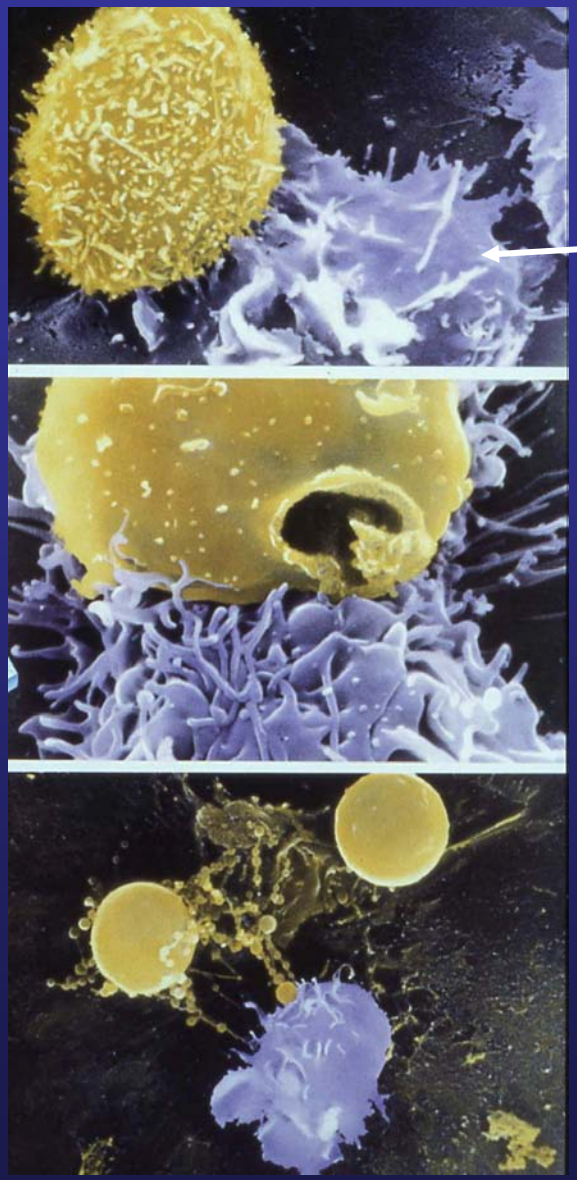
A. Immunologic

B. Stress catecholamines

C. Other

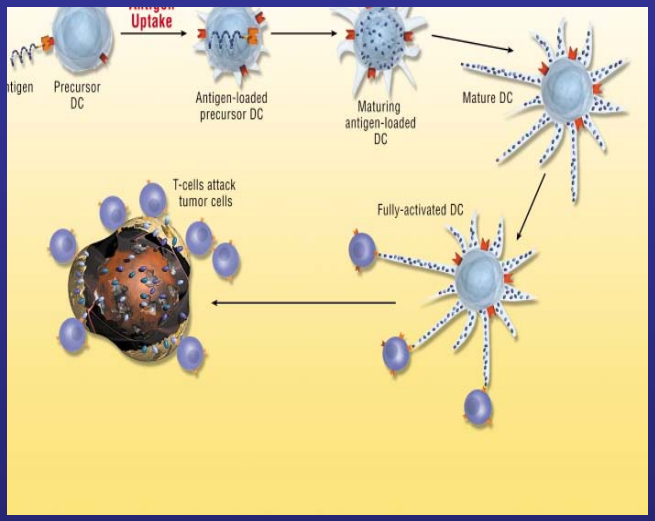
Macrophage Engulfing BCG

Novelli V. Lancet 2006; 367: 1222-4.

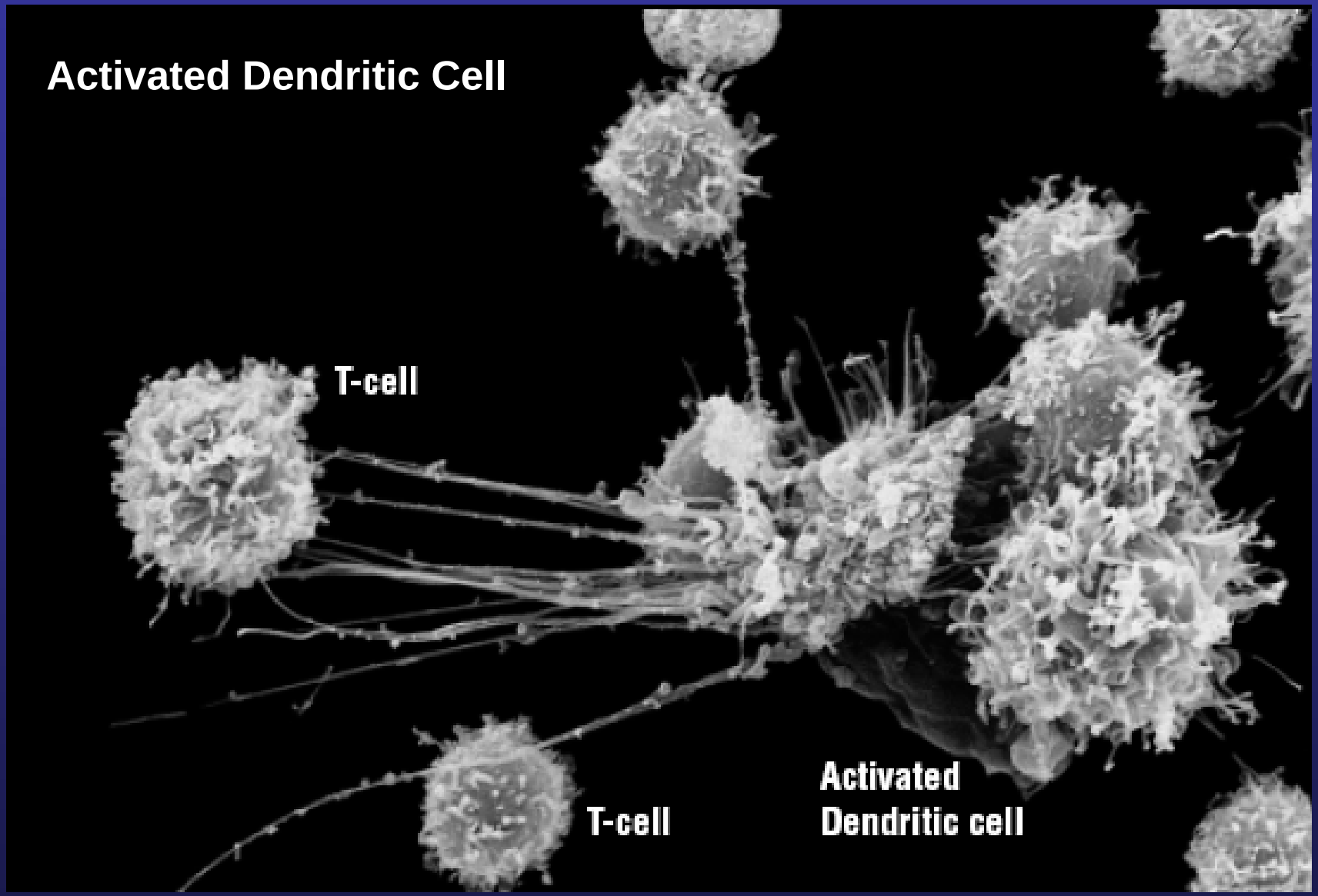


Natural killer cell
Attacking cancer cell

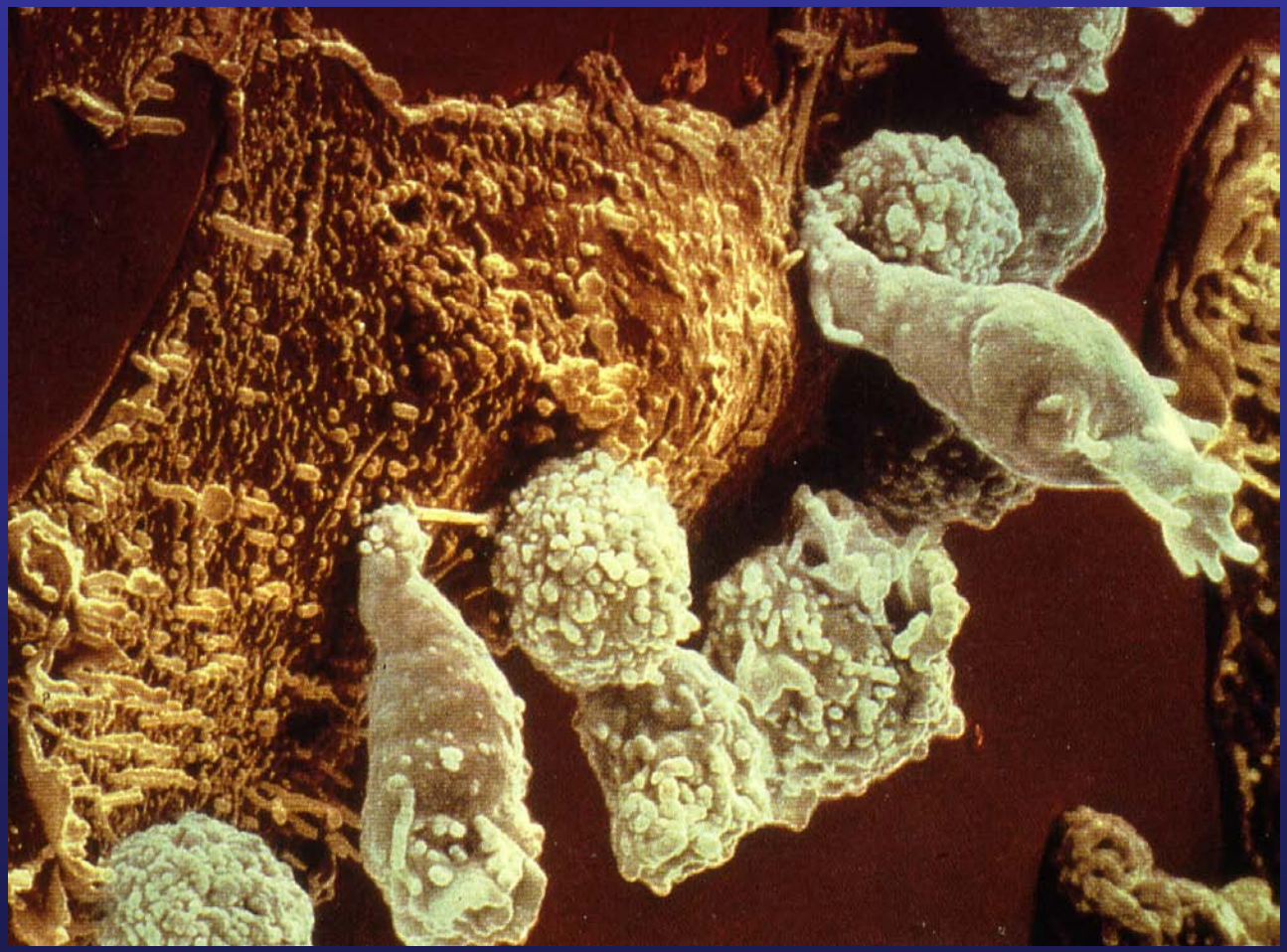
How Dendritic Cells Jump-Start the Immune Response



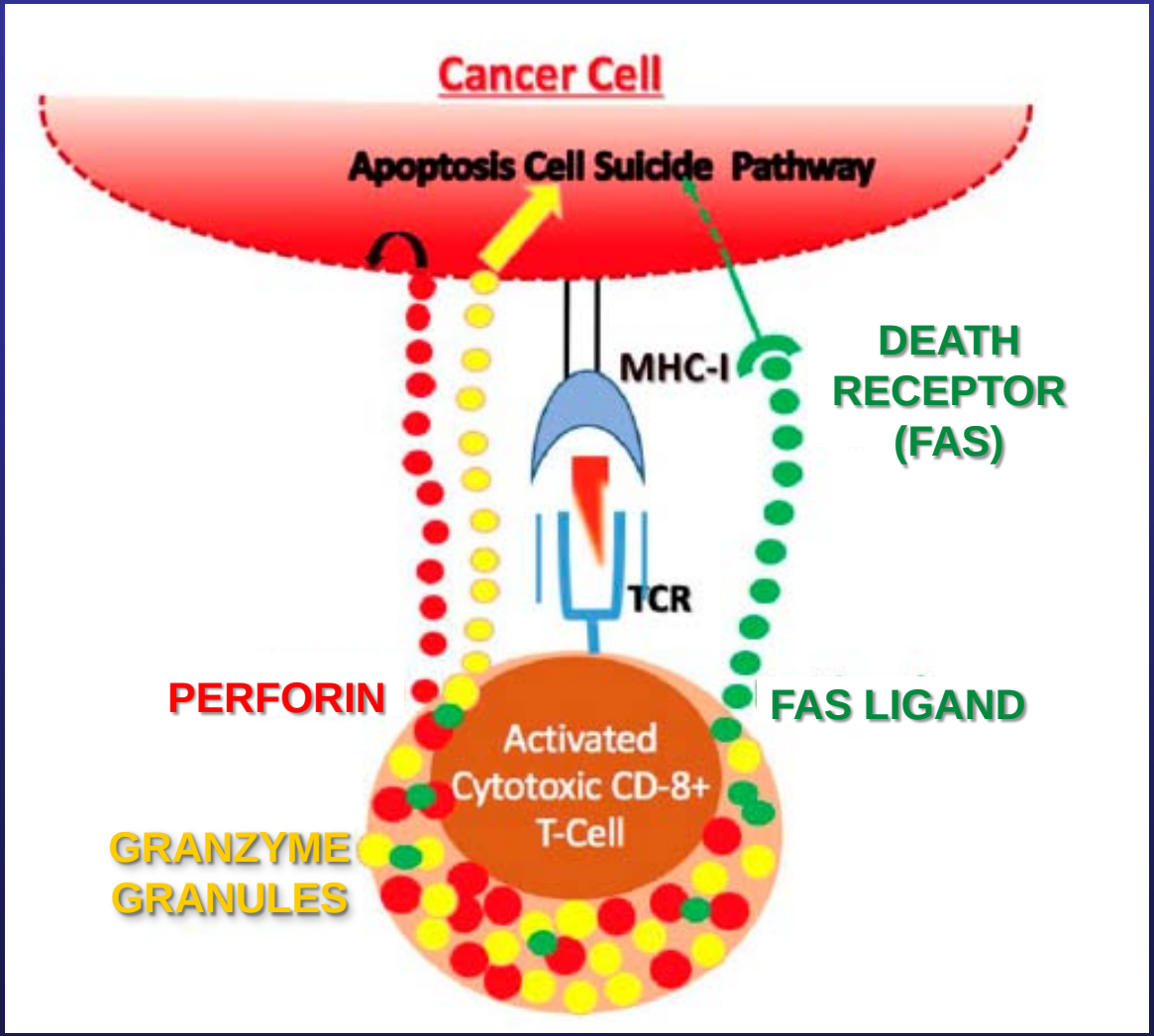
Ref: Valone, F: PCRI Insights 2001: 4: 7.


Activated Dendritic Cell
T-cell
T-cell
Activated
Dendritic cell

Cytotoxic T 8 Cells Attacking Cancer Cell



Mechanism Cell Death by Activated Cytotoxic T-Cells



Ref: Messerschmidt JL, et al. The Oncologist 2016; 21:233 – 243.

Fundamentally, cancer requires at least two “errors / accidents”

- Error at level of DNA (“genomic” error), giving a growth / survival advantage to that cell and its progeny
- A failure of the host immune system to recognize the error, and destroy this new “foreign” cell

NOW,
to the FUTURE
(and PRESENT)


Science
20 December 2013 | $10
Breakthrough of the Year
Cancer Immunotherapy
T cells on the attack

IMMUNOTHERAPY

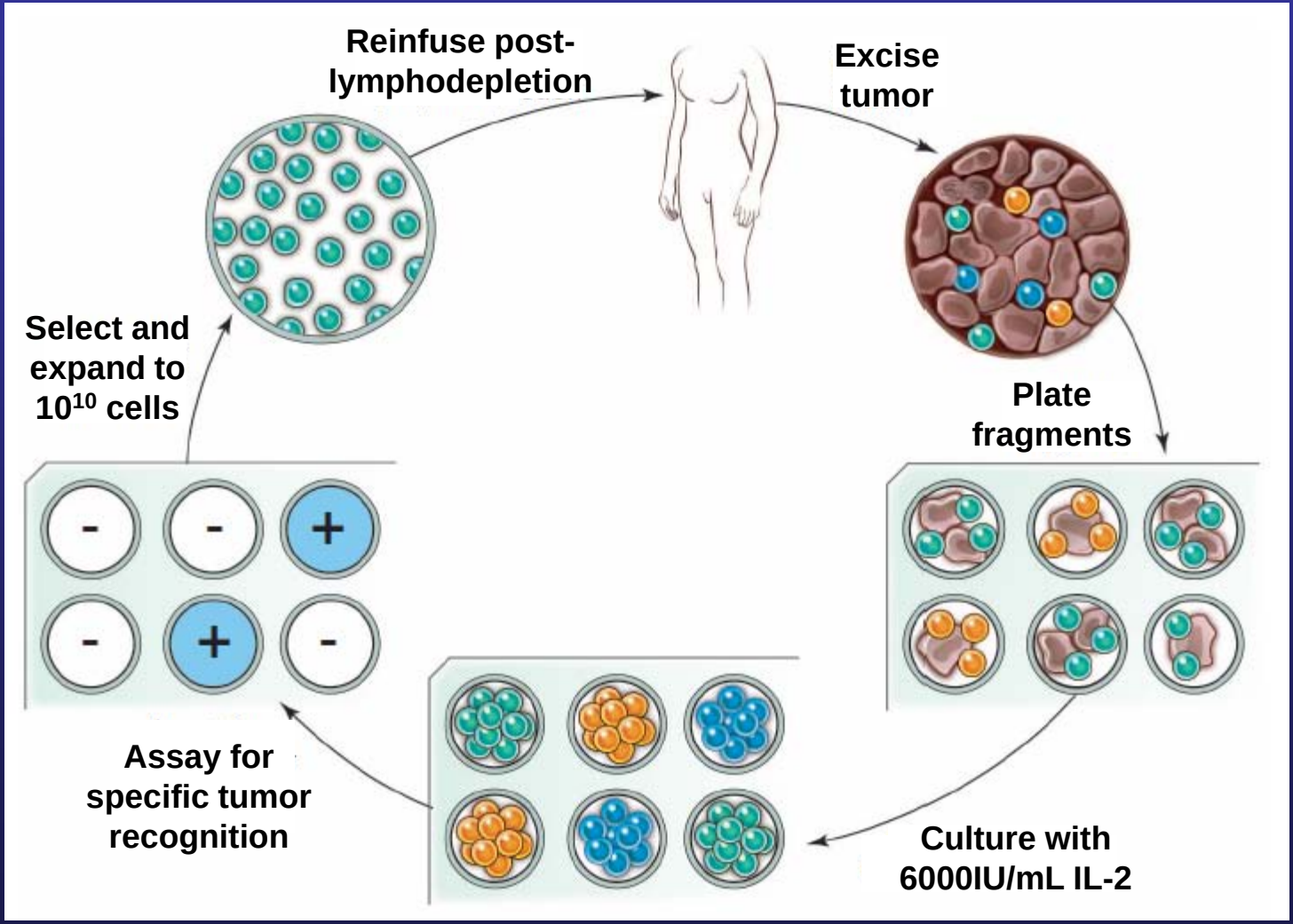
The use of the immune system to treat disease

FIRST EXAMPLE

Coley's Toxins - Injected purulent material from infected cancer material into other cancer patients, with clinical benefit

Coley, WB: Annals of Surgery 1891

Adoptive T cell transfer of autologous CTL's for treatment of cancer



Ref: Rosenberg SA and Restifo NP: Science 2015; 348:62.

History of T Cell Therapy (Melanoma / Renal Cell Cancer)

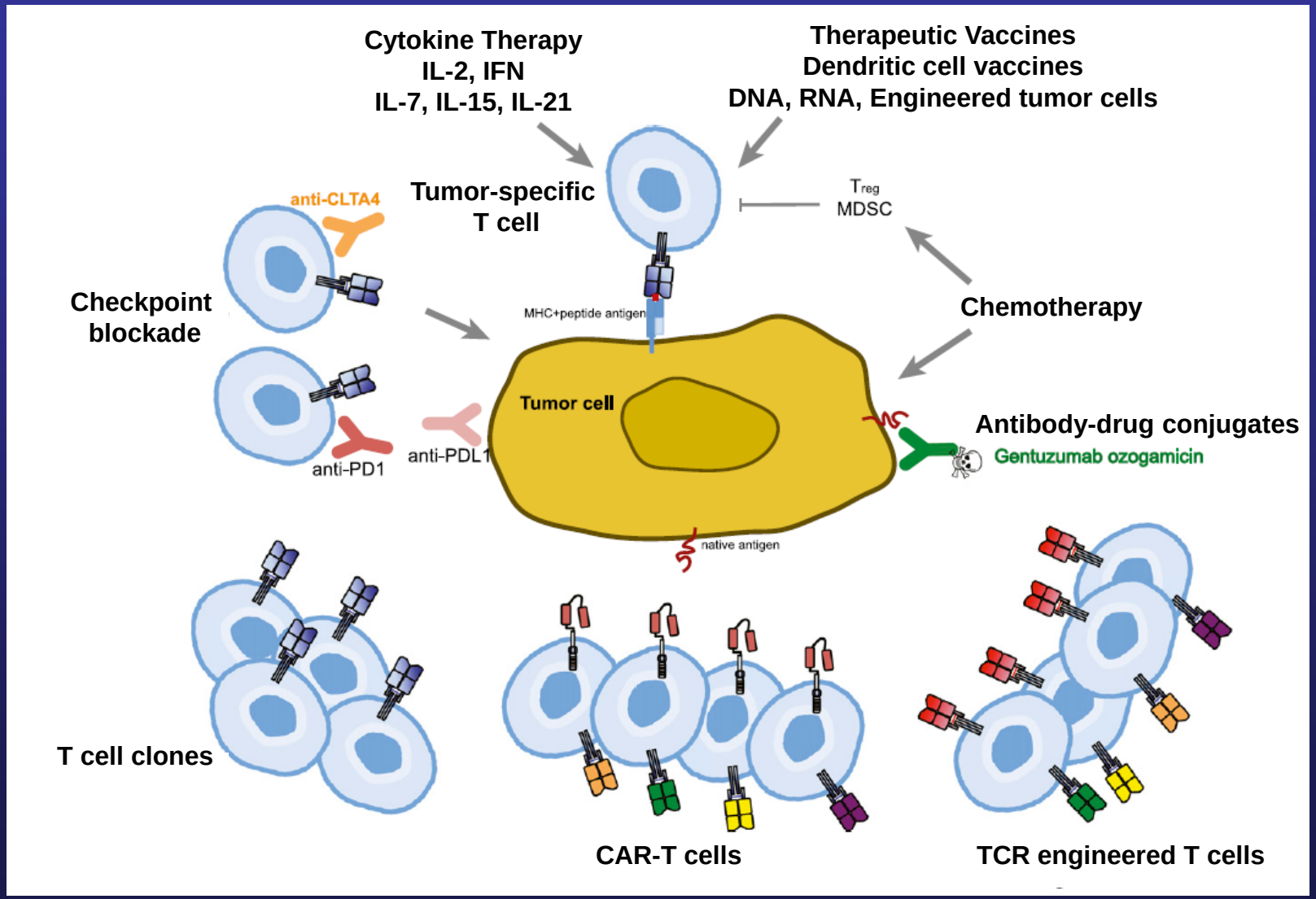
- IL-2 infusions (T cell growth factor) ⟶ 6-7% complete remission; most sustained for ≥ 30 years

↓

- IL-2 plus autologous anti-tumor T cells ⟶ 56% response (52/93) 22% CR, all sustained from 5 to 11+ years

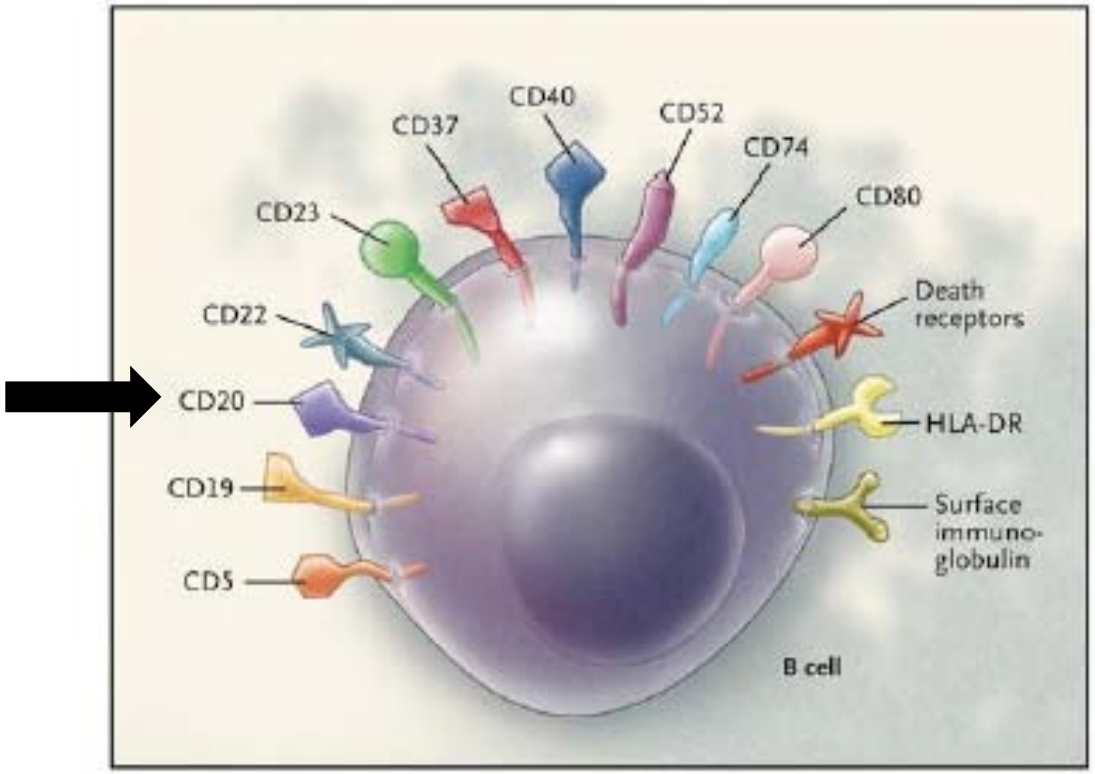
Ref: Rosenberg SA. Clin Ca Res 2015; 21:5409 – 11.

Therapeutic approaches to overcome immune tolerance to cancer cells



Ref: Maus MV et al. Blood 2014; 123:2625 – 2635.

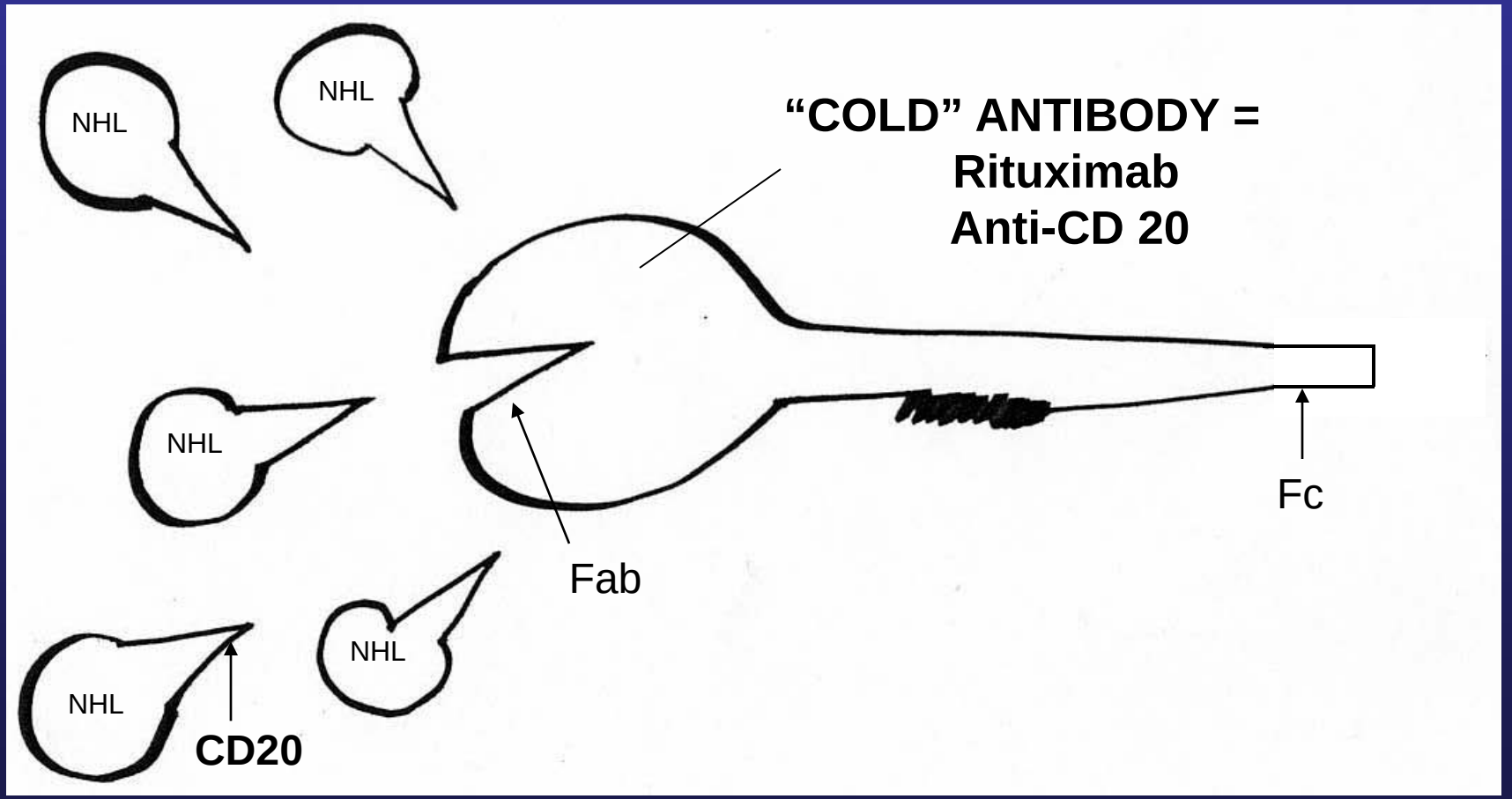
CELL-SURFACE ANTIGENS ON THE B CELL



Cheson BD, Leonard JP. N Engl J Med 2008;359:613-626.

City of Hope

Monoclonal Antibodies Currently in Use for Lymphoma (NHL)



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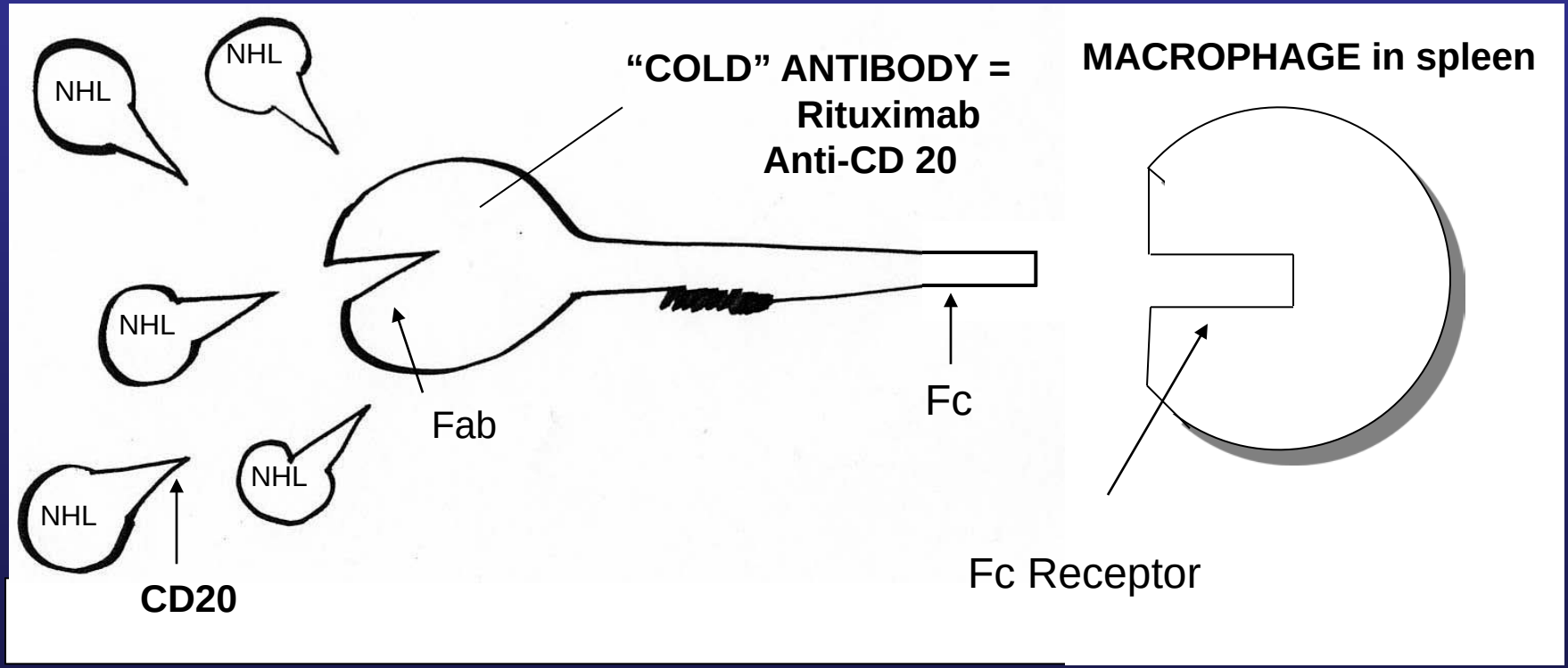
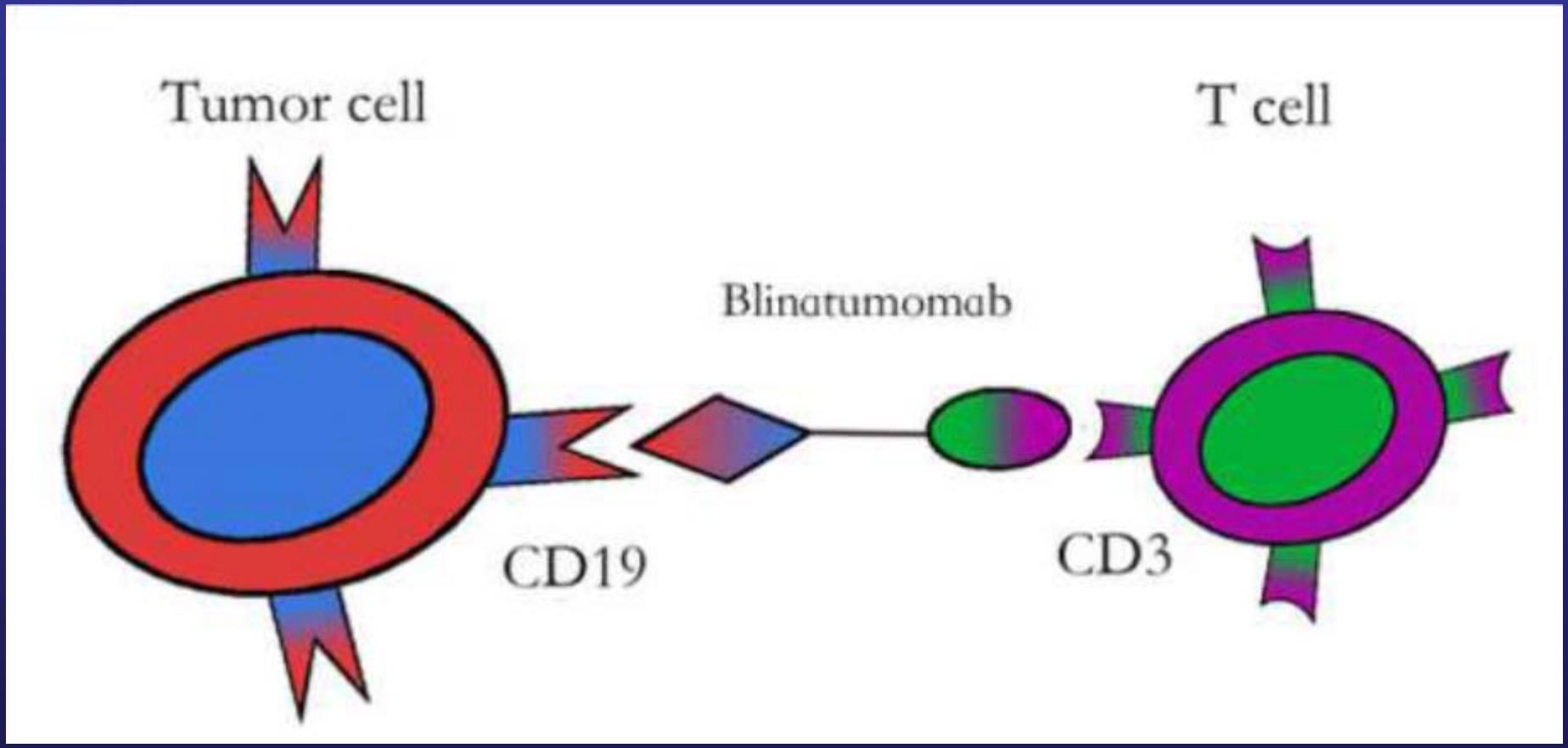


Bi-specific T cell Engager (BiTE) Rx for A.L.L.
Mechanism of Action for Blinatumomab



Ref: Wu J, et al. J Hematol Oncol 2015; 8:104.

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↓

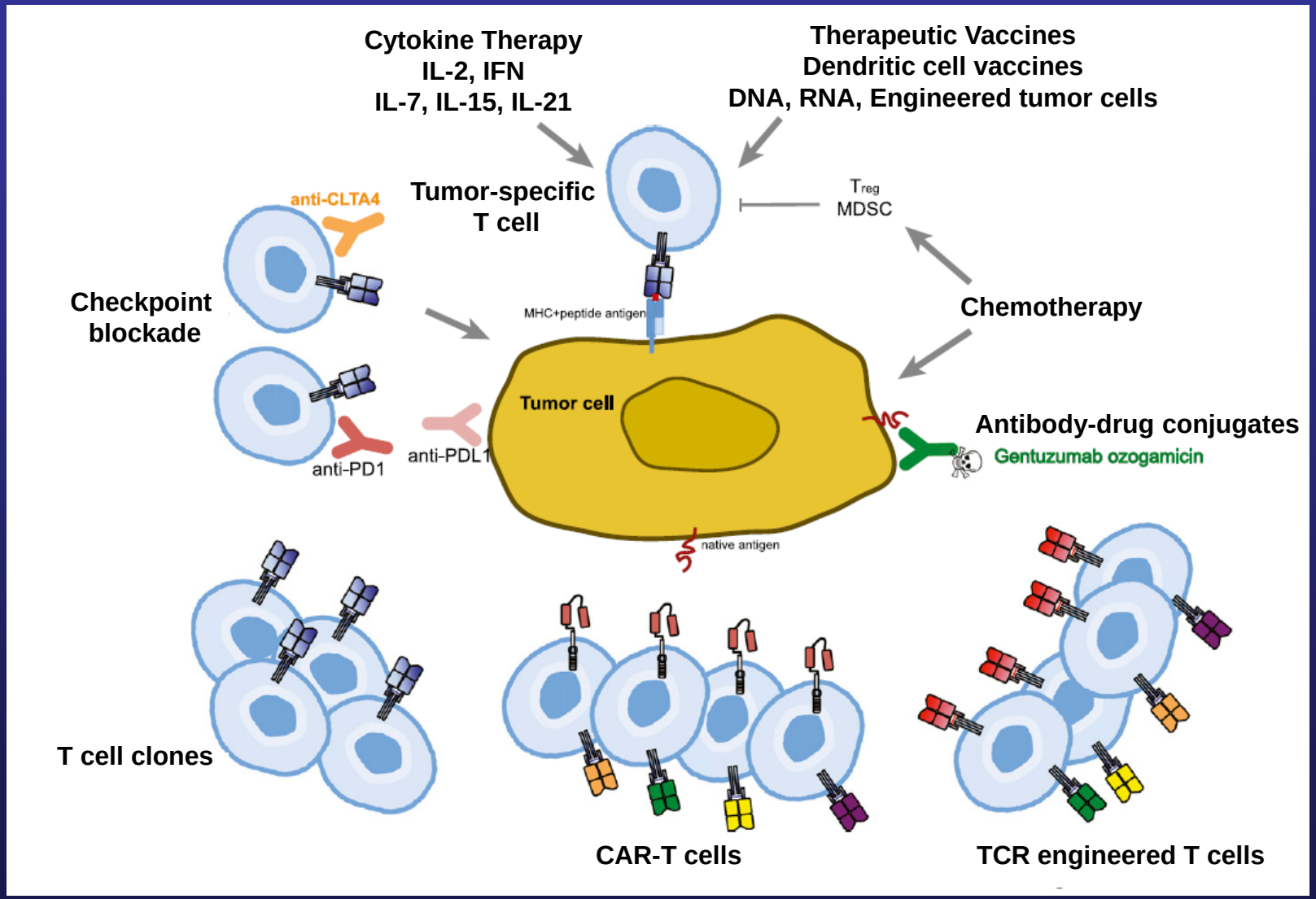
THE FUTURE IS NOW

↙ ↘

Genetic modification of normal lymphocytes with receptors reactive against tumor antigens

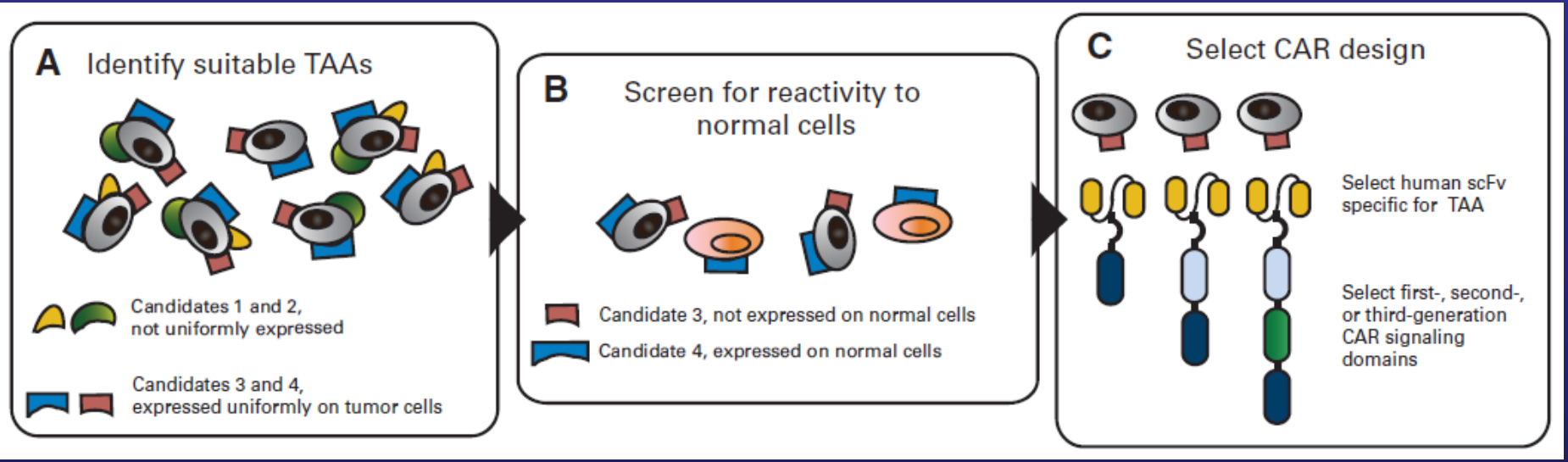
Ref: Rosenberg SA. Clin Ca Res 2015; 21:5409 – 11.

Therapeutic approaches to overcome immune tolerance to cancer cells



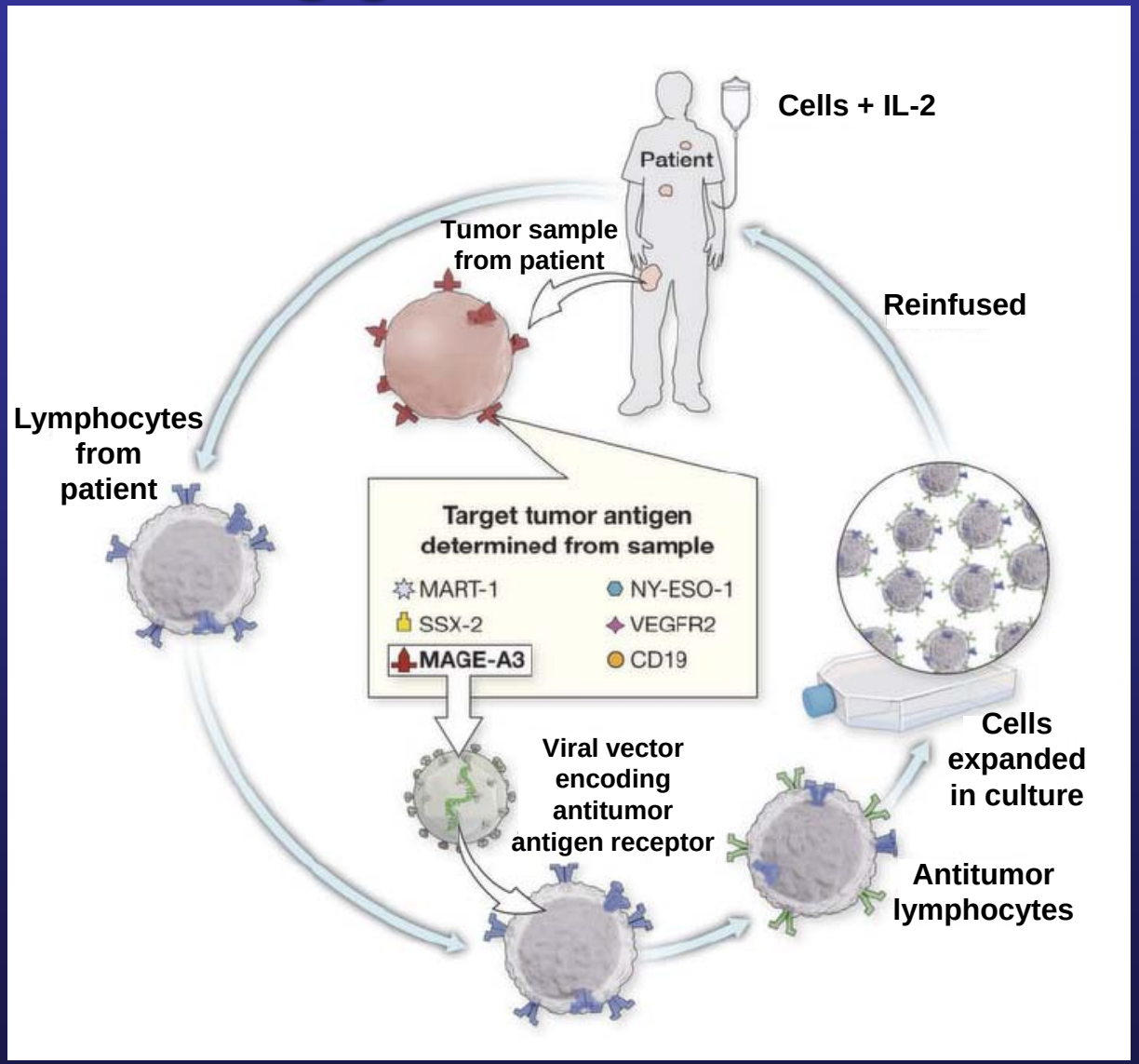
Ref: Maus MV et al. Blood 2014; 123:2625 – 2635.

Pathway for designing optimal Chimeric Antigen Receptor (CAR-T) cells for tumor cell kill



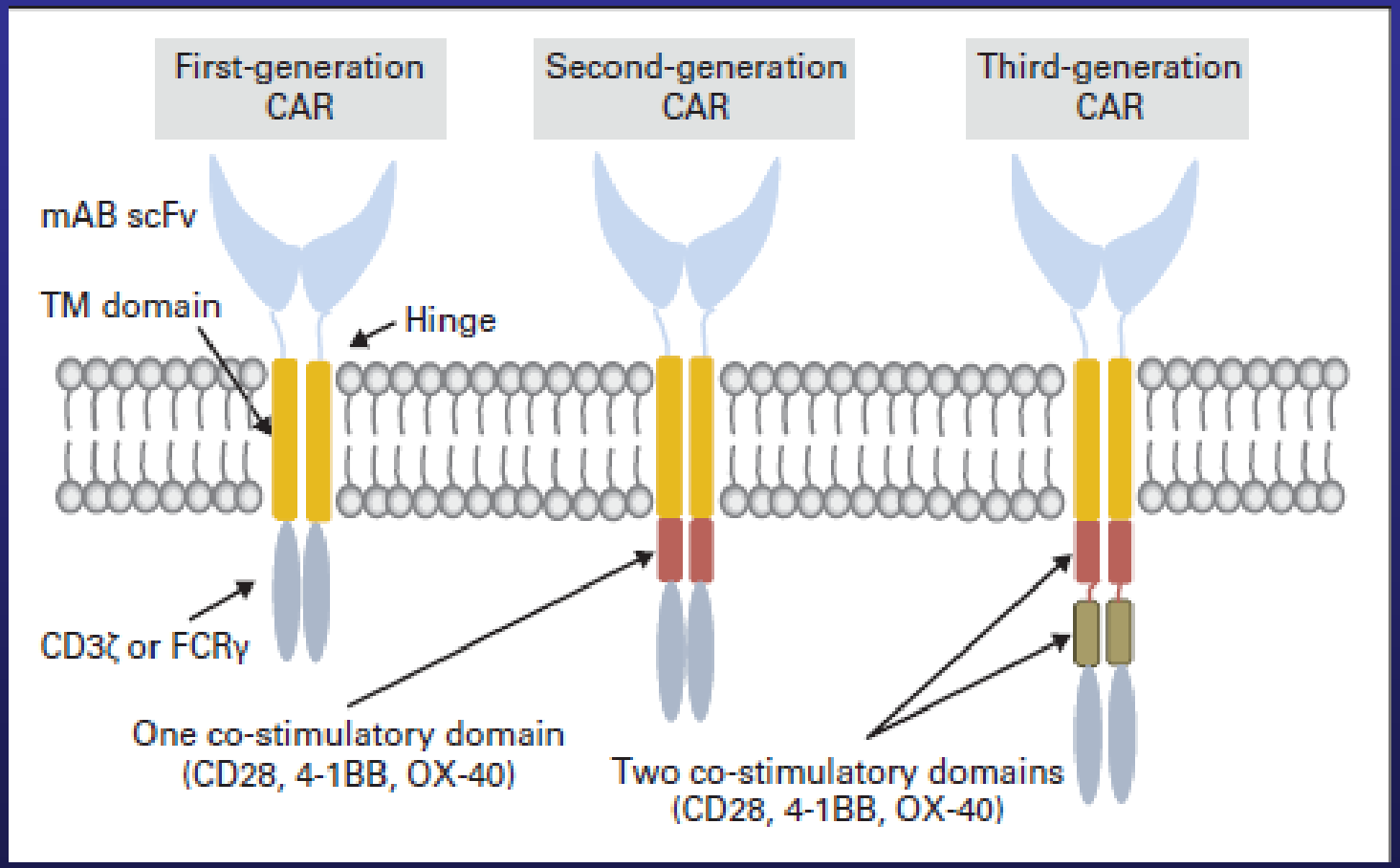
Ref: Curran KJ, et al. JCO 2015; 33:1703 – 1706.

Schema: Personalized / Precision immunotherapy using gene modified cells



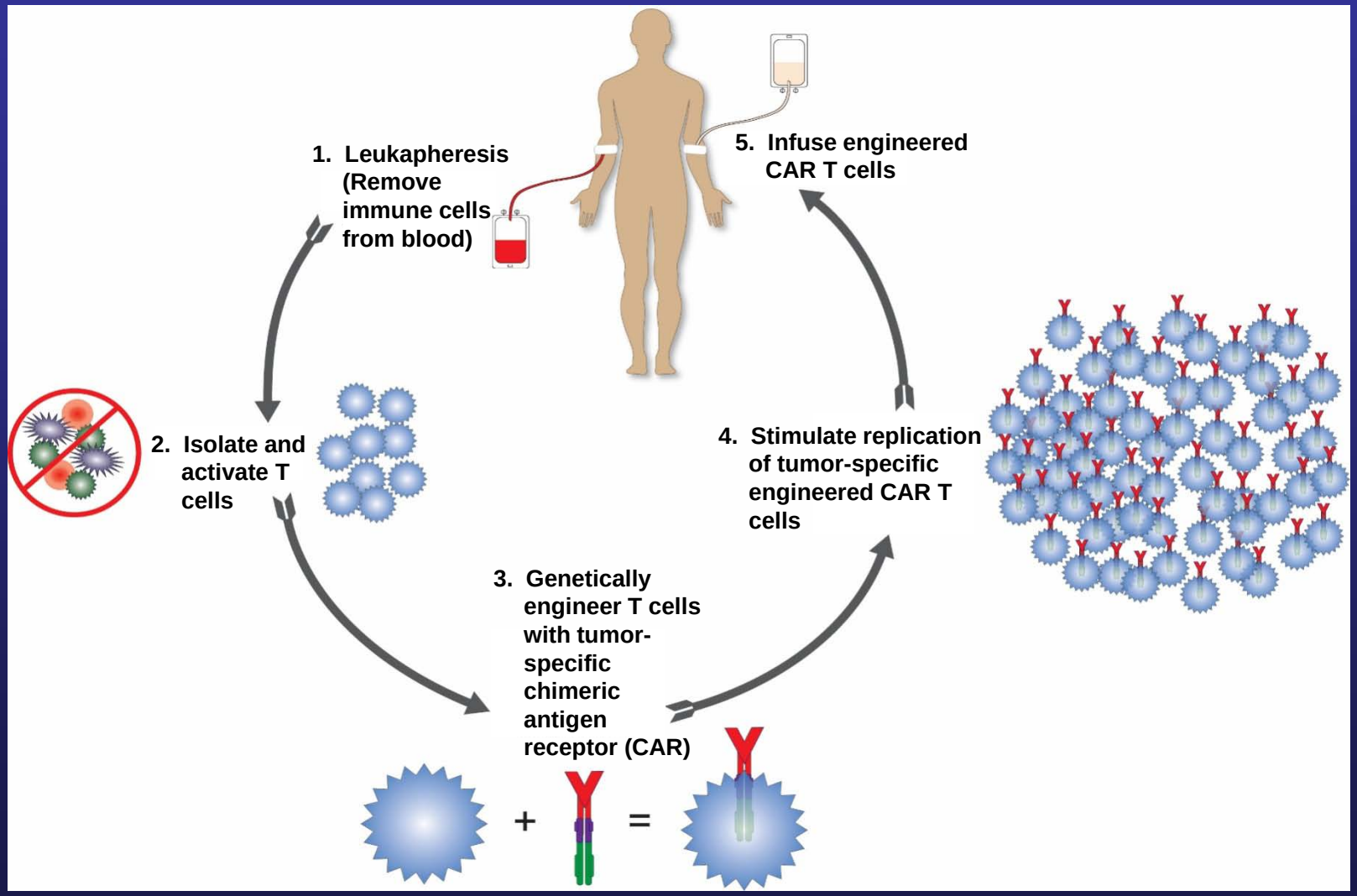
Ref: Rosenberg SA: Sci Trans Med 2012: 4:127.

New generations of CAR-T cells

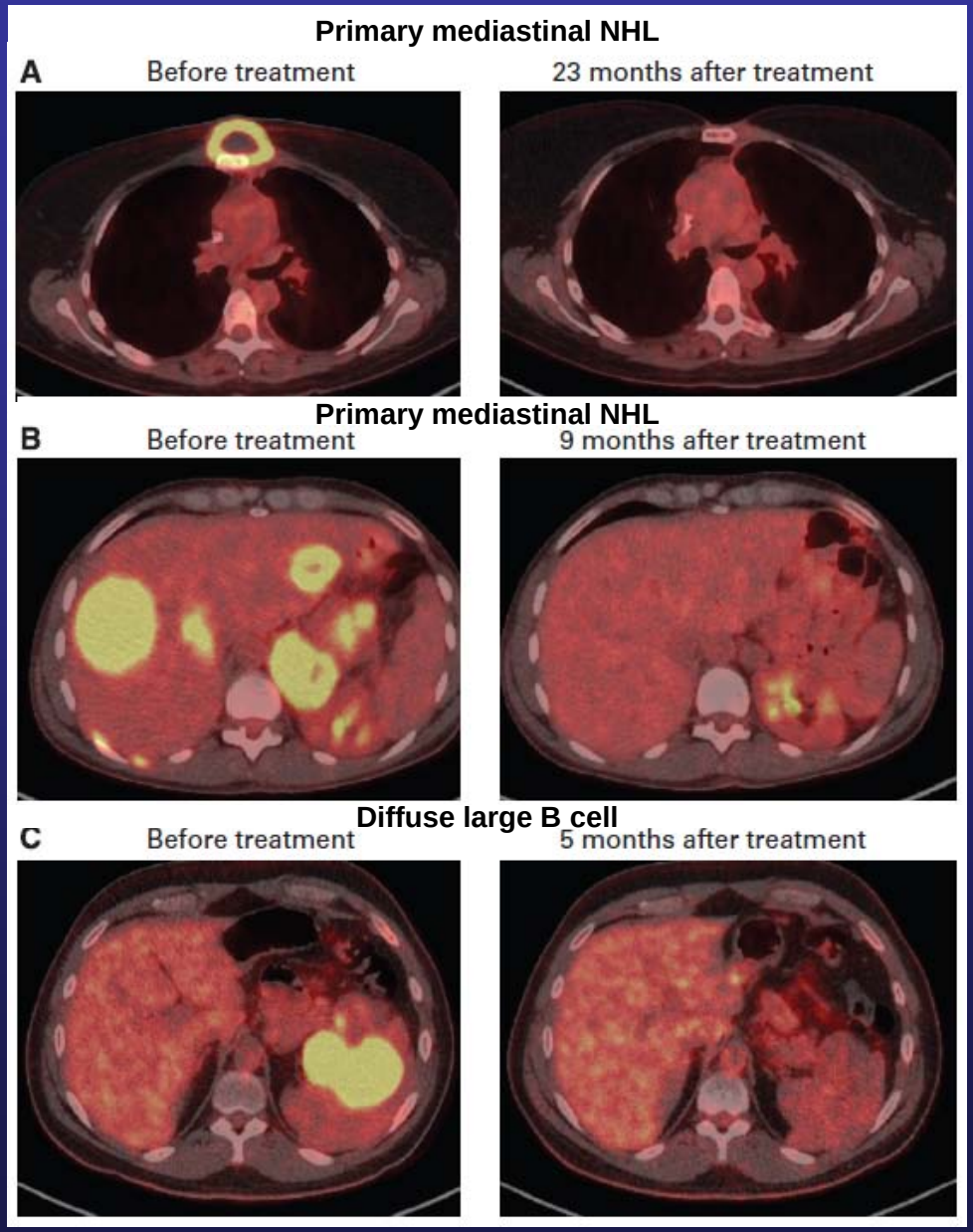


Ref: Park JH, et al. JCO 2015; 33:651.

Method for generation of CAR-T cells against tumor associated antigens

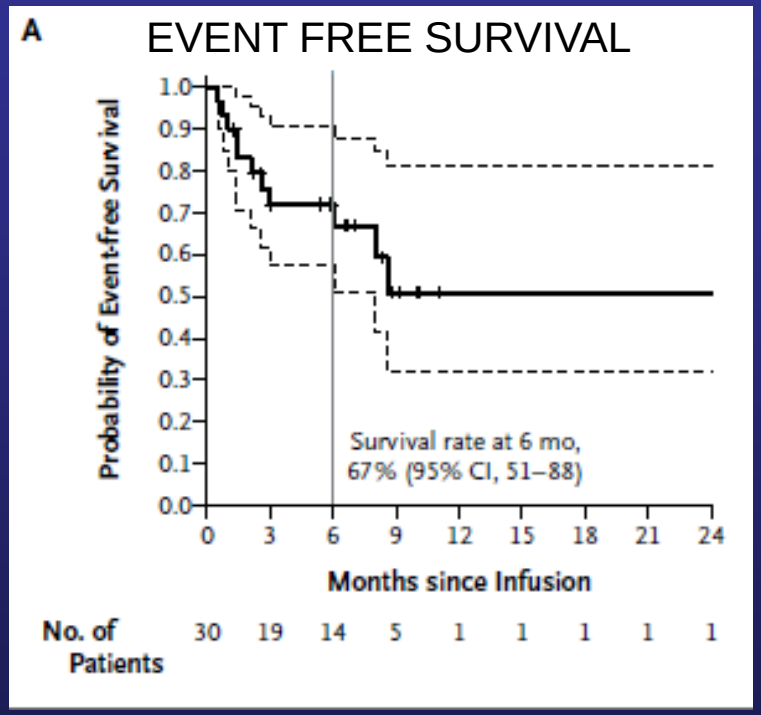


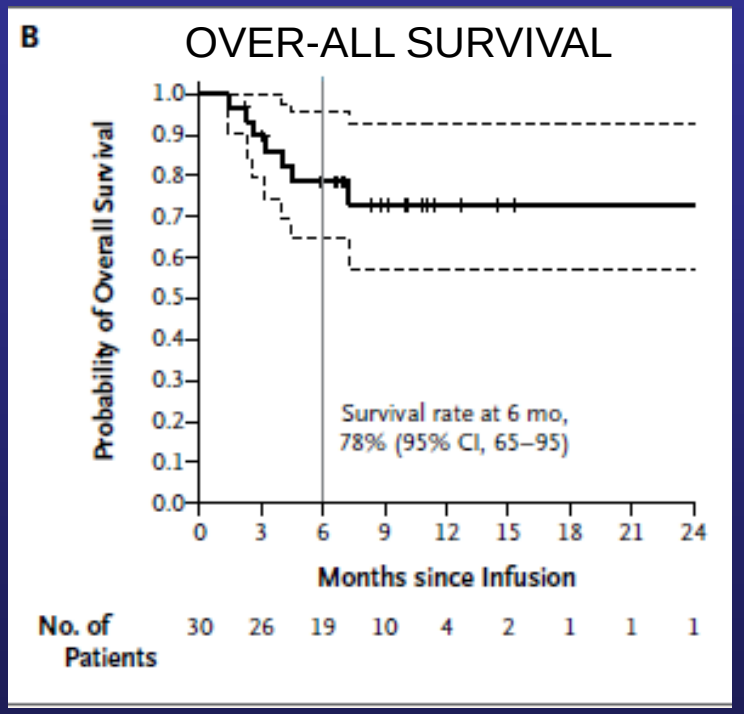
Anti-CD19 CAR-T cell Rx in NHL



Ref: Kochenderfer JN, et al. JCO 2014; 33:540 - 549.

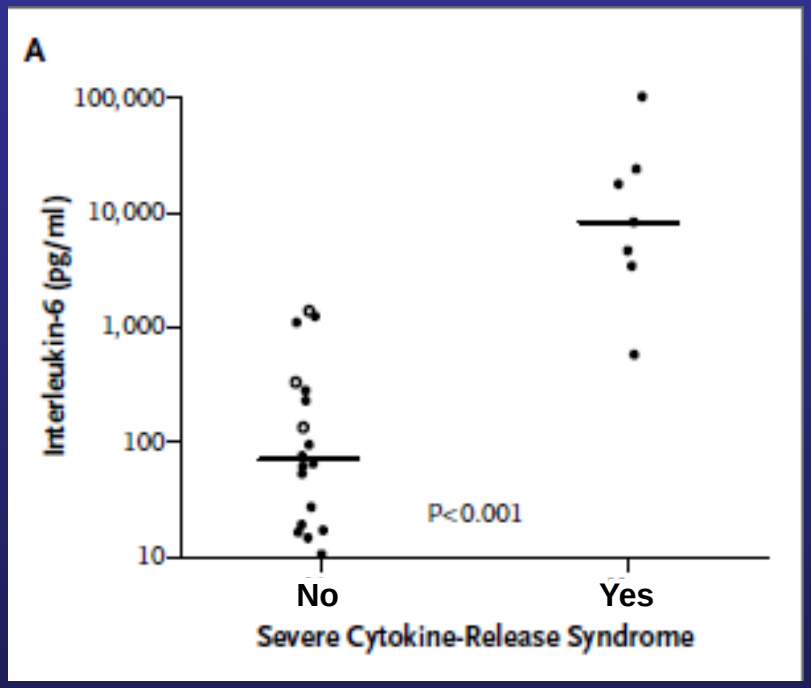
CD19 CAR-T cell Rx in 30 patients with relapsed / refractory ALL

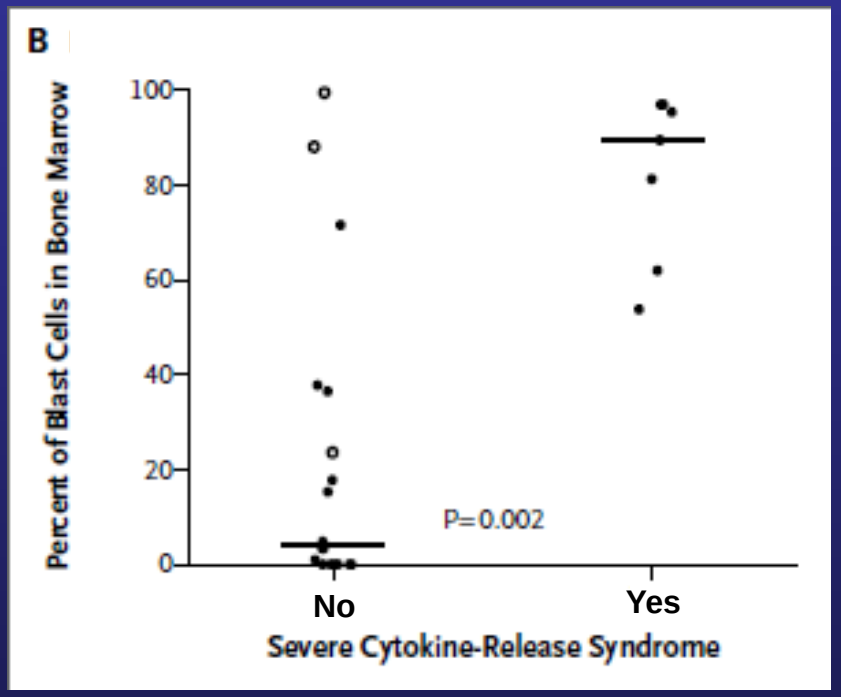




Ref: Maude SL, et al. NEJM 2014; 371:1507 – 1517.

Correlates of Cytokine Release Syndrome after CAR-T cell therapy





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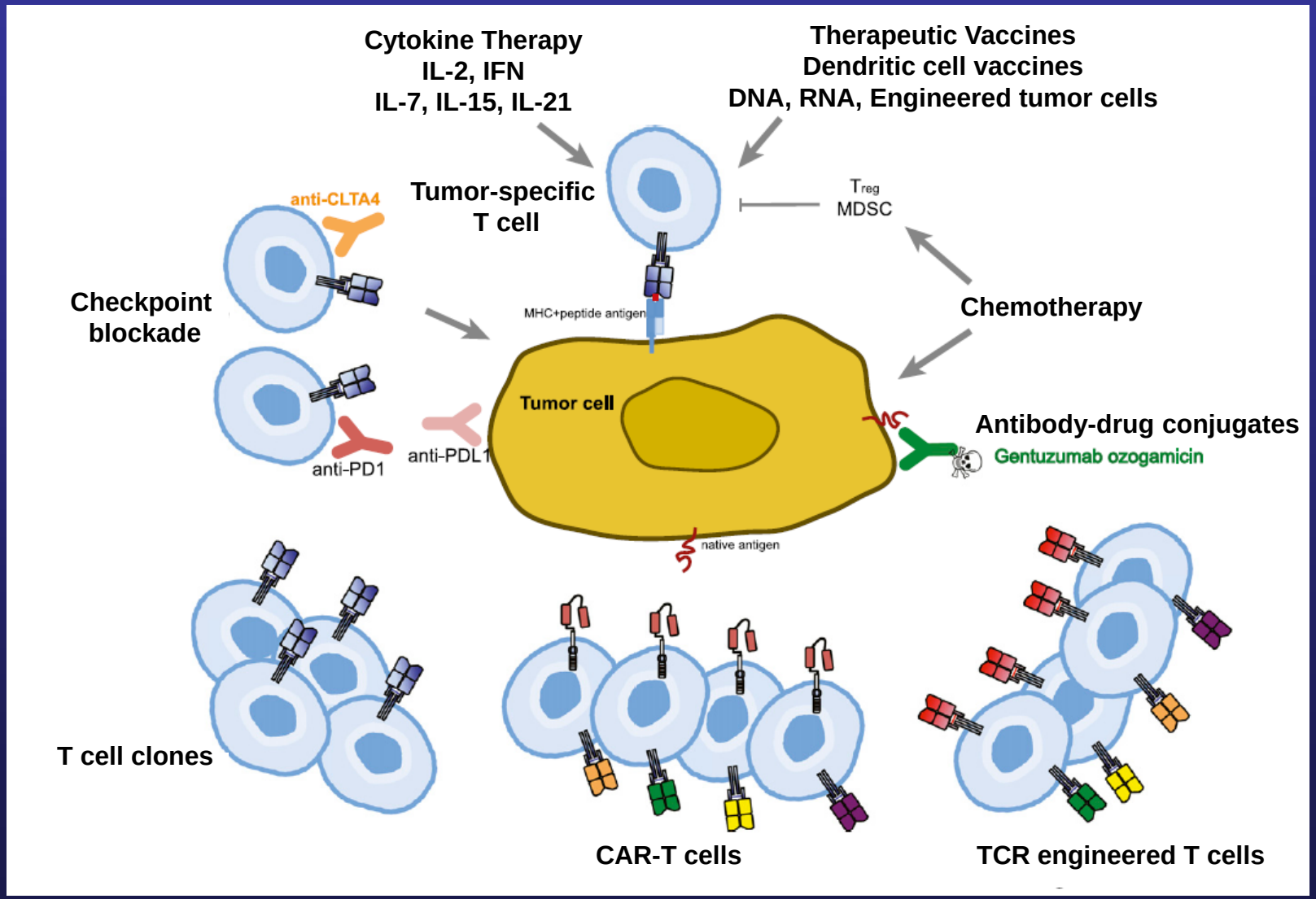
CANCER IMMUNOTHERAPY

Baby's leukemia recedes after novel cell therapy

Therapeutic approaches to overcome immune tolerance to cancer cells



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oncology-times.com

ONCOLOGY TIMES

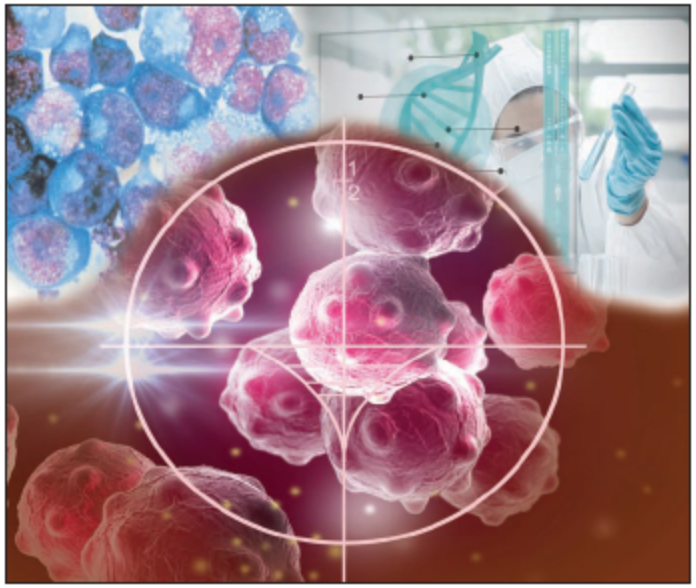
Independent News on
HEMATOLOGY / ONCOLOGY

Immune Checkpoints: Convergence of Cancer Treatment & HIV Cure

BY PAUL VOLBERDING, MD

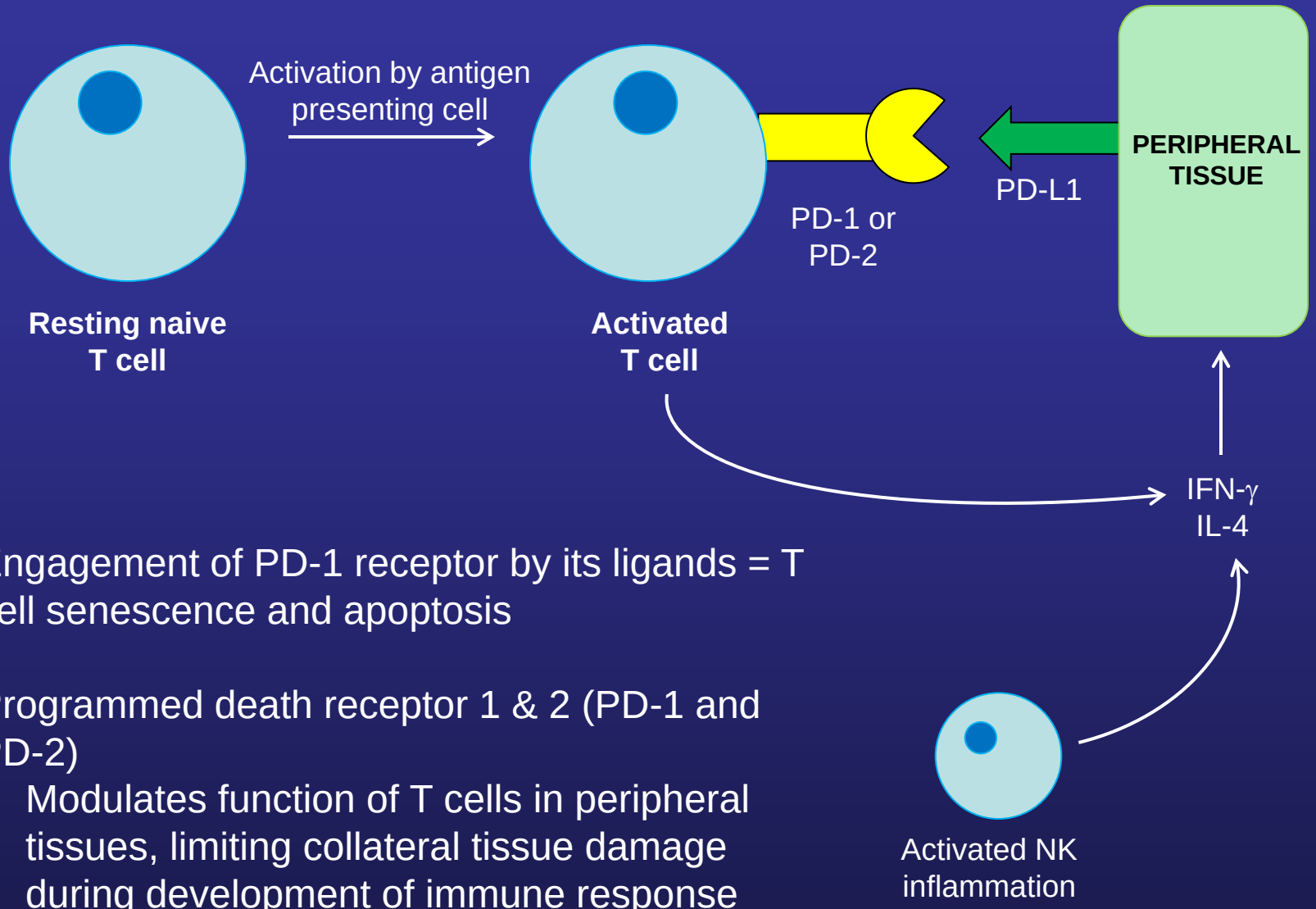
Cancer biology and the immune system have long been known to enjoy an intimate relationship. The increased incidence of some cancers in immunosuppressed individuals led to speculations that oncogenesis events are common but detected by "immune surveillance" systems that might recognize and eliminate newly formed malignant cells before they became an established and independent cancer. The dramatic increase in certain cancers in persons infected with HIV—especially ones with a viral co-infection—offered further support for the linkage of cancers with immune deficiencies. The frequent delay in relapse of cancer following primary therapy might suggest another facet of this immune system-cancer relationship with interesting parallels to HIV infection and the possibility of cure.

Continued on page 4



Immune checkpoints function to maintain self tolerance and limit collateral tissue damage during development of immune responses to infection and inflammation

- PD-1 (Programmed death 1 receptor)
- CTLA-4 (cytotoxic T-lymphocyte associated antigen-2)
- BTLA (B- and T-lymphocyte attenuator)
- LAG-3 (Lymphocyte activation gene 3)
- TIM-3 (T cell immunoglobulin and mucin protein 3)

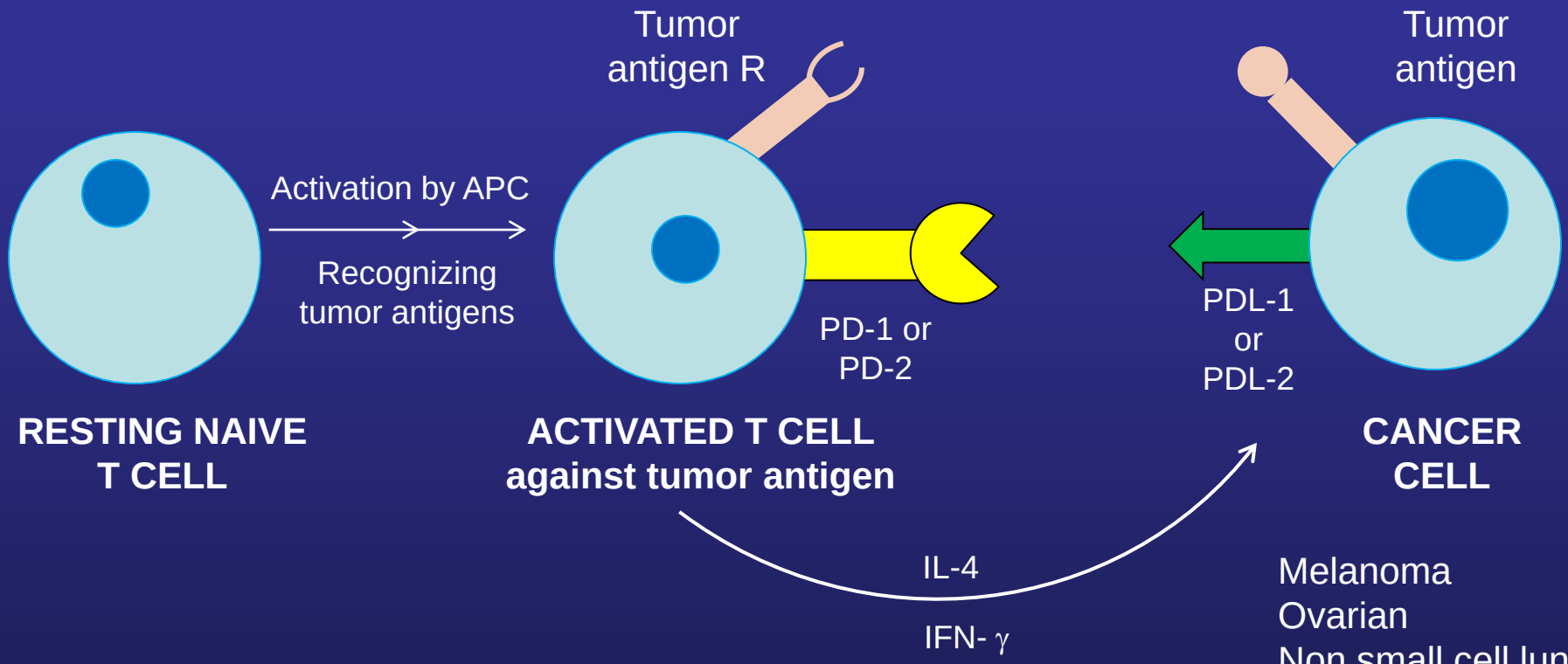


- Engagement of PD-1 receptor by its ligands = T cell senescence and apoptosis

- Programmed death receptor 1 & 2 (PD-1 and PD-2)

  Modulates function of T cells in peripheral tissues, limiting collateral tissue damage during development of immune response

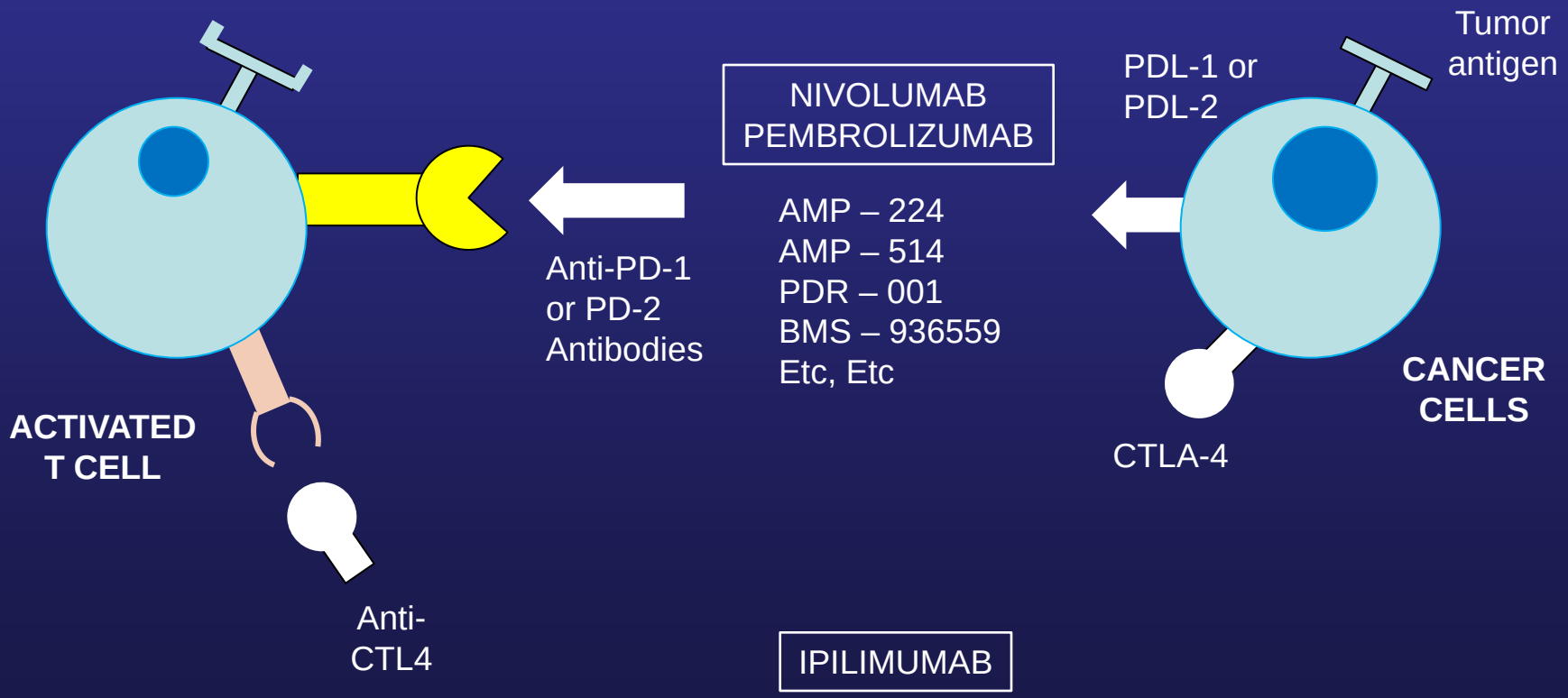
Cancer uses immune checkpoints to evade immune destruction



Melanoma
Ovarian
Non small cell lung
Renal cancer
Gastric cancer
Esophageal cancer
Pancreatic cancer
B cell lymphomas
Brain cancer
Etc, etc

IMMUNE CHECKPOINT INHIBITORS TO TREAT CANCER

- Do not directly target the cancer cells
- Do not activate the immune system to kill cancer, but eliminate the inhibitory pathways that prevent anti-tumor T cell responses



Checkpoint inhibitors currently licensed / USA 2016

Anti-CTLA-4	Ipilimumab	Yervoy	Melanoma (2011)
PD-1 Antibodies	Pembrolizumab	Keytruda	Melanoma (2014) NSC lung (2015)
	Nivolumab	Opdiva	Melanoma (2014) NSC lung (2015

↓

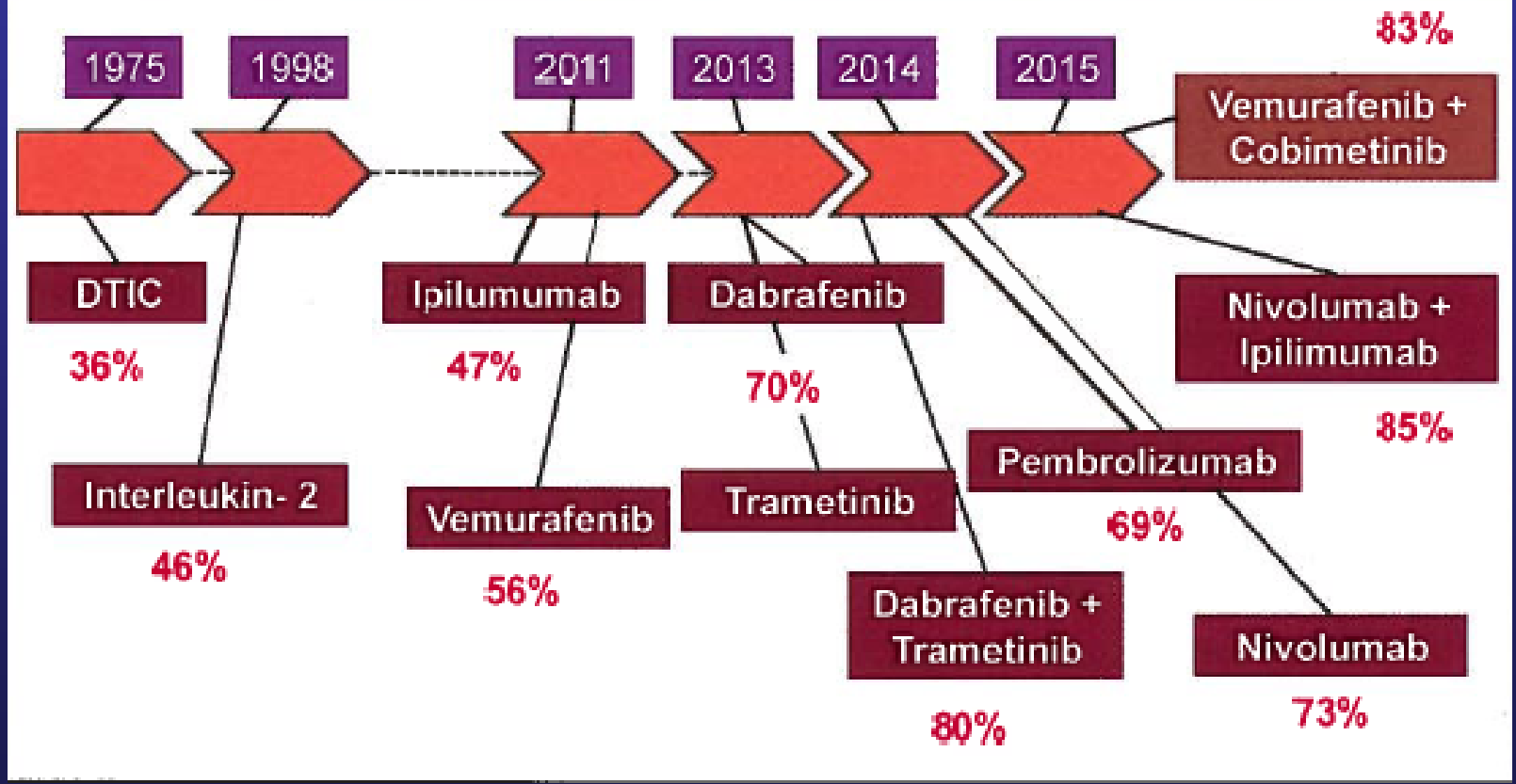
MANY more on the way

Selected results: Phase 3 trials of PD-1/PD-L1/CTLA4 inhibitors

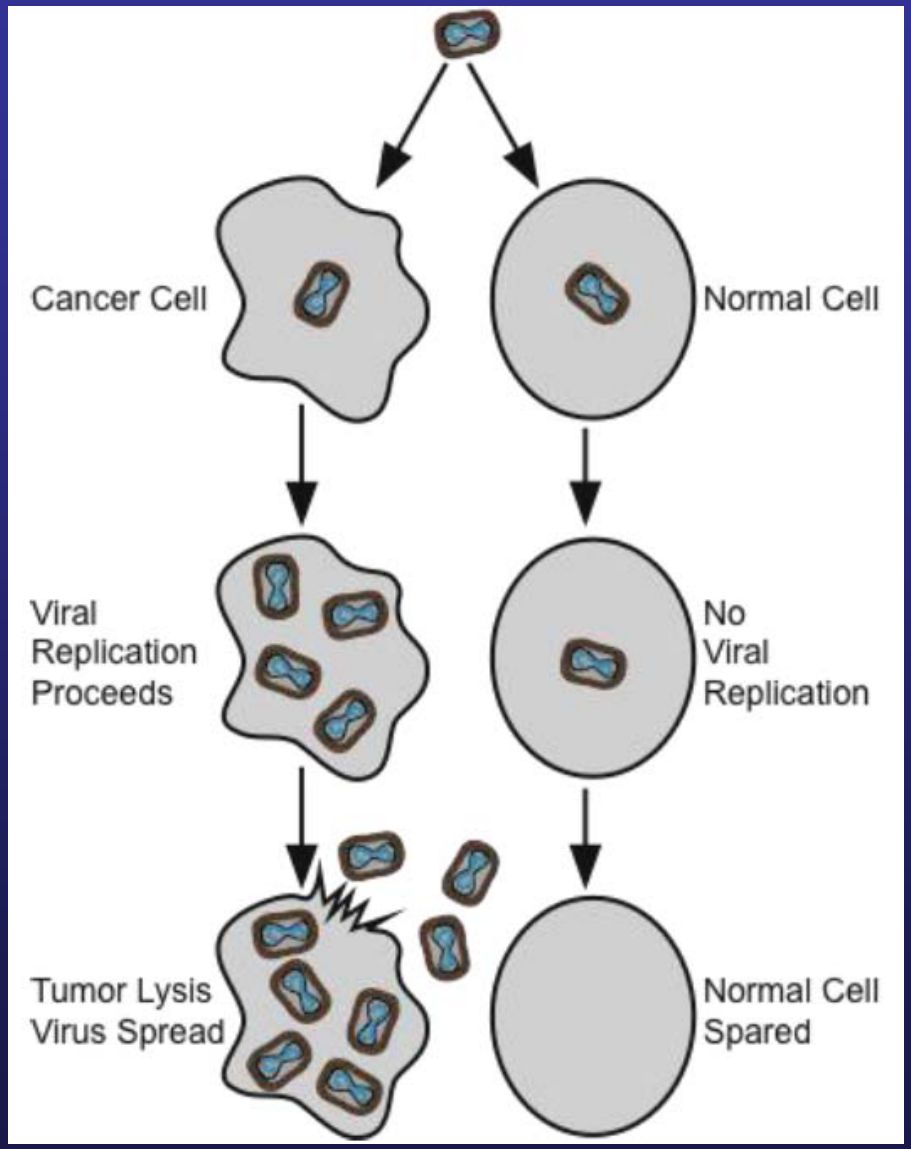
STUDY	PTS	PD Inhibitor	Comparator	ORR%	CR%	PFS	OS @ 1 yr
Check Mate 066	Melanoma, 1st line (N = 418)	Nivolumab		40%	8%	5 mos	73%
		DTIC		14%	1%	2 mos	42%
Check Mate 037	Advanced melanoma, after progression on Ipilimumab (N = 405)	Nivolumab		32%	3%	5 mos	_____
		Investigator choice of chemo		11%	0	4 mos	_____
Check Mate 017	Advanced non small cell lung cancer (N = 272)	Nivolumab		20%	1%	4 mos	42%
		Docetaxel		9%	0	3 mos	24%

Ref: Trivedi MS, et al. Clin Adv in Heme & Onc 2015; 13:858 – 867.

12-month Survival for Patients with Advanced Melanoma



Oncolytic Viruses



Measles Killing Cancer

Modified measles virus targe

www.latimes.com/science/sciencenow/la-sci-sn--measles-virus-cancer-20140516-story.html

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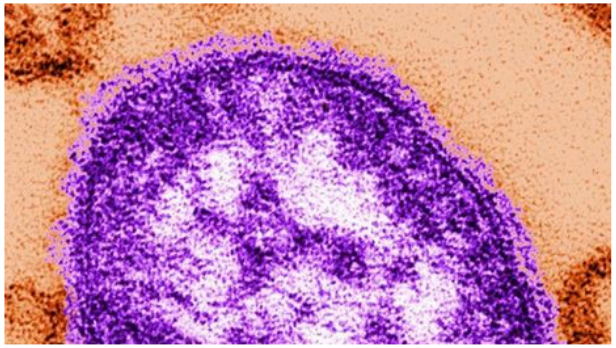
Los Angeles Times
Science / Science Now

This article is related to: Measles, Mayo Clinic

Modified measles virus targets and destroys cancer, study says



A single virus particle, or virion, of the measles virus. (Centers for Disease Control and Prevention)

By MONTE MORIN
contact the reporter

Oncolytic Virus Therapy

Tumor selective due to deletion of genes crucial for viral replication in normal cells, but not necessary in cancer cells

EX: Oncolytic B18R Vaccinia Virus

- Deletion of thymidine kinase – enzyme needed for nucleic acid metabolism
- Deletion of B18R gene – encodes decoy receptor for Type 1 IFN's

EX: T-VEC-genetically modified herpes I

- Insertion of GM-CSF gene, promoting local Ag presentation and systemic anti-tumor immunity

Poliovirus Shows Complete Response in Several Glioblastoma Patients (PMO 2015; 4:329)

PVS – RIPO oncolytic virus

Attenuated, live oral (Sabin) polio vaccine

Remove disease causing genes and replace with gene from cold-causing rhinovirus

↓

Cannot cause polio

Polio virus receptor = CD155

- Used for cell entry
- Cancer cells express CD155

↓

Oncolytic virus causes cell death

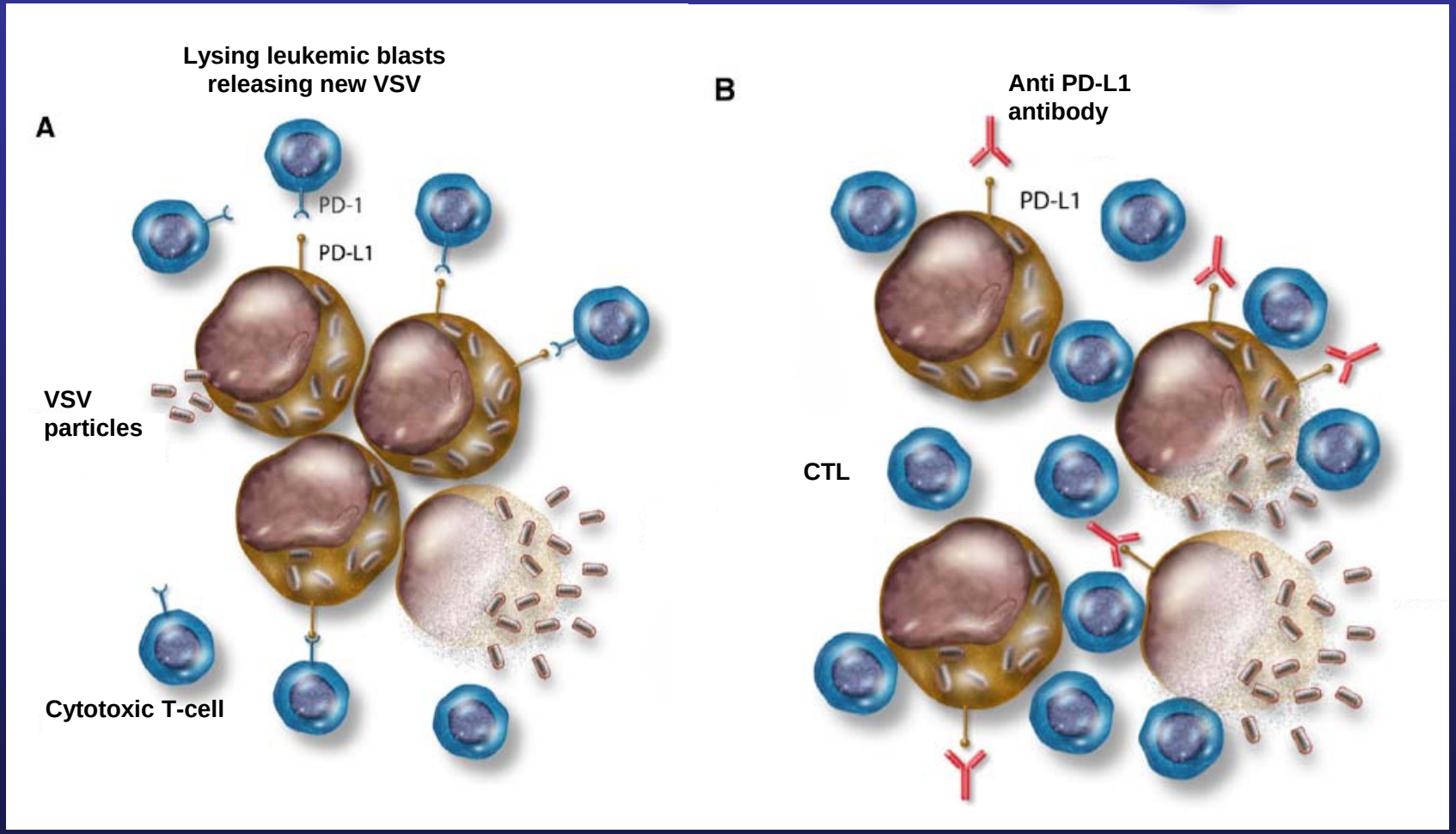
Rx = One injection into tumor (1×10^7)
Phase I, 15 pts with recurrent glioblastoma

Results = Over-all Survival
12 mos = 70%
18 mos = 44%
24 mos = 29%

2 patients remain in CR > 3 yrs

Ref: Gromeier M, et al. 19th Annual meeting of Society for Neuro-Oncology, Miami, 11/2015.

Combining Oncolytic Virus Therapy with Checkpoint Inhibition



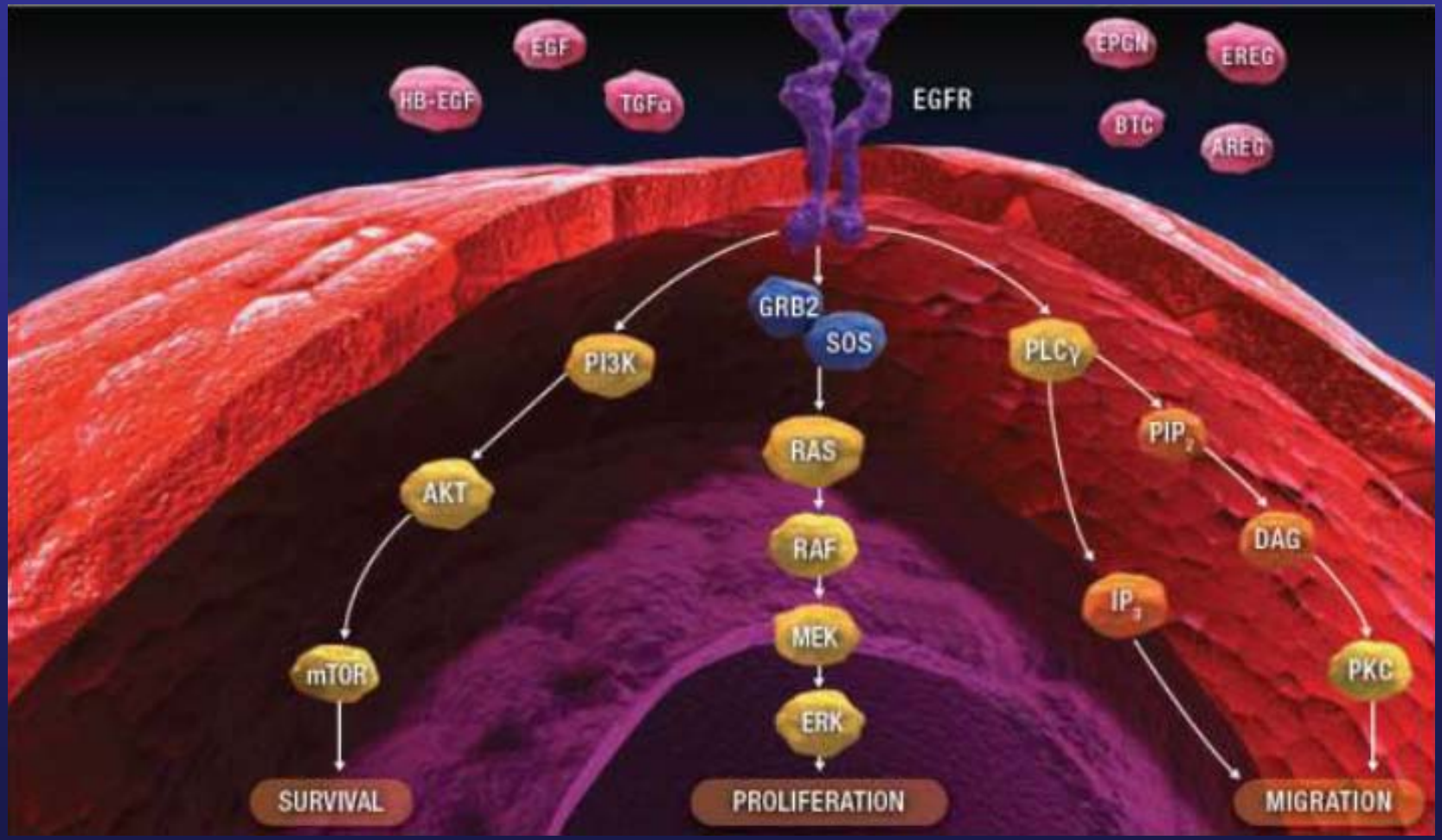
Ref: Kadia TM. Blood 2016; 127:1381 – 1383.

Another major frontier in cancer therapy seeks to elucidate the precise error at the level of the DNA which caused that cancer in that patient, and to reverse / stop that error

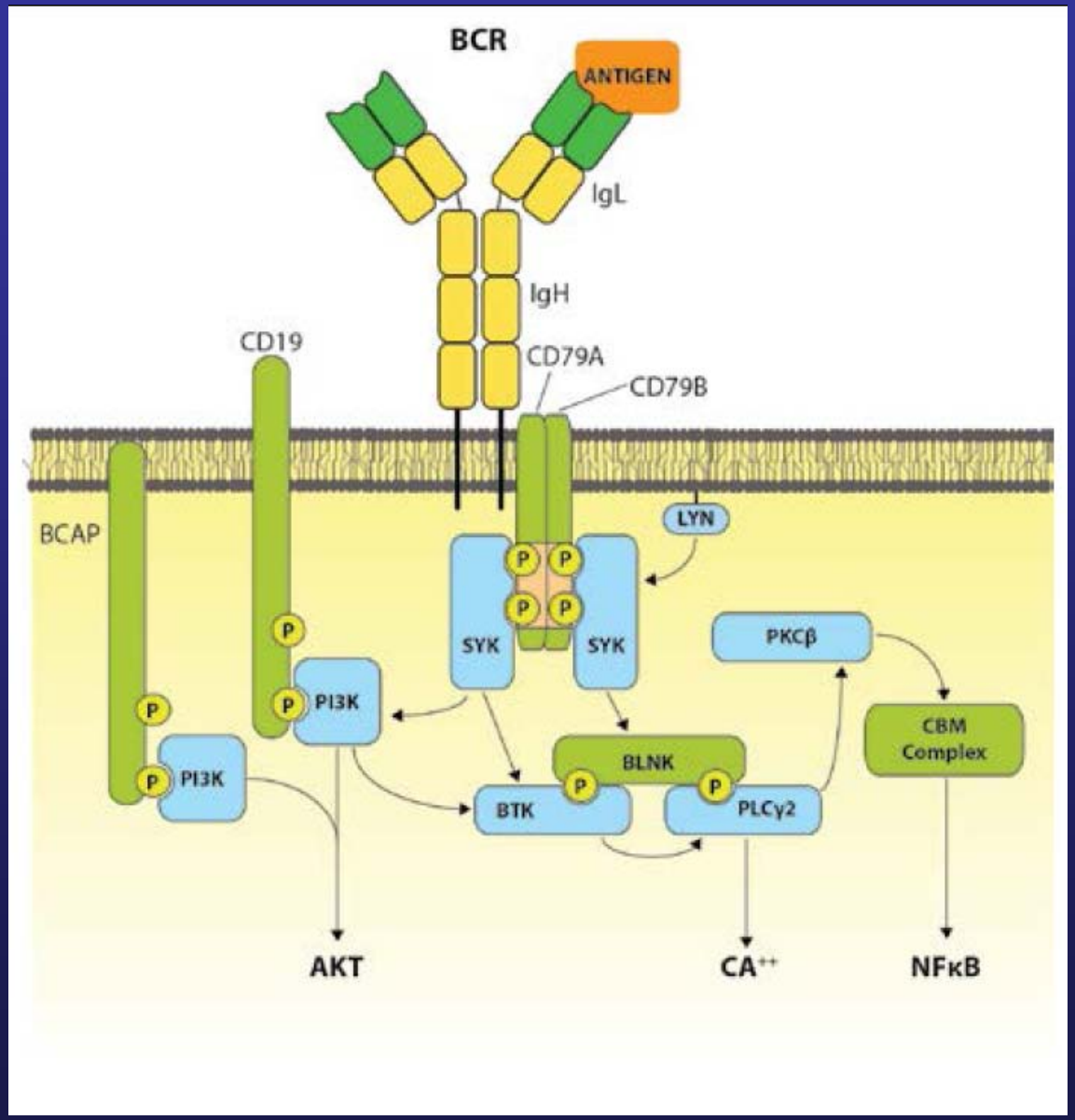
↓

Small Molecule Signaling Inhibitors

Signaling cascades represent another mechanism to treat specific mutations causing a given cancer

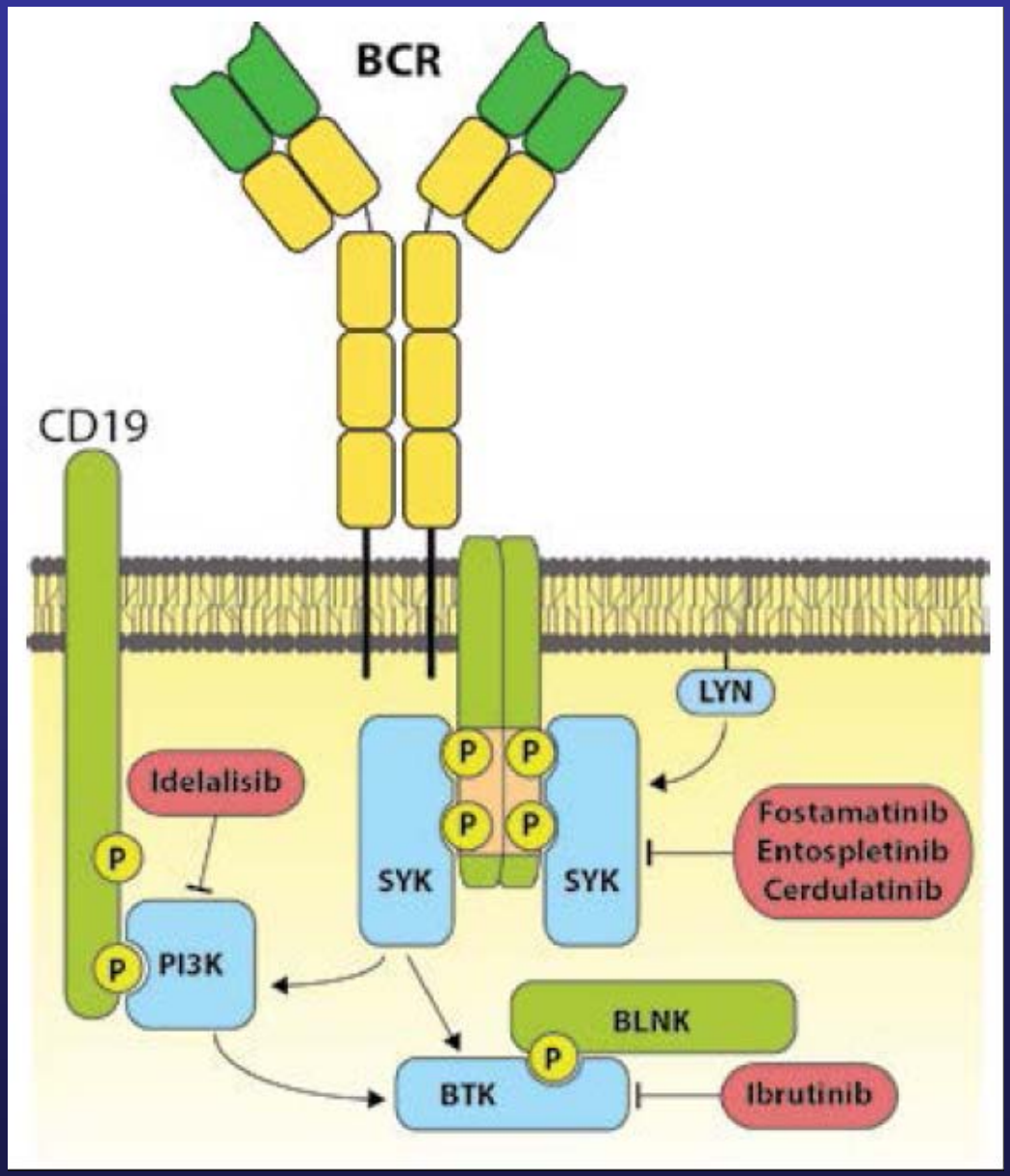


B cell signaling pathway



Ref: Koehrer S and Burger JA. Clin Adv in Heme & Onc 2016; 14:55 – 65.

B cell receptor inhibitors



Ref: Koehrer S and Burger JA. Clin Adv in Heme & Onc 2016; 14:55 – 65.

Precision (Personalized) Cancer Treatment

Matches patients with therapies based on specific biomarkers (mutations, neoantigens, cell surface antigens) in that cancer and that patient

- Using the immune system
- Using oncolytic viruses
- Using small molecular inhibitors to block signaling

↓

MORE to come

Impact of Precision (Personalized) Cancer Treatment

Meta-analysis of 570 studies on 32,149 patients with diverse cancers on phase 2 trials

- Personalized strategy was an independent predictor of better outcomes and fewer toxic deaths
- Chemo had worse outcome than personalized approach
- Use of non personalized target agents was associated with poorer outcome than chemo

Ref: Schwaederle M, et al. JCO 2015; 33:3817 – 5.

CANCER WILL BE CURABLE

(or, you can just live with it)

BACK TO THE FUTURE

Tate, London

Sir Luke Fildes, *The Doctor* (1891)

…was the “peace” of his presence augmenting the patient’s immune system??

HIV Management 2016

THE NEW YORK COURSE