Radiation and Immunotherapy: How to Ignite Long Term Anti-Cancer Response

Cancer and the Immune System: The Basics

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ROSWELL PARK CANCER INSTITUTE

Current Strategies to Combat Cancers

Mechanics - surgery, 1600BC

Physics - radiotherapy, 1890s

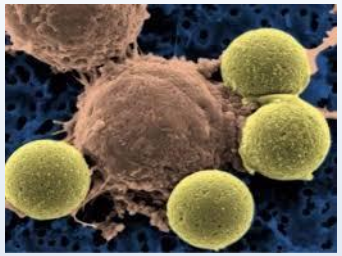
Chemistry - chemotherapy,1940s

Biology – antibodies, cytokines

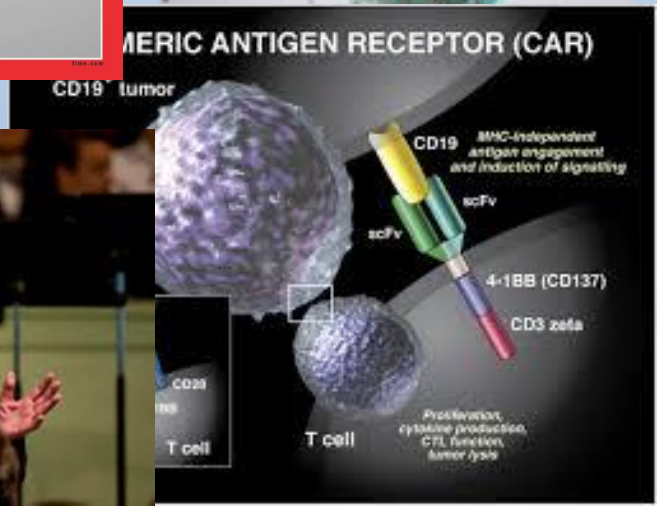
1980s

} Immunotherapy!

Immunotherapy (& Immunology) at the Center Stage of Cancer Therapy



- FDA approvals: Provenge, CTLA4 blockade, PD1/PDL1 blockers
- Big Pharma &Biotech Enter Cell-based Immunotherapies (DC, CAR-T, TIL...)
- 2013 Science Breakthrough of the Year; Time Magazine Cover Story- April 4th, 2016
- 2011 Nobel Prize: Ralph Steinman (Dendritic cell function)
- 2015 Lasker Award- James Allison



The challenge: Only a subset of patients respond, in certain cancers. Also, the toxicity is significant in many patients.

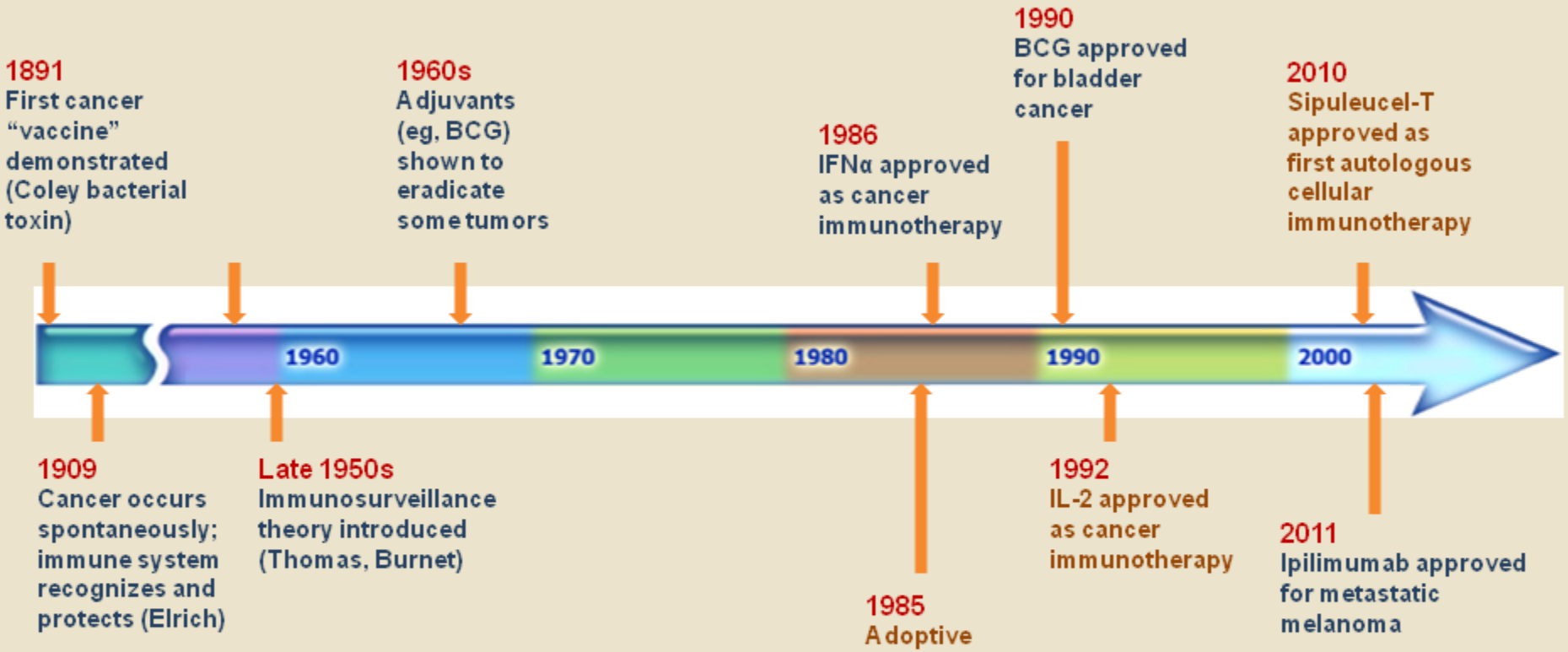
Some basic tumor immunology leading to the current immunotherapies;

Immune contexture- a new diagnostic tool?

Role for radiation?

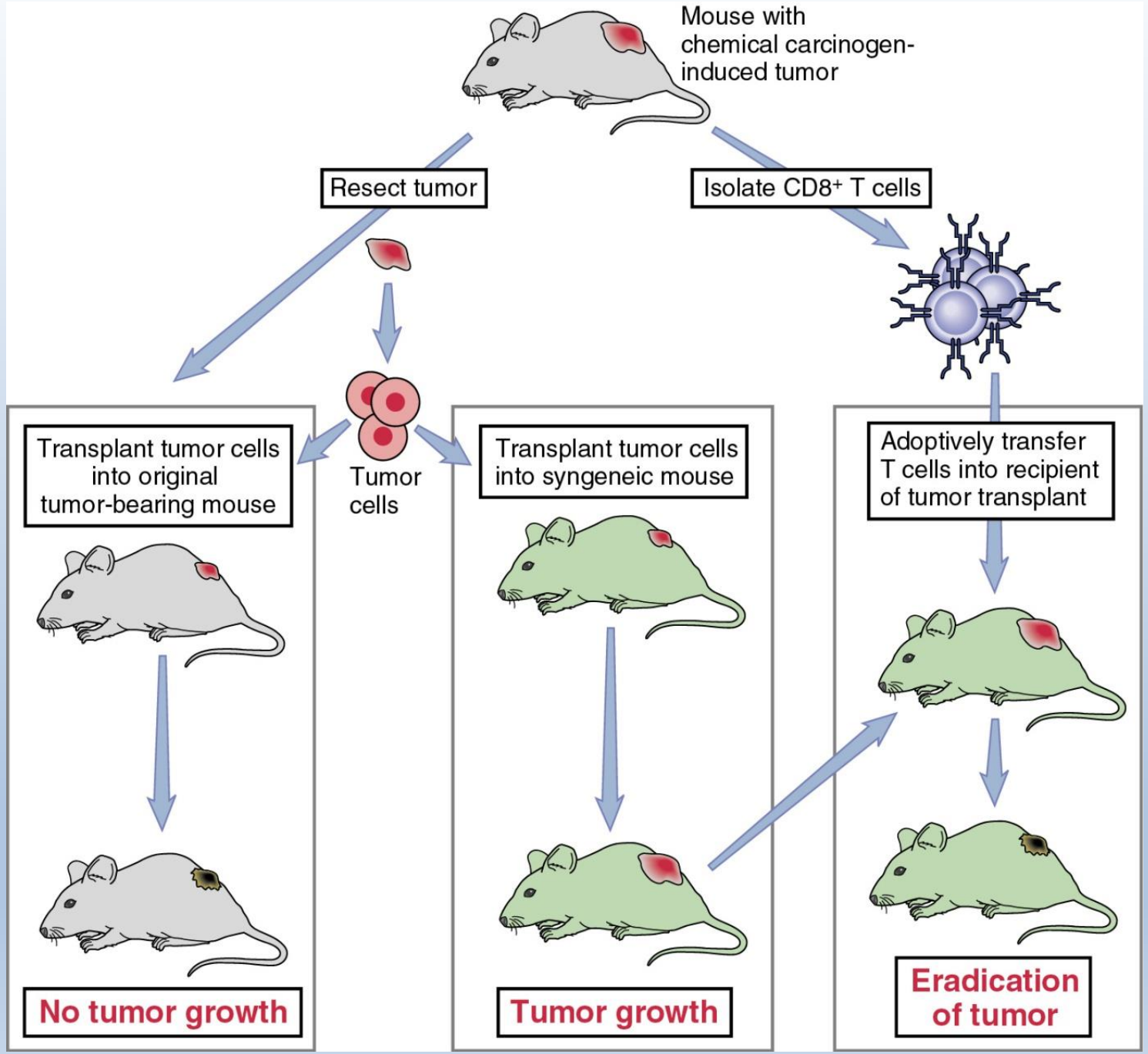
New role for medical physicists?

Timeline of the Development of Immunotherapy



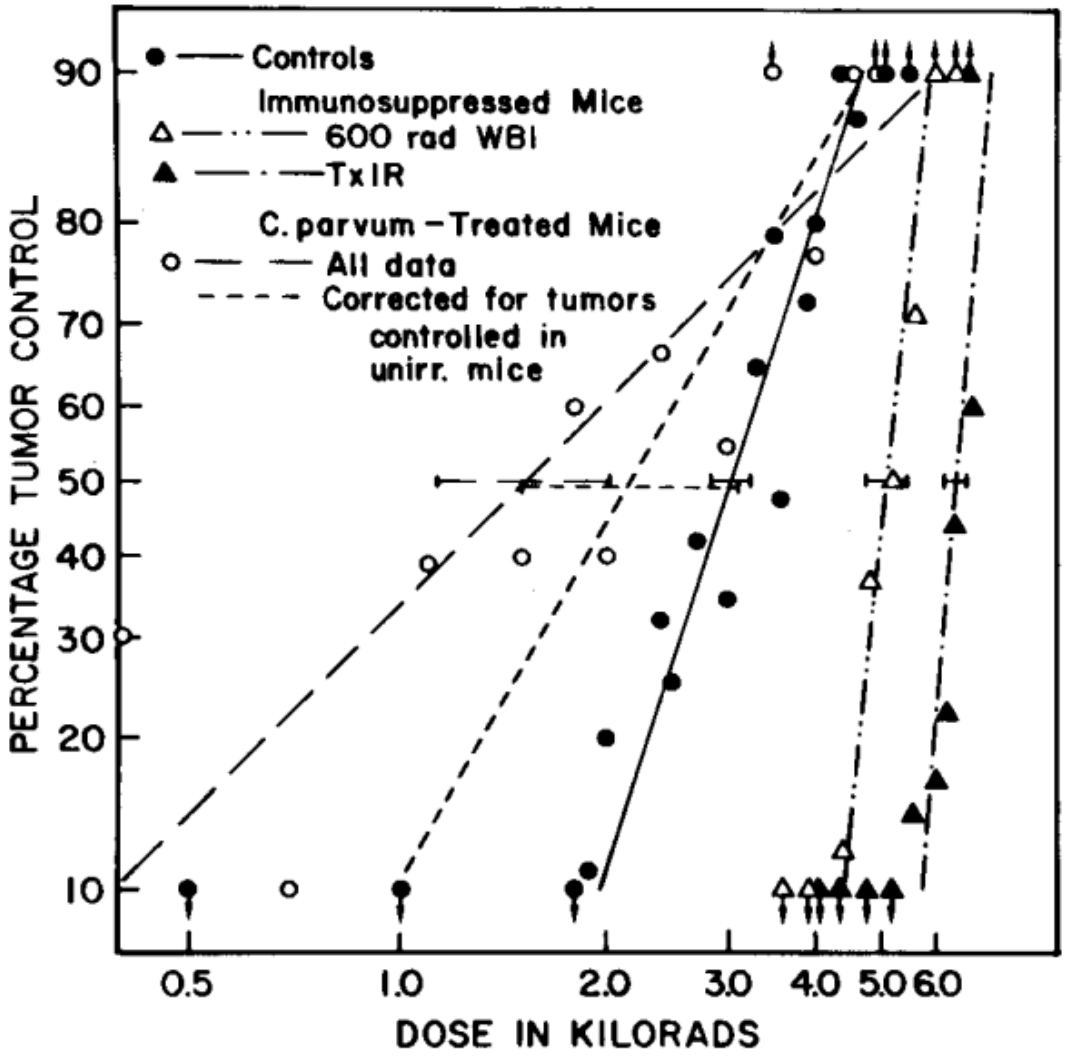
BCG = Bacille Calmette-Guérin
IFN = interferon
IL = interleukin
TIL = tumor-infiltrating lymphocyte

Coley WB. Ann Surg 1891;14:199–220
Kim CJ et al. *Cancer Control*. 2002;9:22-30.
Dudley ME et al. *Science*. 2002;298:850-854.
Nature Milestones Cancer 2006; S7-S23.
Cancer: Principles and Practice of Oncology. 9th ed. 2011.


Mouse with chemical carcinogen-induced tumor
Resect tumor
Isolate CD8+ T cells
Transplant tumor cells into original tumor-bearing mouse
Tumor cells
Transplant tumor cells into syngeneic mouse
Adoptively transfer T cells into recipient of tumor transplant
No tumor growth
Tumor growth
Eradication of tumor

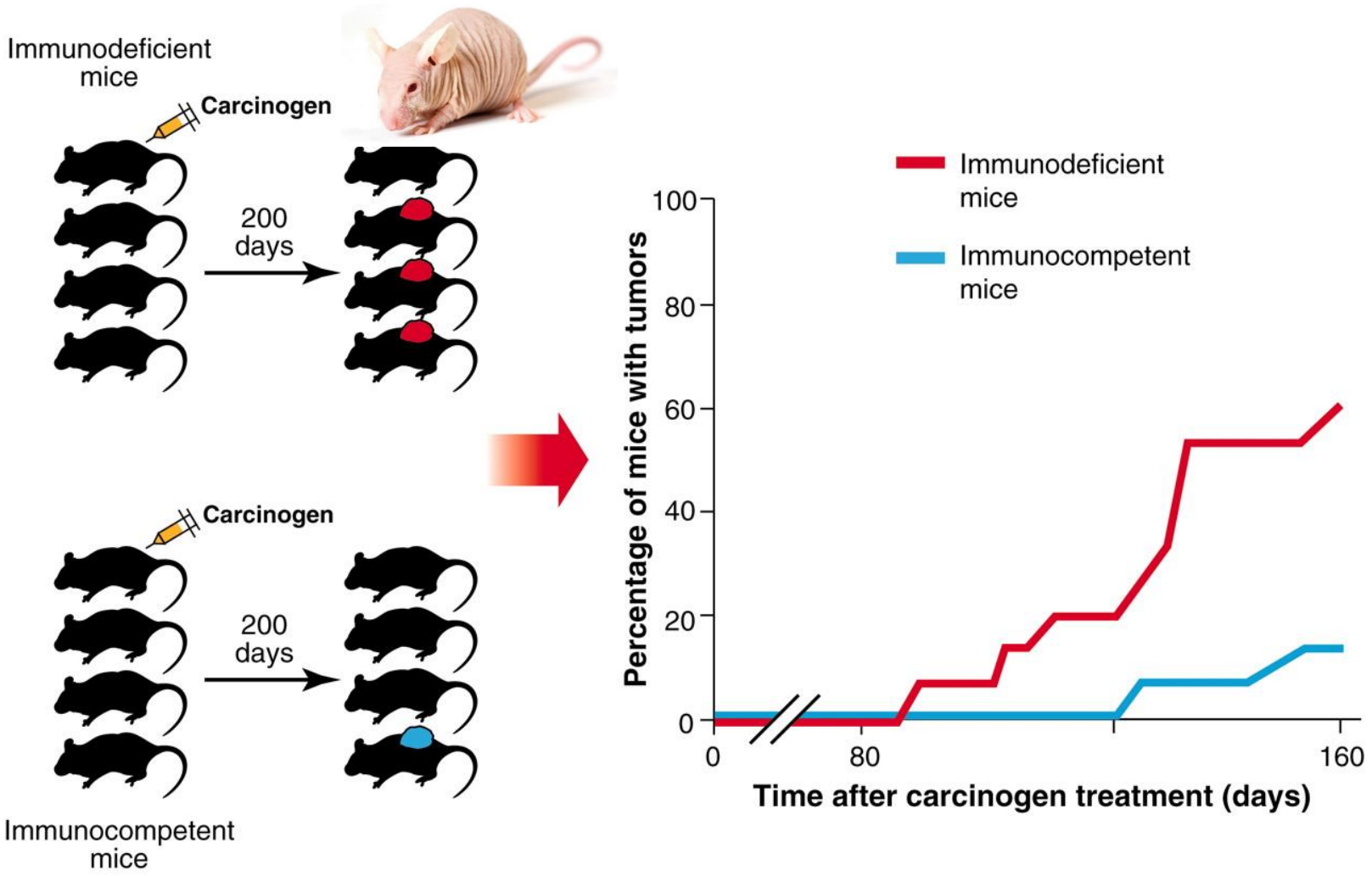
Early recognition that the immune status in the host influences anti-tumor cell efficacy of ionizing radiation

Fig. 1 from Helen Stone et al, J Natl Cancer Inst 1979



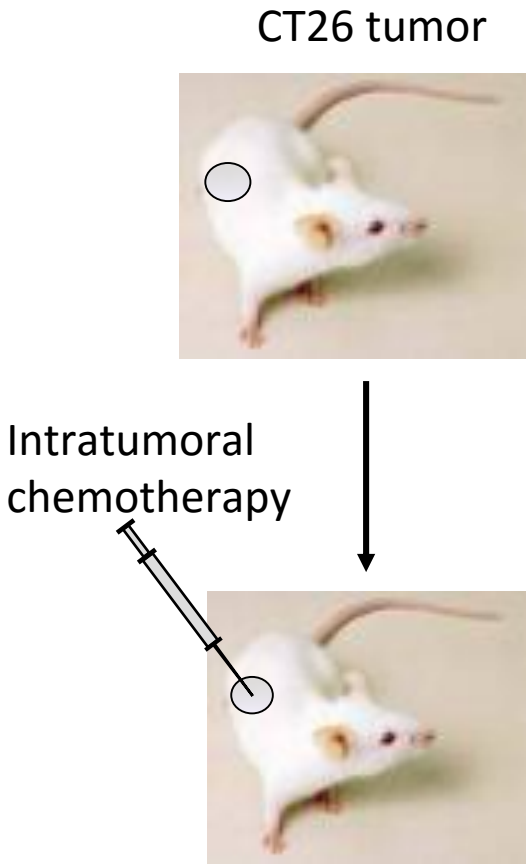
Cryptosporidium parvum is a protozoan.

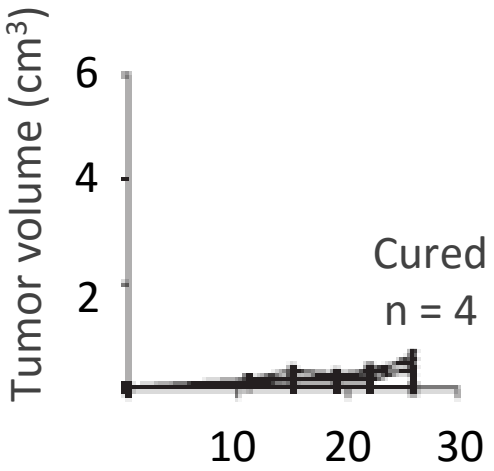
The immune status of mice is a critical determinant of their susceptibility to tumors induced by chemical carcinogens.



R D Schreiber et al. Science 2011;331:1565-1570

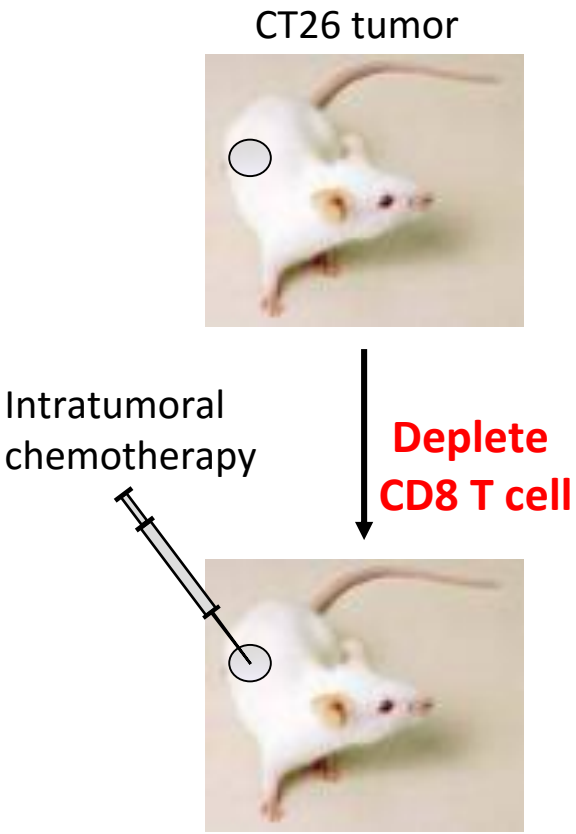
The power of adaptive immunity in the response to chemotherapy

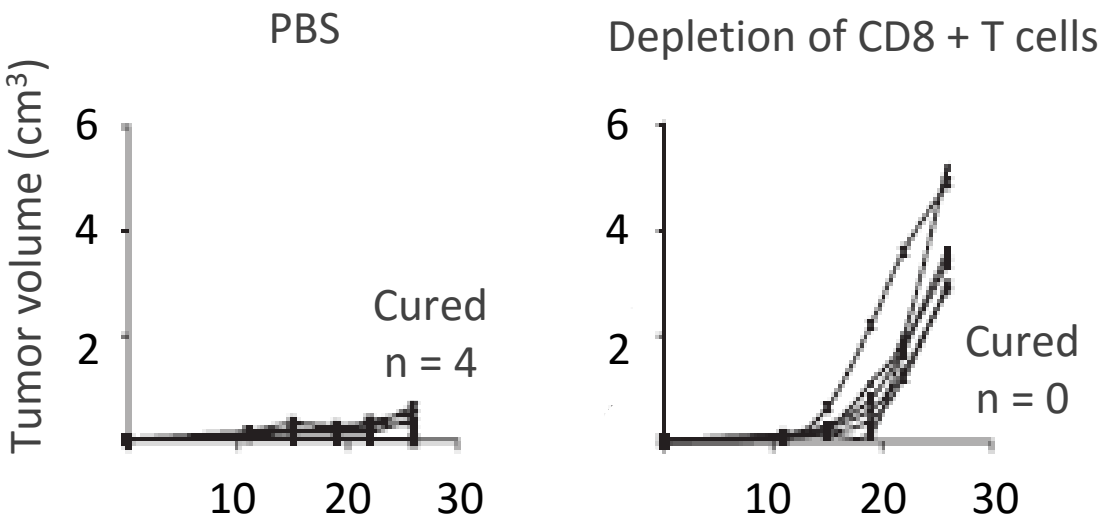




Obeid et al, Nature Medicine, 2007

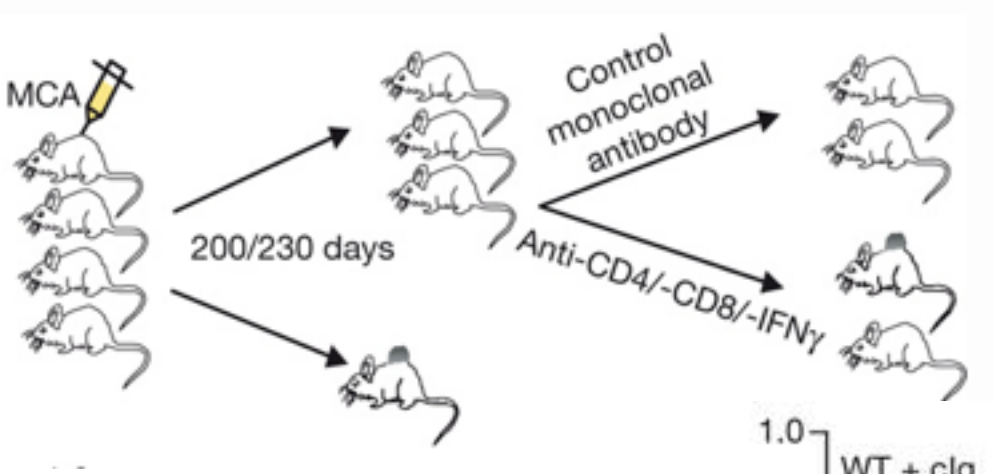
And, specifically a role for $CD8^+$ T lymphocytes

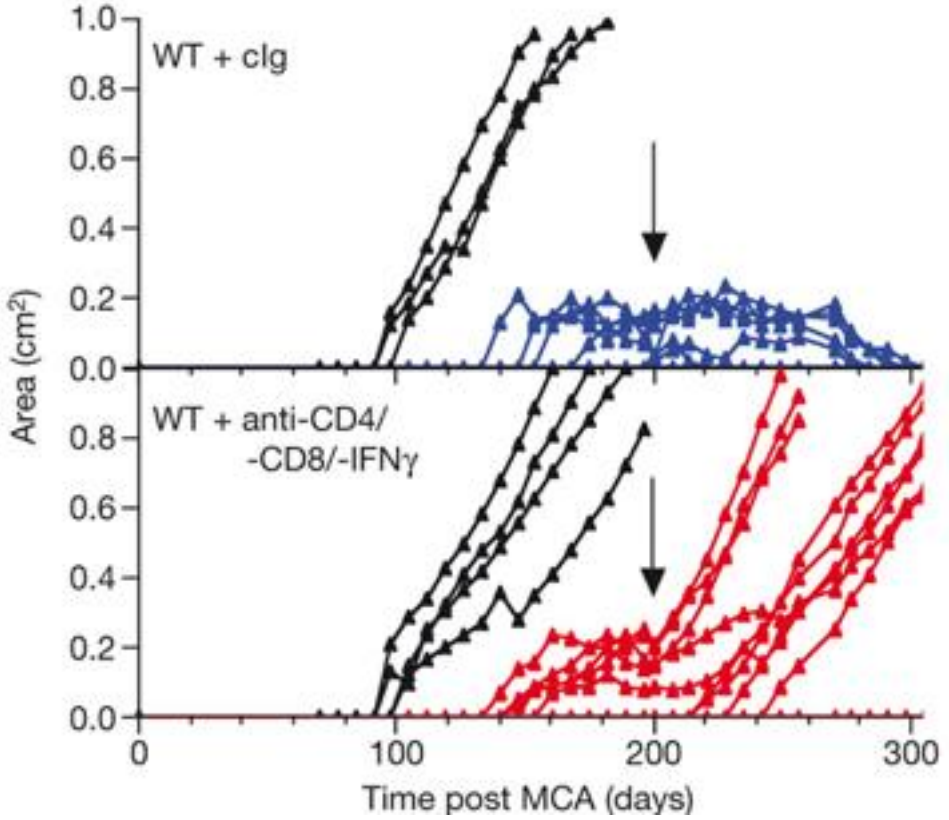




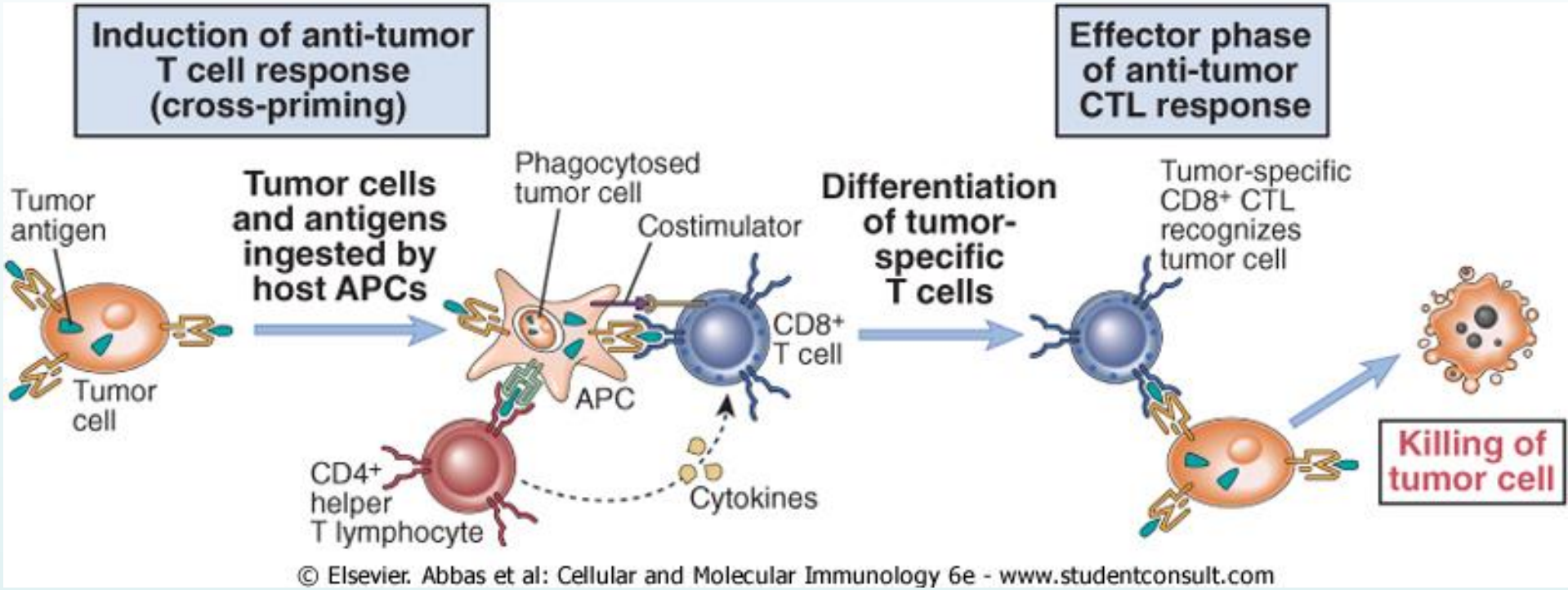
Obeid et al, Nature Medicine, 2007

T cells control latent tumors





Koebel et al. Nature;450:903, 2007



Tumor antigens:

Tumor-specific: TSA

Oncogenic mutants of normal cellular genes:ras, bcr-abl, p53
Randomly mutated genes: TSTA´s (tumor-specific transplantation antigens)

Can be identified: biochemical
cDNA cloning

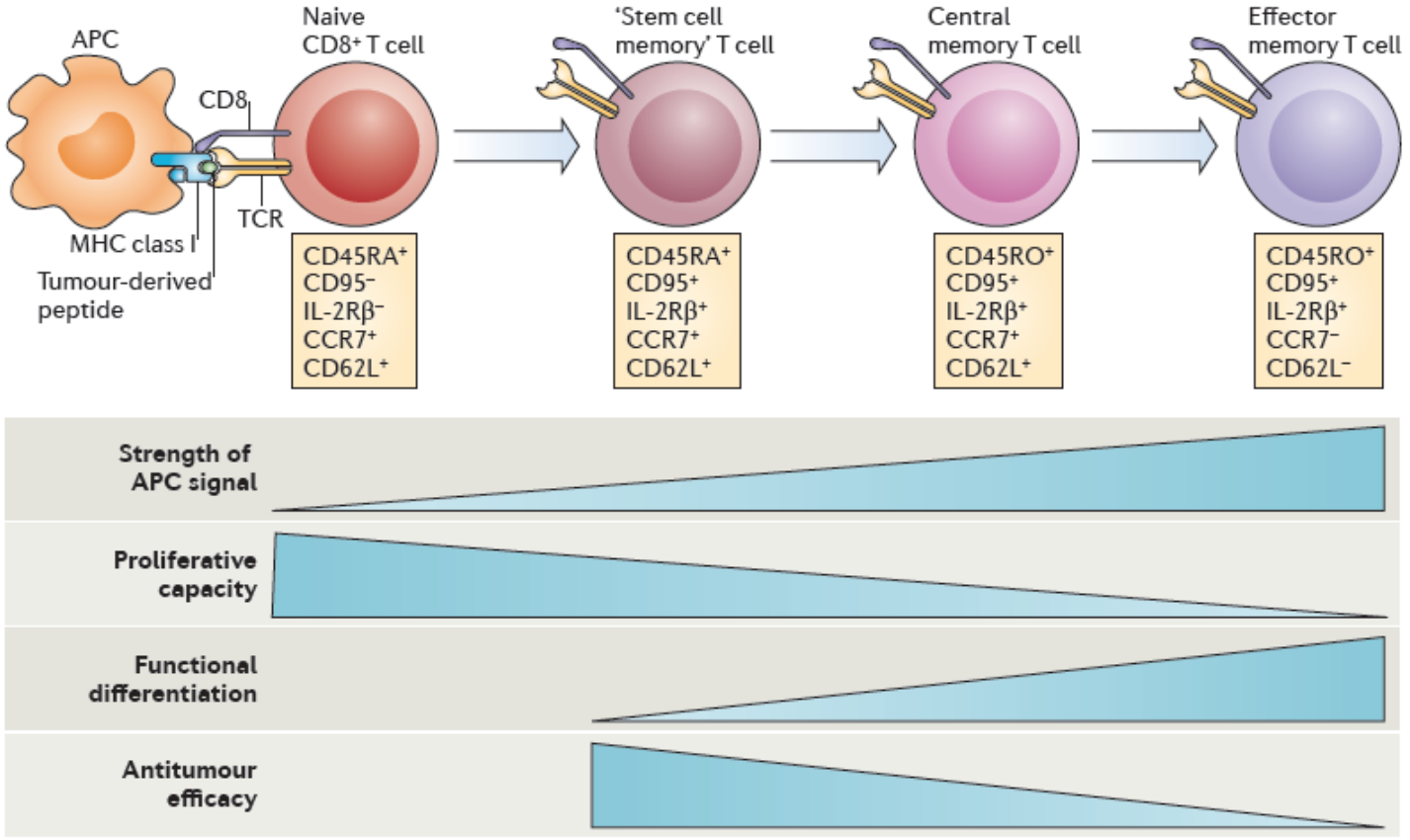
Tumor-associated: TAA
Normal cellular proteins aberrantly expressed

Tyrosinase - melanomas (enzyme melanin biosynthesis)
Cancer/testis antigens: expressed testis and trophopblasts
Oncofetal antigens: developing fetal tissue
- CEA: carcinoembryonic antigen - colo and many cancers,
- AFP: α-fetoptotein - hepatocellular cancer and others
- not specific, can be induced inflammatory conditions

Altered glycolipid and glycoprotein antigens:
- gangliosides - in melanomas
- Mucin-1 - O-linked carbohydrates

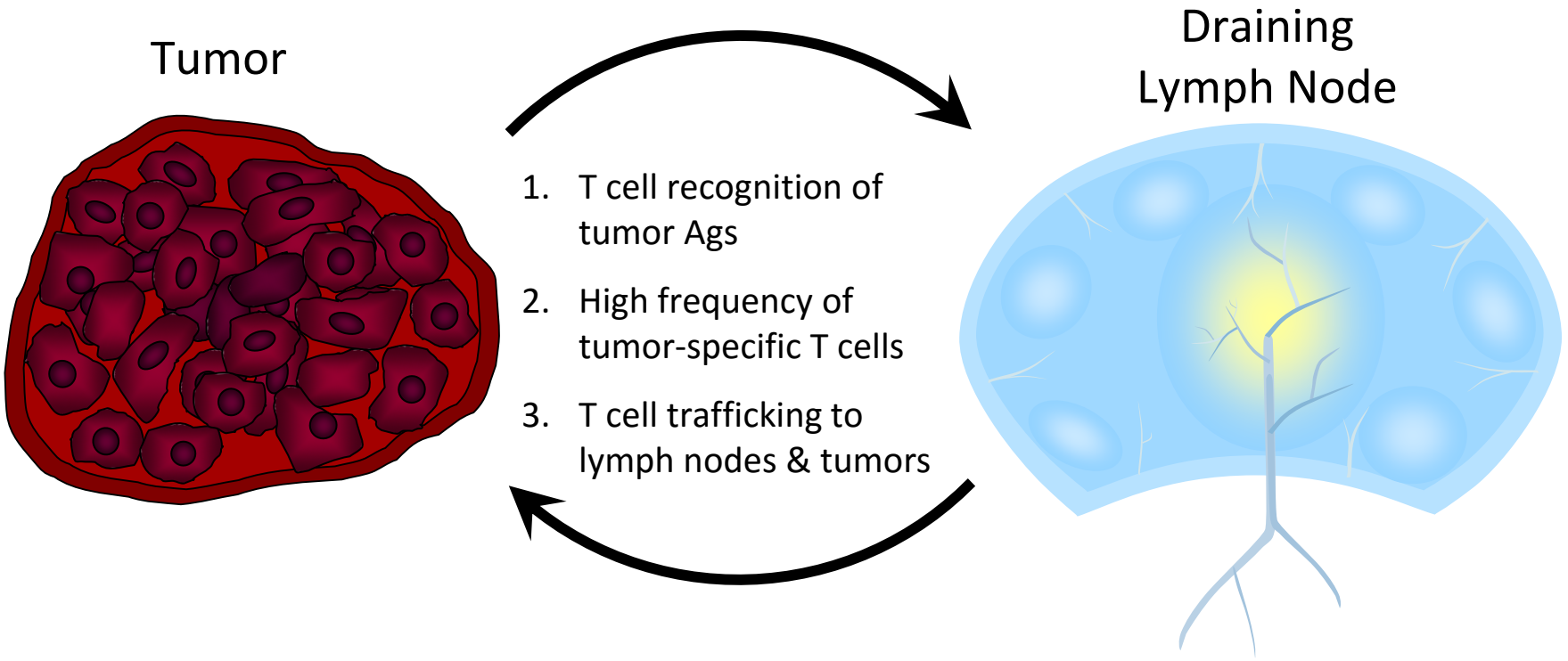
Tissue-specific differentiation antigens

Antigen Presenting Cells Initiate a Cascade of Specific T Cell Activities

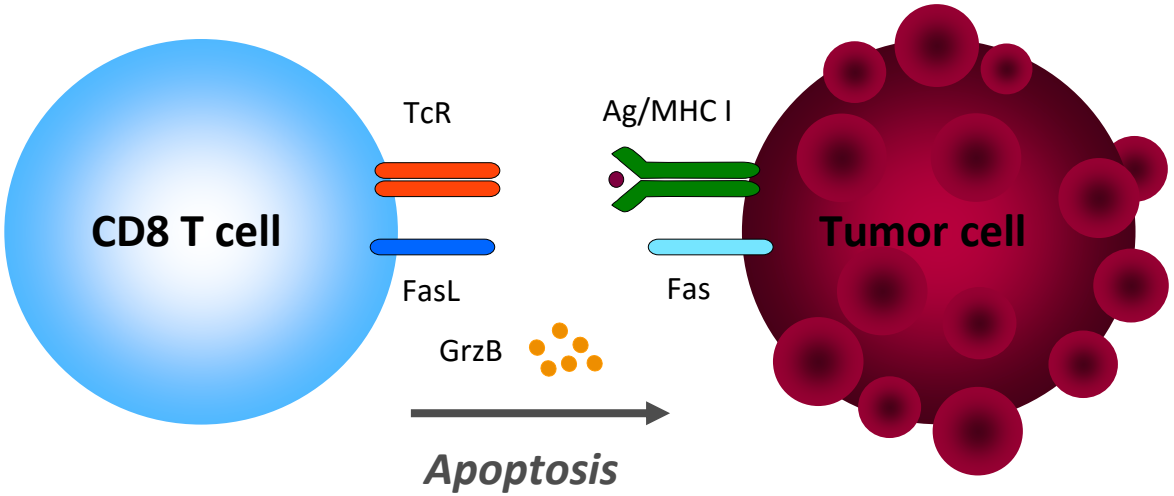


Restifo et al., Nat. Reviews in Immunology, 2012

Adaptive Tumor Immunity:

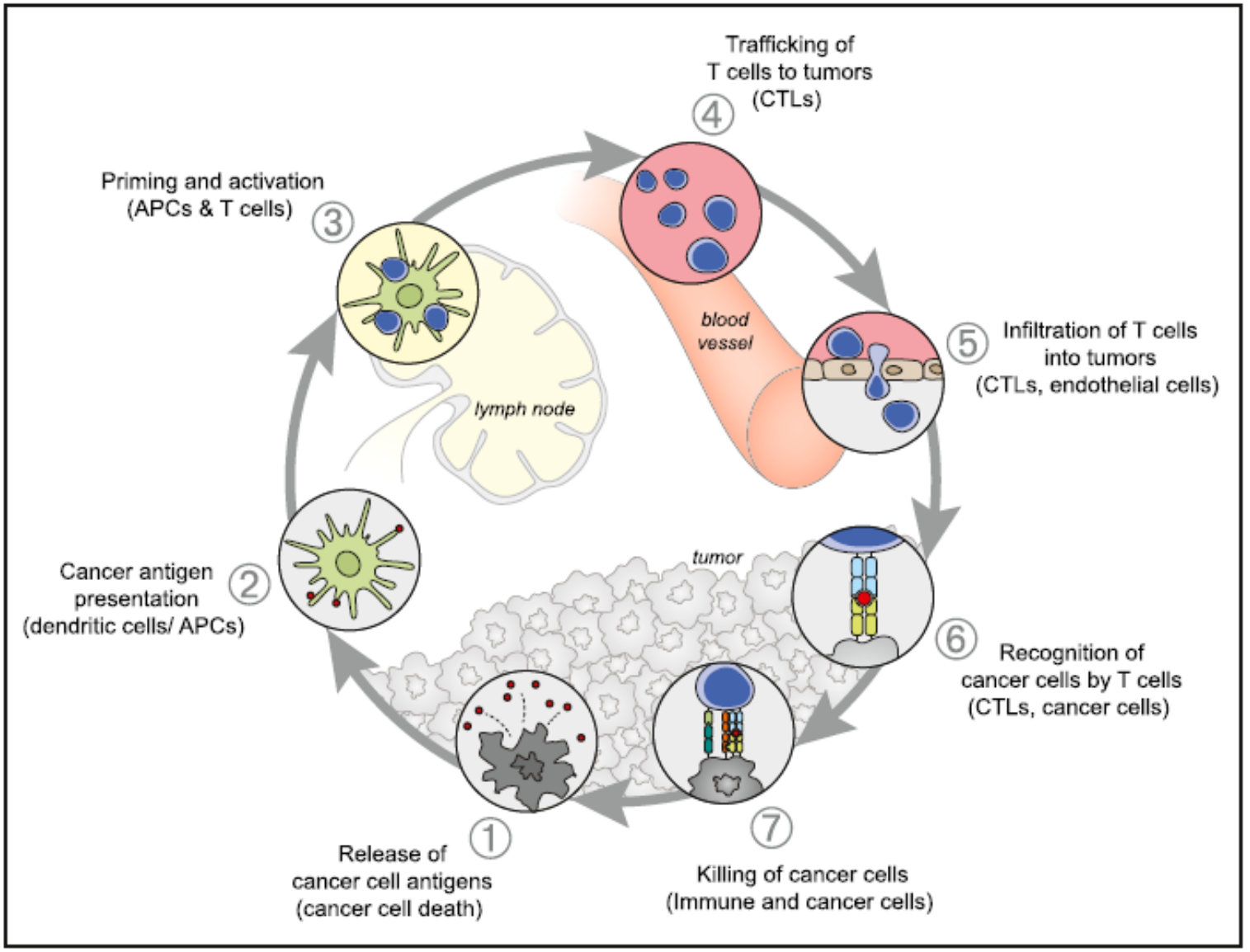


Advantages of T Cell-Based Cancer Immunotherapy



1. Exquisite specificity for target; limit collateral damage.
2. Target non-resectable tumors.
3. T cells can target tumors at sites throughout the body.
4. Long-lasting protection.

The Cancer-Immunity Cycle



Chen and Mellman Immunity 39; 2013

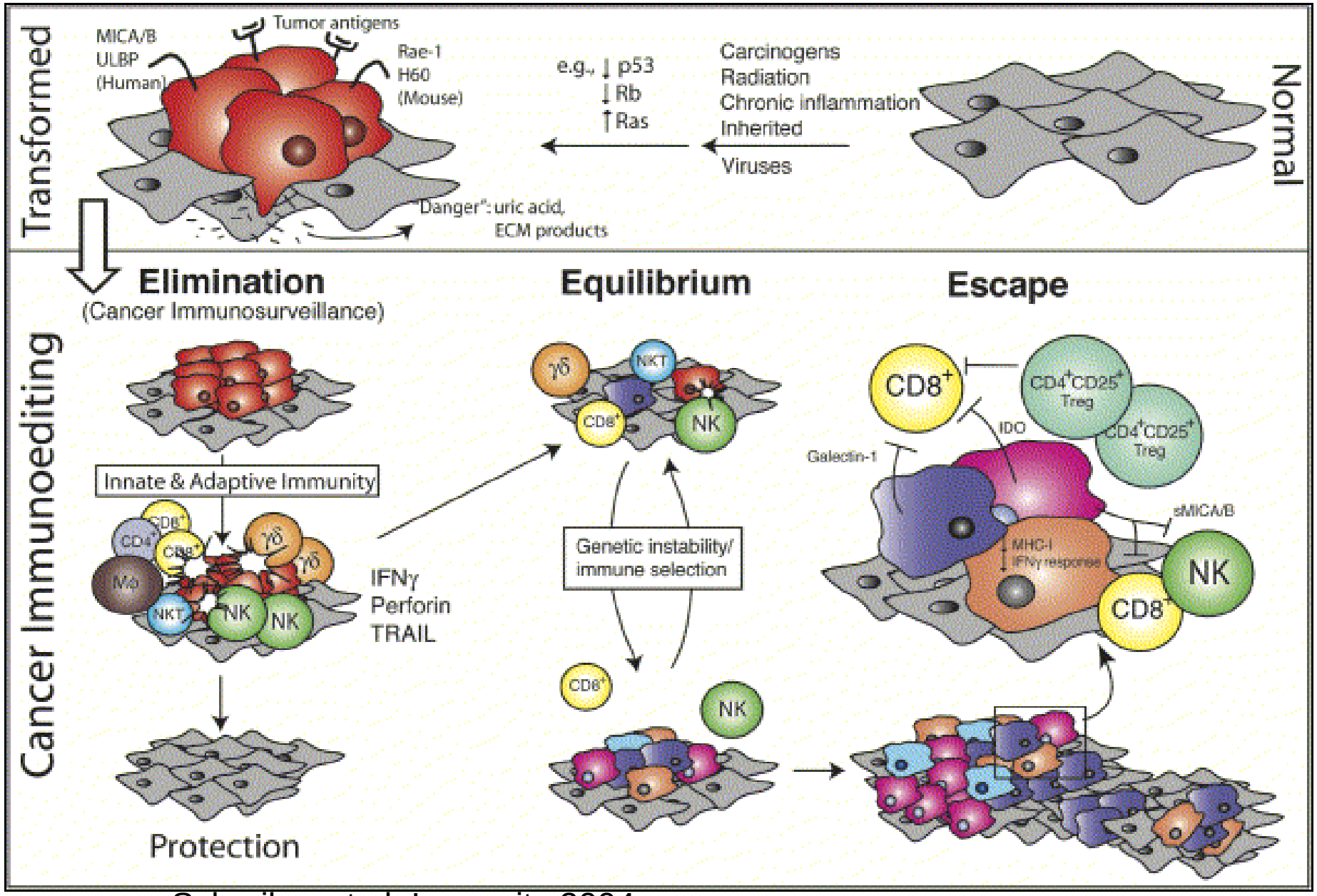
Immunological Surveillance
Ehrlich, Burnet & Thomas

Paul Ehrlich (1909) First to conceive of the concept of Cancer Immunosurveillance. Predicted that cancer would occur at "incredible frequency" if host defenses did not prevent the outgrowth of continuously arising cancer cells.

Lewis Thomas (1957) "primary function of cellular immunity….is to protect from neoplastic disease"

Macfarland Burnet (1957) "It is by no means inconceivable that small accumulations of tumour cells may develop and because of their possession of new antigenic potentialities provide an effective immunological reaction with regression of this tumor and no clinical hint of its existence"

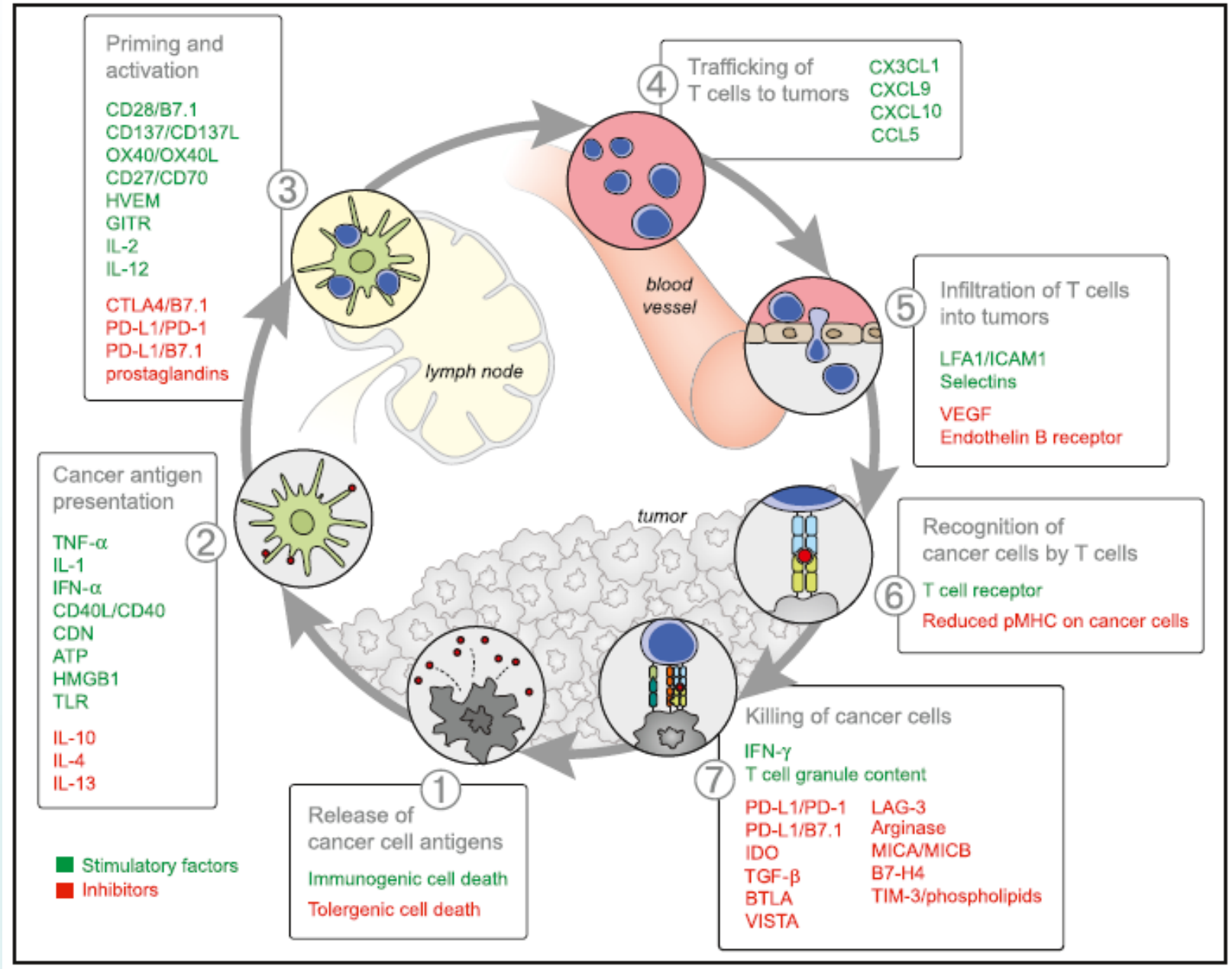
Tumor Elimination - Equilibrium - Escape



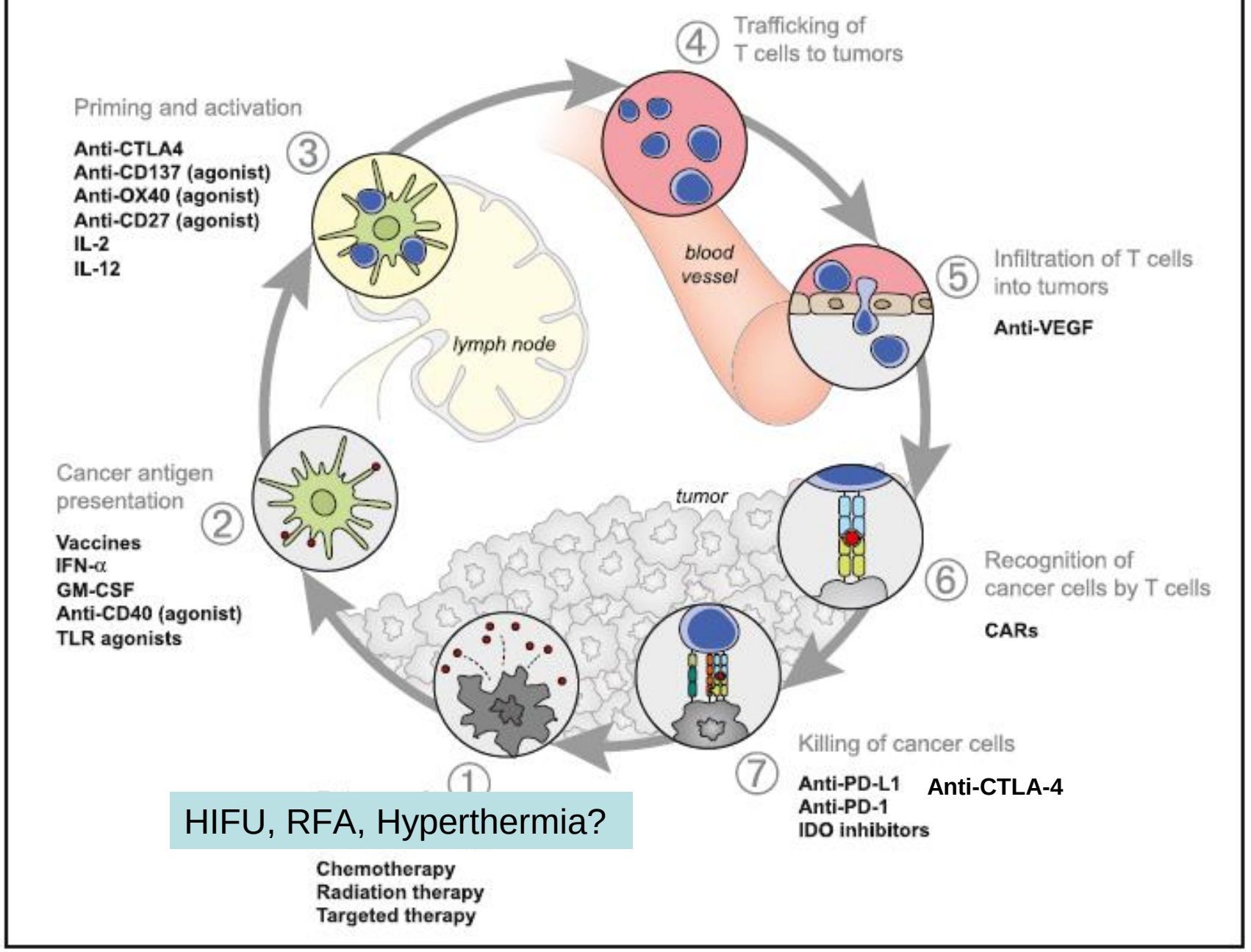
Schreiber et al. Immunity 2004

Mechanisms of Tumor Escape from Immune Responses

- Loss of MHC or TAP
- Loss of co-stimulatory molecules
- Antigenic variation
- Secretion of immunosuppressive factors
  - e.g. TGF-b, IL-10
- T cells don’t penetrate solid tumors
- Exhaustion of T cells
- T regulatory cells suppress anti-tumor responses

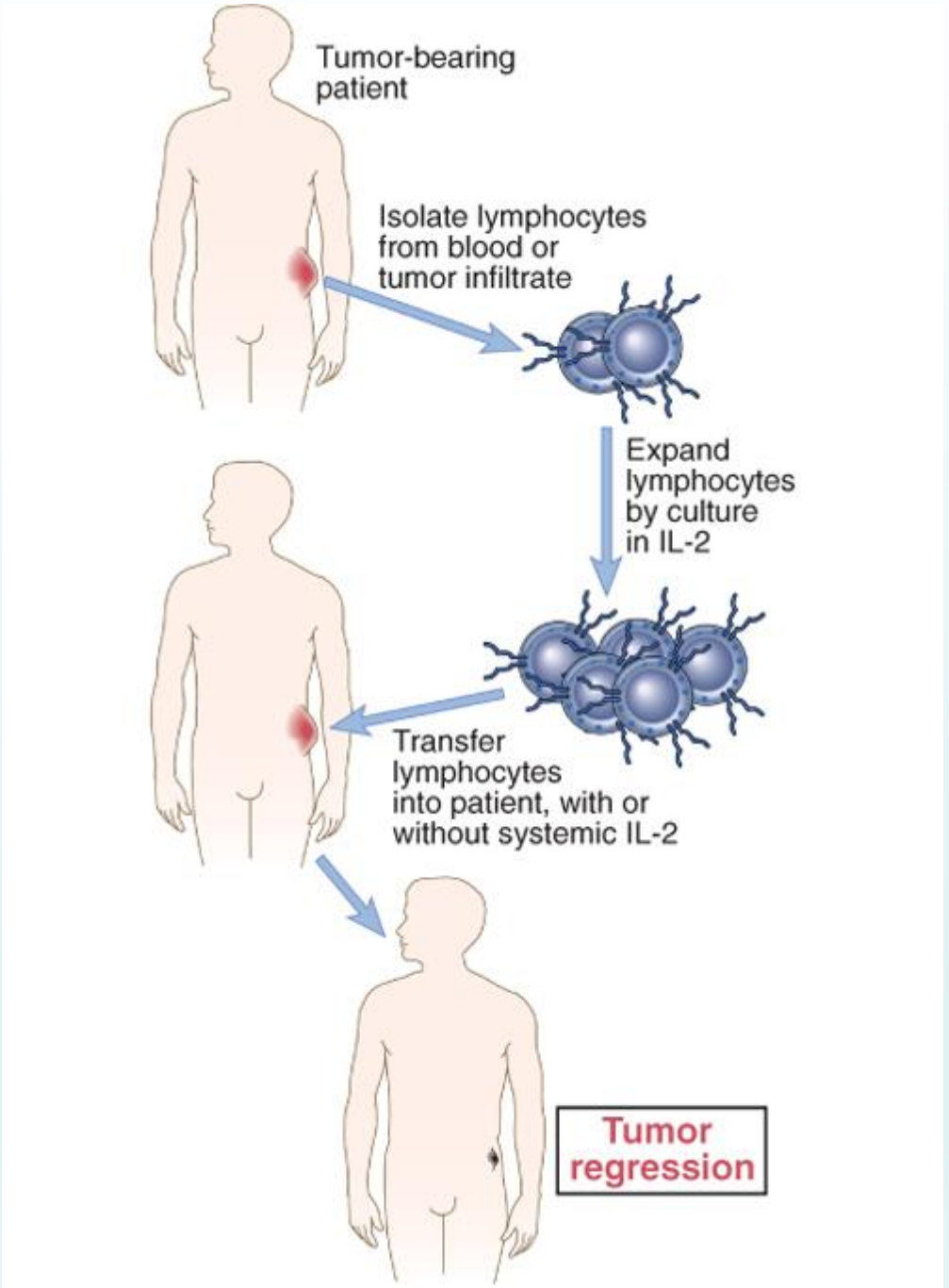


Chen and Mellman Immunity 39; 2013

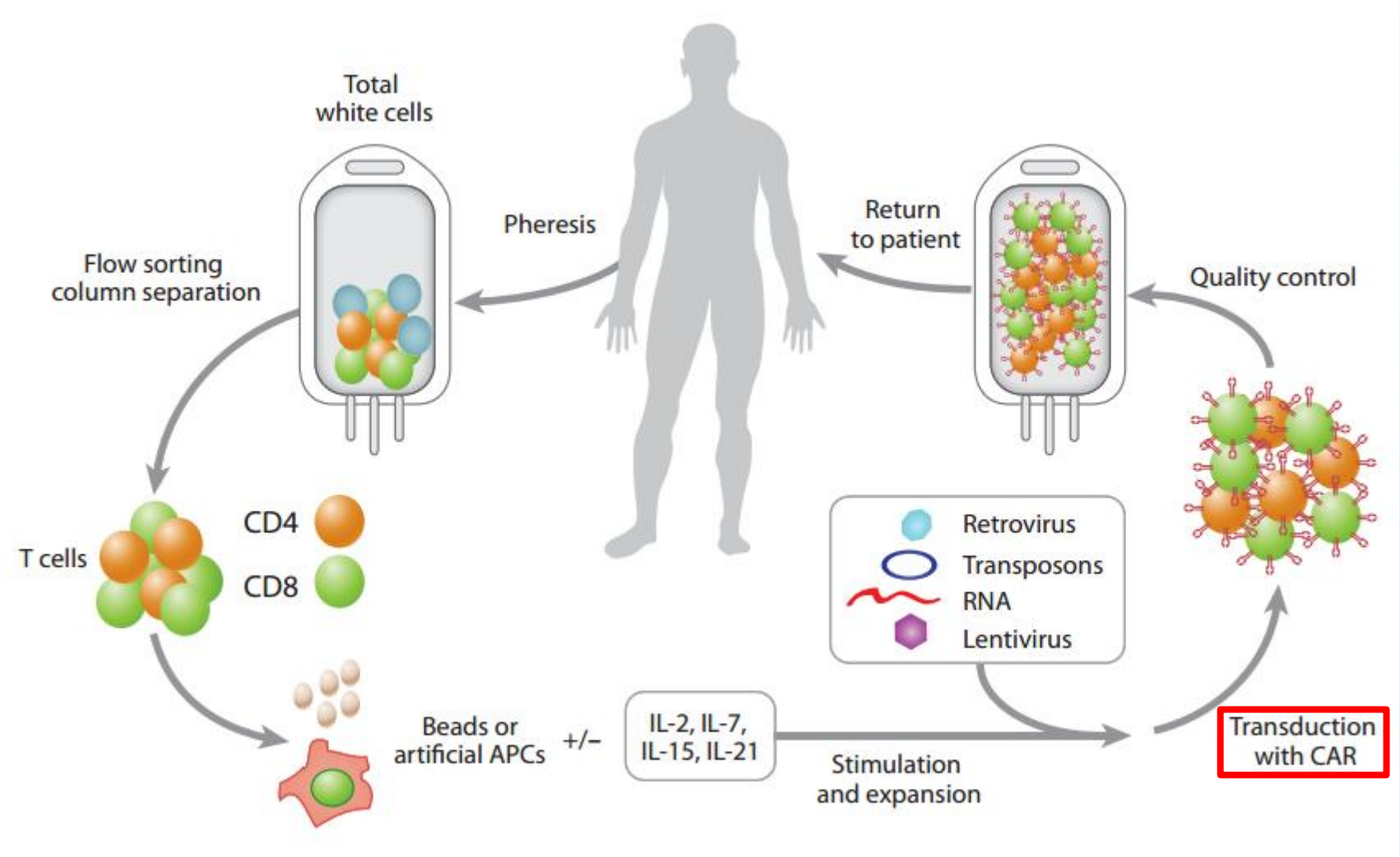


Chen and Mellman Immunity 39; 2013

Adoptive T cell Therapies Help to Overcome Some Barriers to Effective T Cell Control of Tumors.

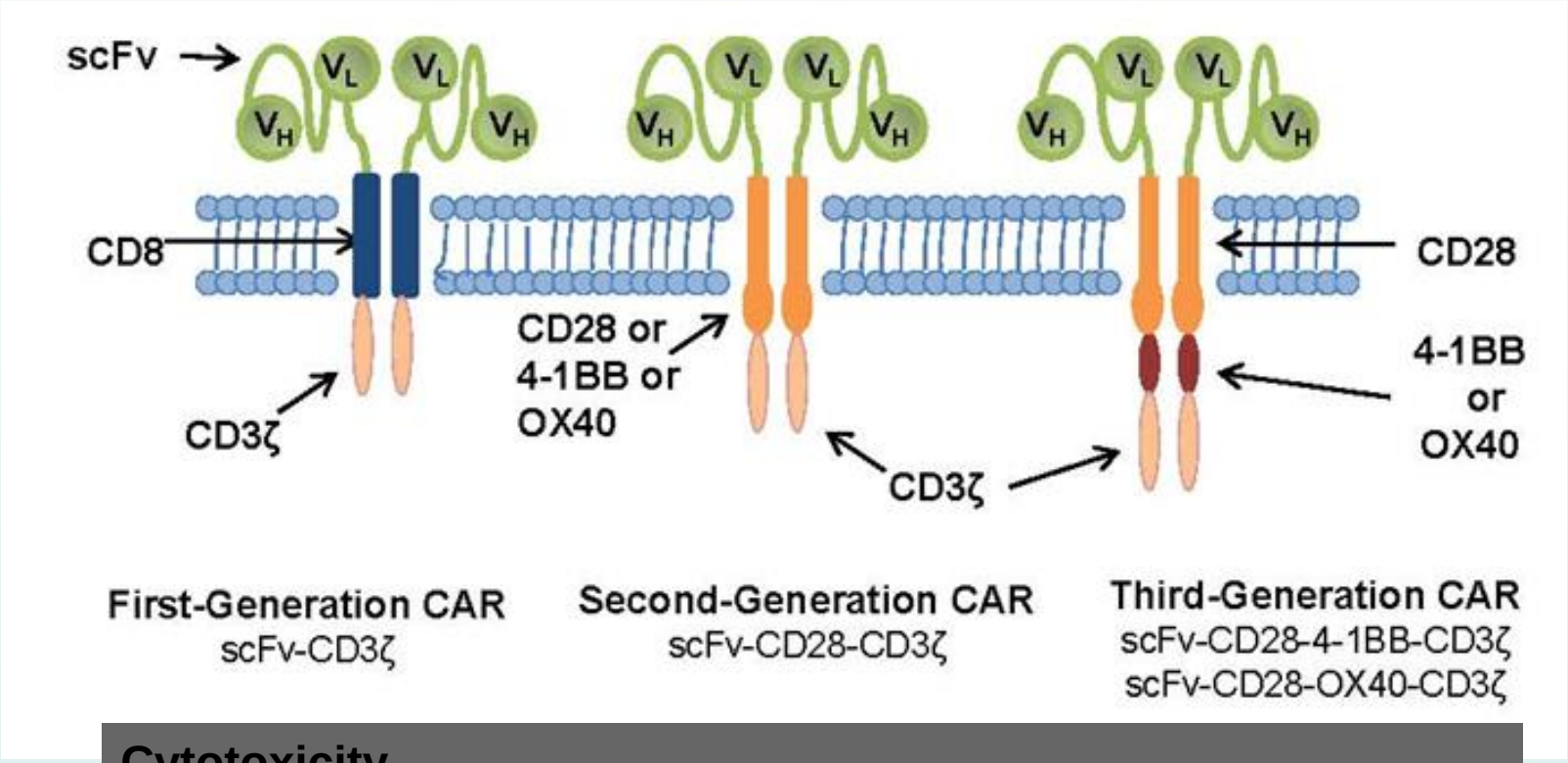


CAR T cell transfer immunotherapy

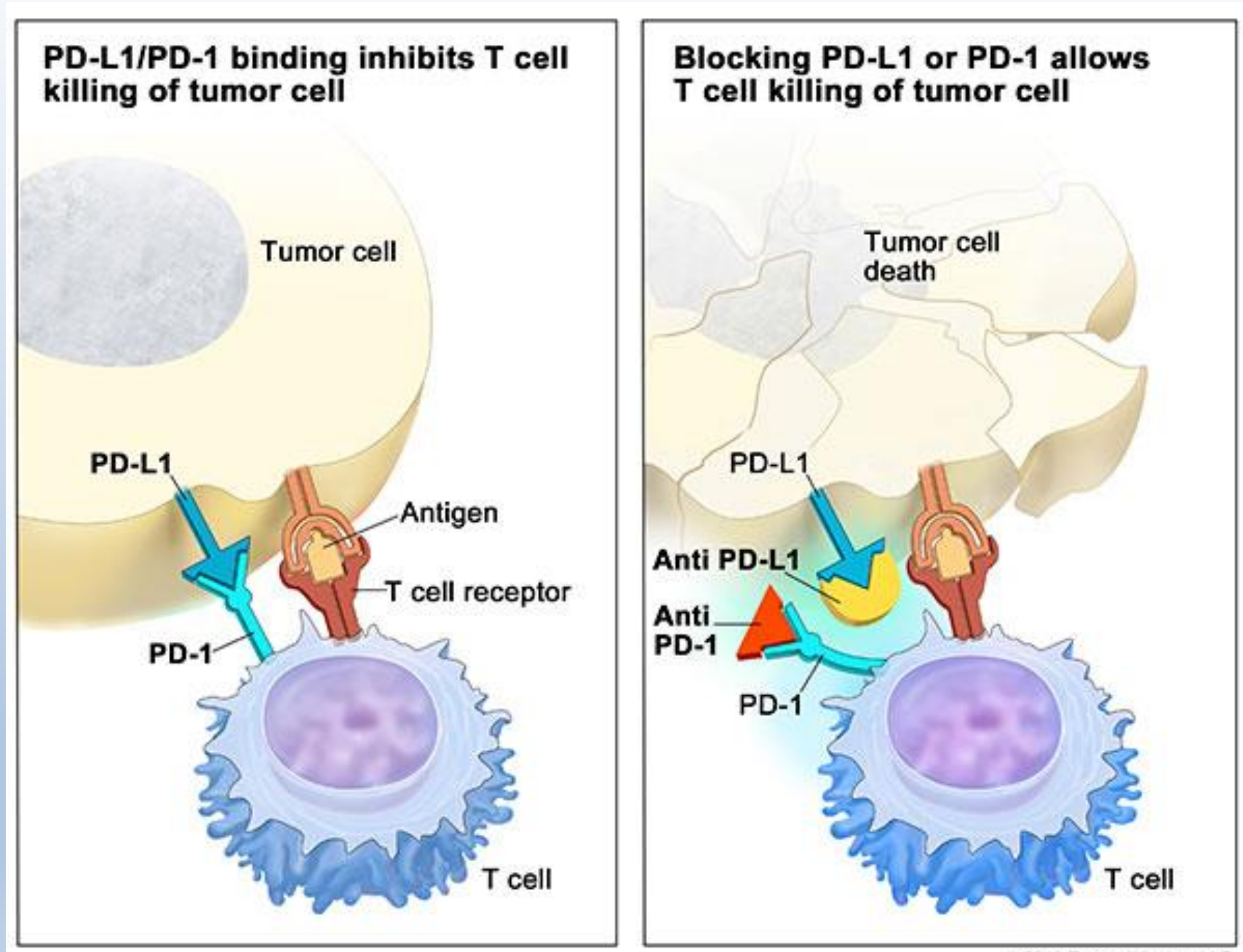


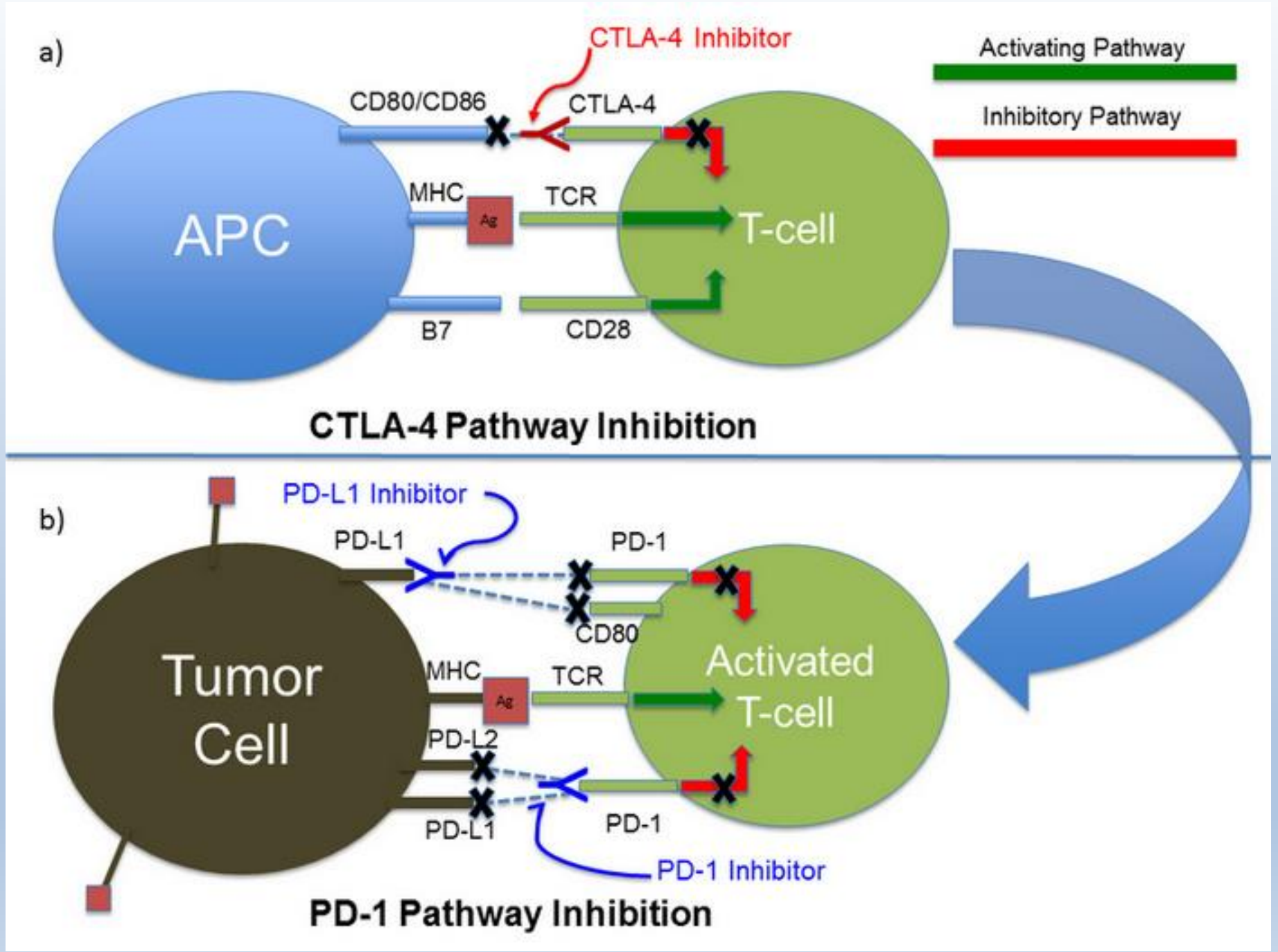
Barrett et al, Annu Rev Med, 2014

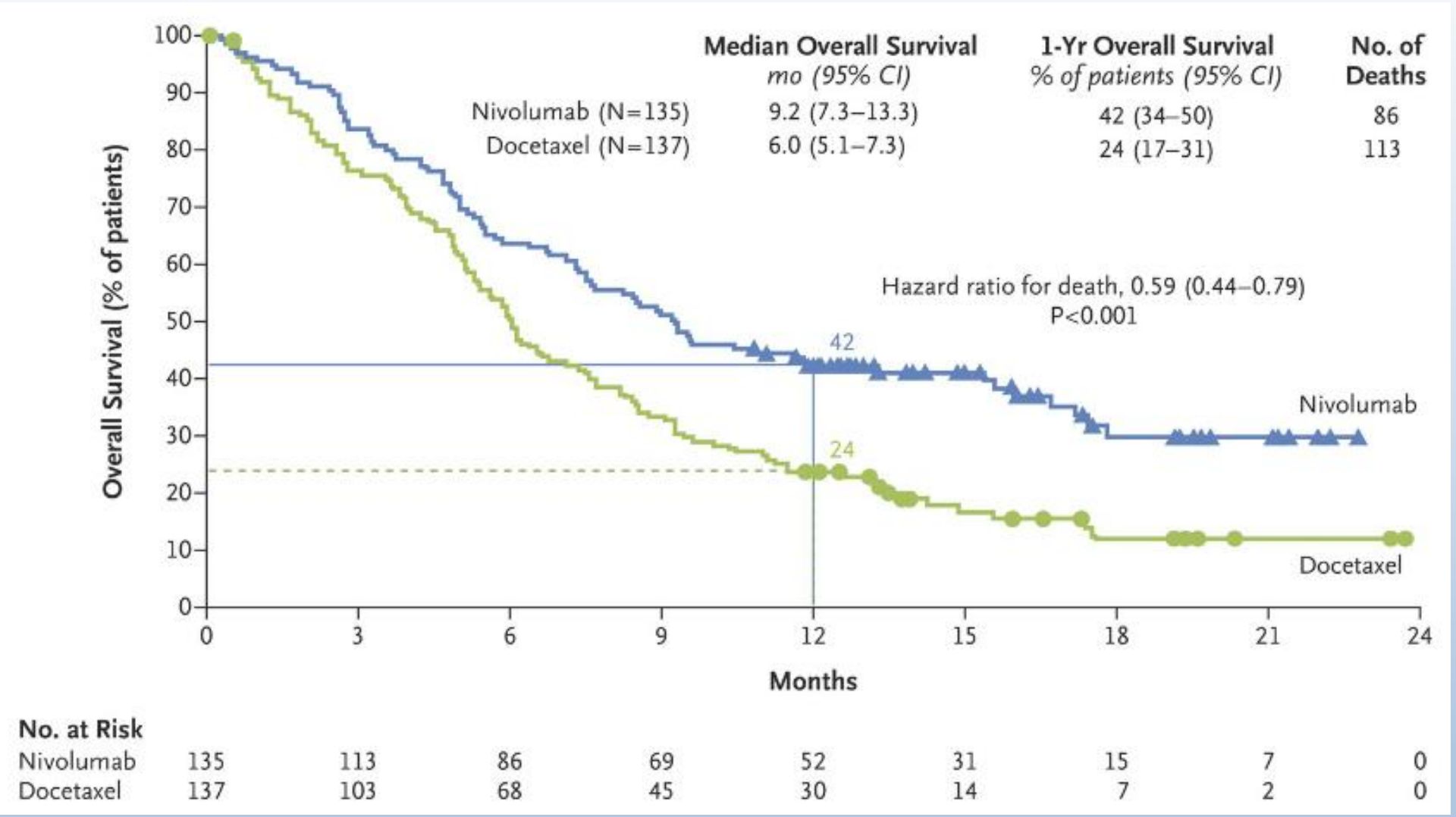
1st, 2nd, and 3rd generation CARs



Barrett et al, Annu Rev Med, 2014
Casucci et al, J Cancer, 2011
Park, Disc Med, 2010




a)
CTLA-4 Inhibitor
Activating Pathway
Inhibitory Pathway
CD80/CD86
CTLA-4
APC
MHC
Ag
TCR
T-cell
B7
CD28
CTLA-4 Pathway Inhibition
b)
PD-L1 Inhibitor
PD-L1
PD-1
CD80
Tumor Cell
MHC
Ag
TCR
Activated T-cell
PD-L2
PD-L1
PD-1
PD-1 Inhibitor
PD-1 Pathway Inhibition

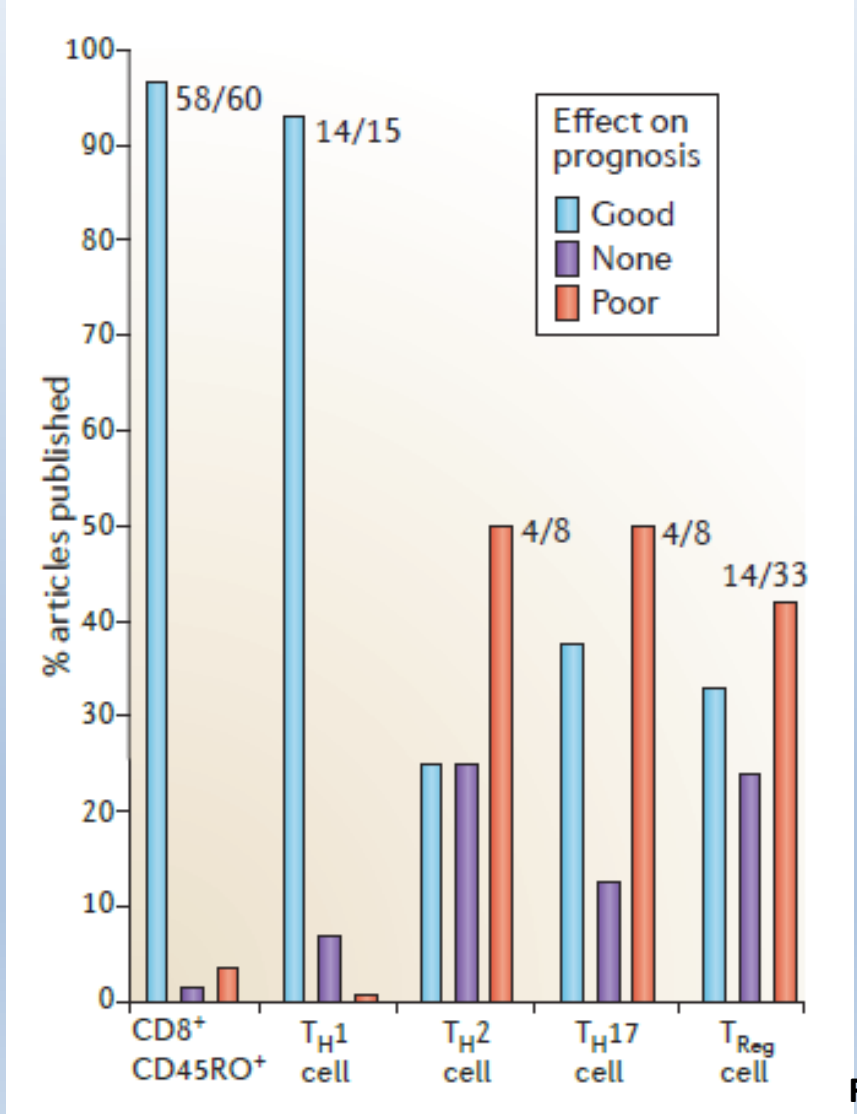


Survival with nivolumab significantly better survival vs. docetaxel in patients with previously treated squamous-cell NSCLC

$P < 0.001$

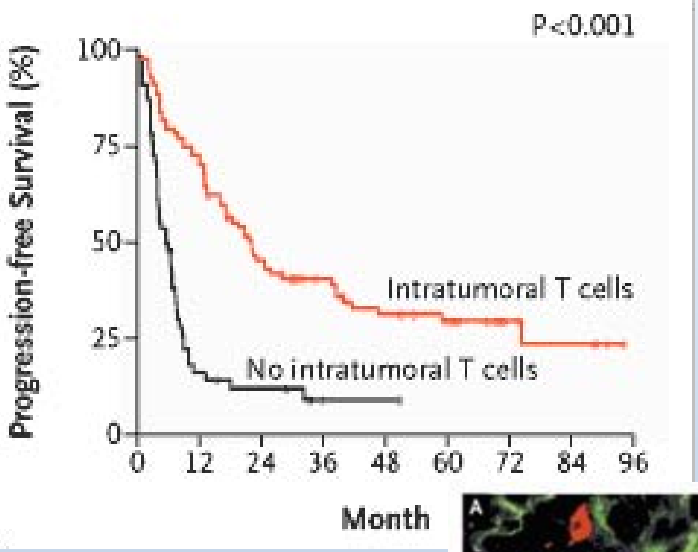
Brahmer et al, NEJM 2015

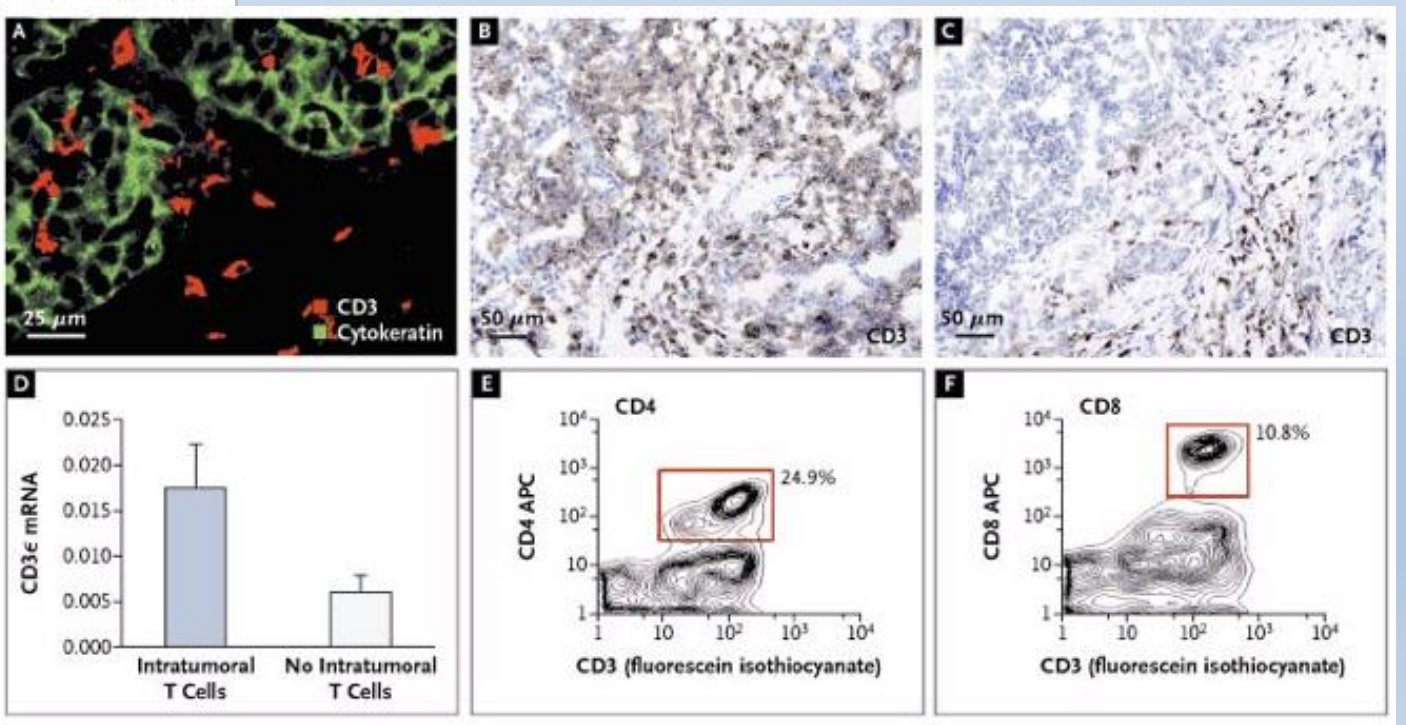
Different immune cell infiltrates are associated with good or poor prognosis



Fridman/Galon Nat Rev Cancer 12 (2012)

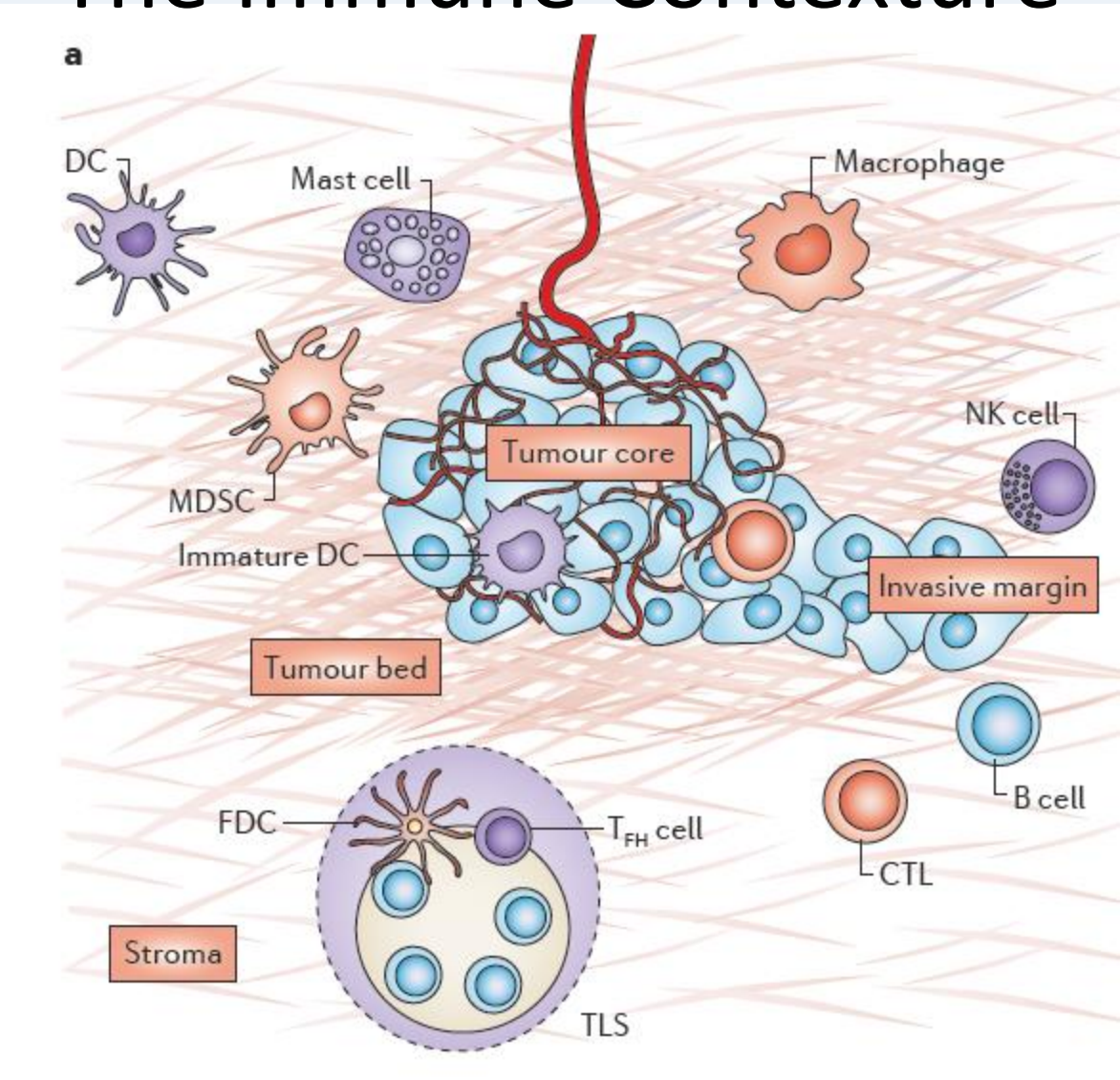
Tumor-infiltrating lymphocytes-Correlation with survival in ovarian cancer patients



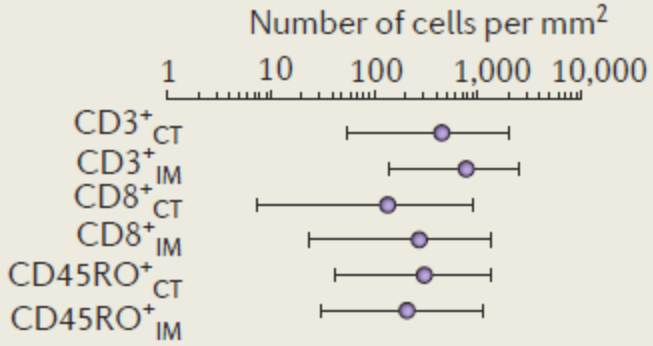


Zhang et al. NEJM 348:203, 2003

The Immune Contexture



Fridman/Galon Nat Rev Cancer 12 (2012)

Immune contexture	Parameters: positive association with survival
Type	CTLs ($CD3^+CD8^+$)
	Memory T cells ($CD45RO^+$)
Location	Core of the tumour
	Invasive margin
Density	
Functional orientation	T_H1 cell-associated factors (IFNγ, IL-12, T-bet and IRF1)
	Cytotoxic factors (granzymes, perforin and granulysin)
	Chemokines (CX3CL1, CXCL9, CXCL10, CCL5 and CCL2)
	T_H17 cells, T_{Reg} cells and T_H2 cells have a variable effect on survival, depending on tumour type
TLS	Presence and quality

Fridman/Galon Nat Rev Cancer 12 (2012)

Cancer classification using the “Immunoscore”: a worldwide task force

- Currently histopathological stage scoring is based on TNM
- Patients of same stage can have very different outcomes
- Little value in predicting response to therapy
- Long-term outcome may involve immune response
- “Immunoscore”= immunological biomarker

Galon et al. J Trans Med, 2012

Vol. 11, 728–734, January 15, 2005 Clinical Cancer Research

Immune-Mediated Inhibition of Metastases after Treatment with Local Radiation and CTLA-4 Blockade in a Mouse Model of Breast Cancer

Sandra Demaria, Noriko Kawashima, Anne Marie Yang, Mary Louise Devitt, James S. Babb, James P. Allison, and Silvia C. Formenti

Annals of Oncology 24: 75–83, 2013
doi:10.1093/annonc/mds213
Published online 2 August 2012

Ipilimumab in combination with paclitaxel and carboplatin as first-line therapy in extensive-disease-small-cell lung cancer: results from a randomized, double-blind, multicenter phase 2 trial†

M. Reck[1*], I. Bondarenko[2], A. Luft[3], P. Serwatowski[4], F. Barlesi[5], R. Chacko[6], M. Sebastian[7], H. Lu[8], J. -M. Cuillerot[8] & T. J. Lynch[9]

Irradiation and anti–PD-L1 treatment synergistically promote antitumor immunity in mice

JCI, 2014

Liufu Deng,[1] Hua Liang,[1] Byron Burnette,[1] Michael Beckett,[1] Thomas Darga,[1] Ralph R. Weichselbaum,[1] and Yang-Xin Fu[2]

[1]Department of Radiation and Cellular Oncology, The Ludwig Center for Metastasis Research, and [2]Department of Pathology, University of Chicago, Chicago, Illinois, USA.

Am J Clin Oncol. 2015 Feb;38(1):90-7. doi: 10.1097/COC.0b013e3182868ec8.

Immune-priming of the Tumor Microenvironment by Radiotherapy: Rationale for Combination With Immunotherapy to Improve Anticancer Efficacy.

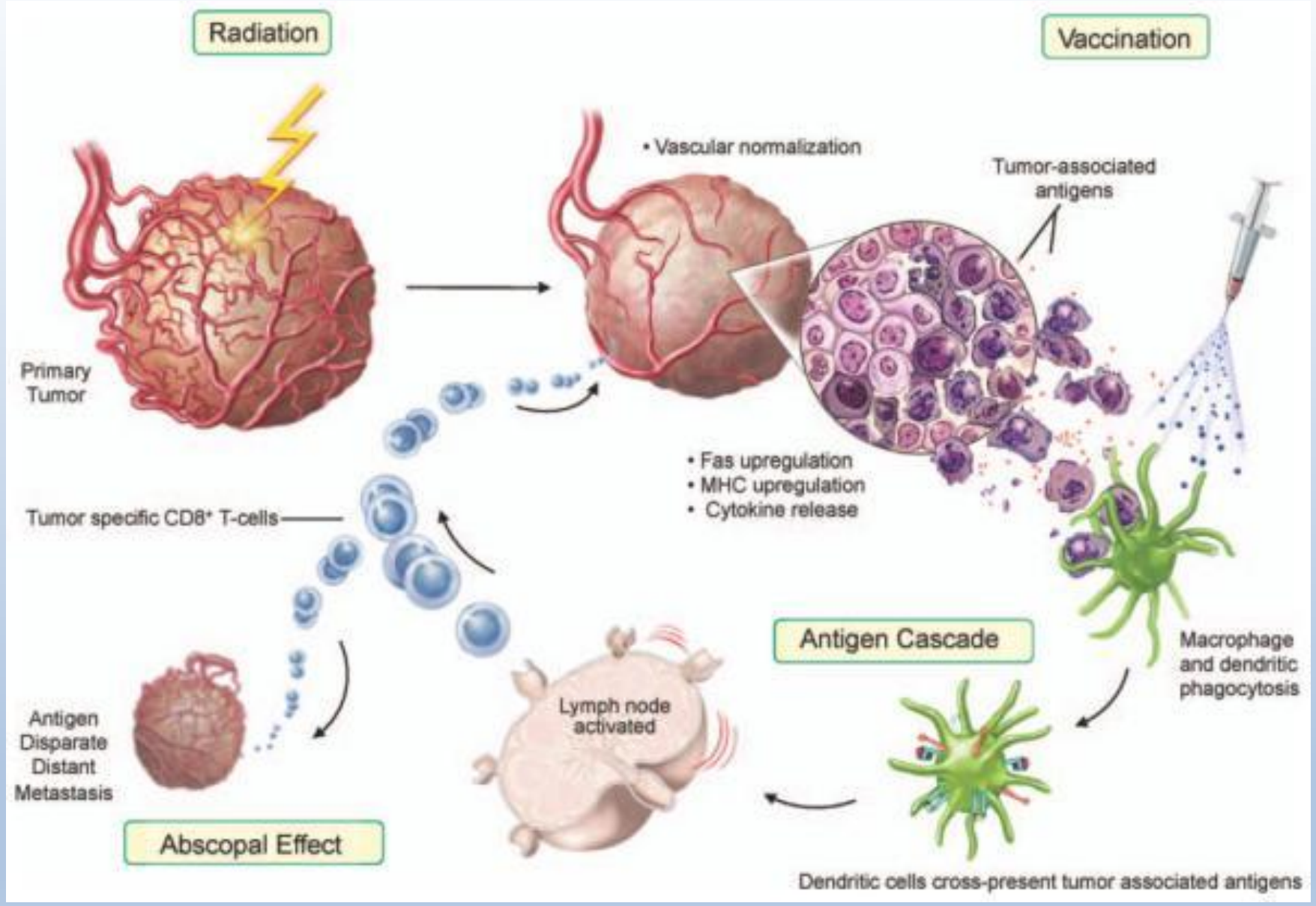
Shahabi V[1], Postow MA, Tuck D, Wolchok JD.

International Journal of Radiation Oncology biology • physics

www.redjournal.org

Anti-PD-1 Blockade and Stereotactic Radiation Produce Long-Term Survival in Mice With Intracranial Gliomas

Zeng et al, 2013



Mansoor M. Ahmed et al., Immunobiology of Radiotherapy: New Paradigms. Radiation Research, 2014.

A growing awareness of problems in reproducibility of pre-clinical research, including cancer research

***NATURE* | PERSPECTIVES OPEN**

•A call for transparent reporting to optimize the predictive value of preclinical research: **Story C. Landis et al.,** *Nature* **490**, 2012

"We recognize that achieving a meaningful improvement in the quality of reporting will require a concerted effort by investigators, reviewers, funding agencies and journal editors. Requiring better reporting of animal studies will raise awareness of the importance of rigorous study design to accelerate scientific progress."

Preclinical Data on Efficacy of 10 Drug-Radiation Combinations: Evaluations, Concerns, and Recommendations. Helen B. Stone , Eric J. Bernhard, C. Norman Coleman , James Deye , Jacek Capala, James B. Mitchell and J. Martin Brown

BACKGROUND: Clinical testing of new therapeutic interventions requires comprehensive, high-quality preclinical data. Concerns regarding quality of preclinical data have been raised in recent reports. This report examines the data on the interaction of 10 drugs with radiation and provides recommendations for improving the quality, reproducibility, and utility of future studies.

CONCLUSIONS: There is a need for improved experimental design, execution, and reporting of preclinical testing of agents that are candidates for clinical use in combination with radiation.

Improved design, execution, common measures of enhancement, and consistent interpretation of preclinical studies of drug-radiation interactions will provide rational guidance for prioritizing drugs for clinical radiotherapy trials and for the design of such trials.

The Importance of Dosimetry Standardization in Radiobiology

Marc Desrosiers, Larry DeWerd, James Deye, Patricia Lindsay, Mark K. Murphy, Michael Mitch, Francesca Macchiarini, Strahinja Stojadinovic, and Helen Stone. Journal of Research of the National Institute of Standards and Technology, 2013

1) Radiation equipment and methods are increasing in variety and complexity.
2) Radiation biologists rarely receive training in radiation dosimetry.
3) Radiation biologists usually use irradiation equipment dedicated to research that is not shared with and calibrated by their clinical colleagues.
4) Radiobiologists now rarely work with radiation physicists as part of their joint routine duties, and there are fewer radiation physicists who are trained in the unique characteristics of the equipment used and problems involved in performing dosimetry in support of radiation biology.

As with the collaboration between the biologist and statistician, which aids in determining the required sample size of the experiments, the biologist-physicist collaboration can aid in determining the accuracy and precision required by a given experimental design and the methods needed to achieve these.