

**AEI / University of Chicago Law School Conference**

**Oncology Drug Development: Rethinking FDA Oversight**

**Thursday March 13, to Friday March 14, 2008, AEI, Washington, DC**

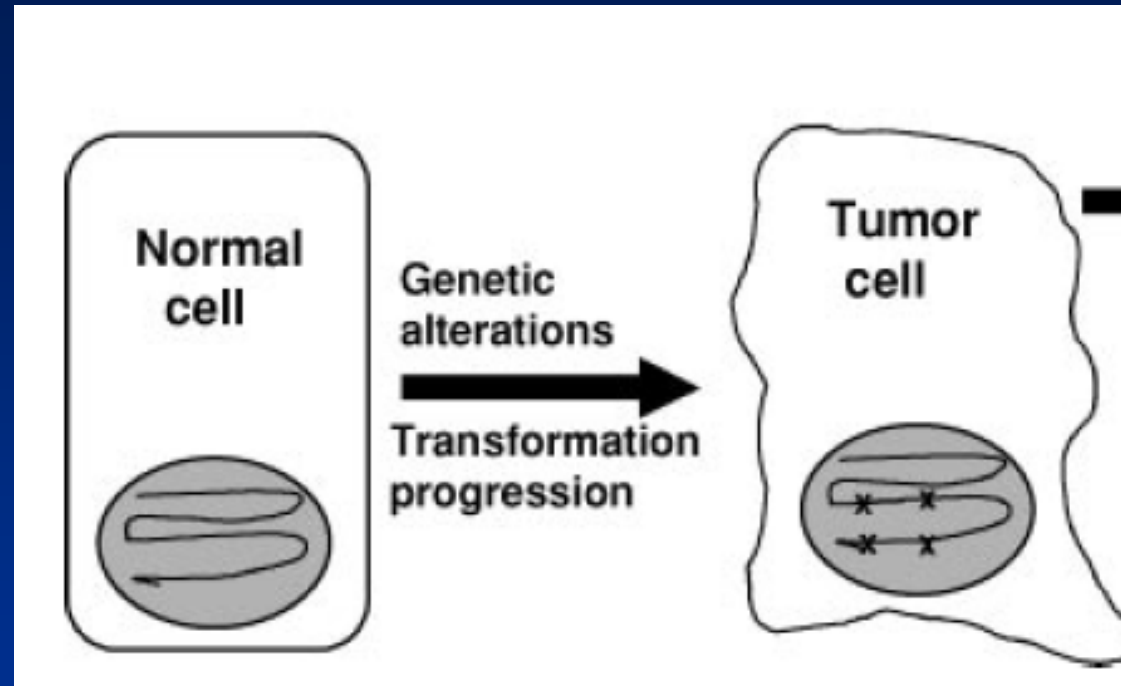
# **Cancer Immunotherapy:**

**Development at the Intersection of  
Science, Economics and Regulation**

**John E. Calfee, Ph.D.  
American Enterprise Institute**

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The George Washington University  
School of Medicine and Health Sciences**

# Normal Cell → Cancer Cell

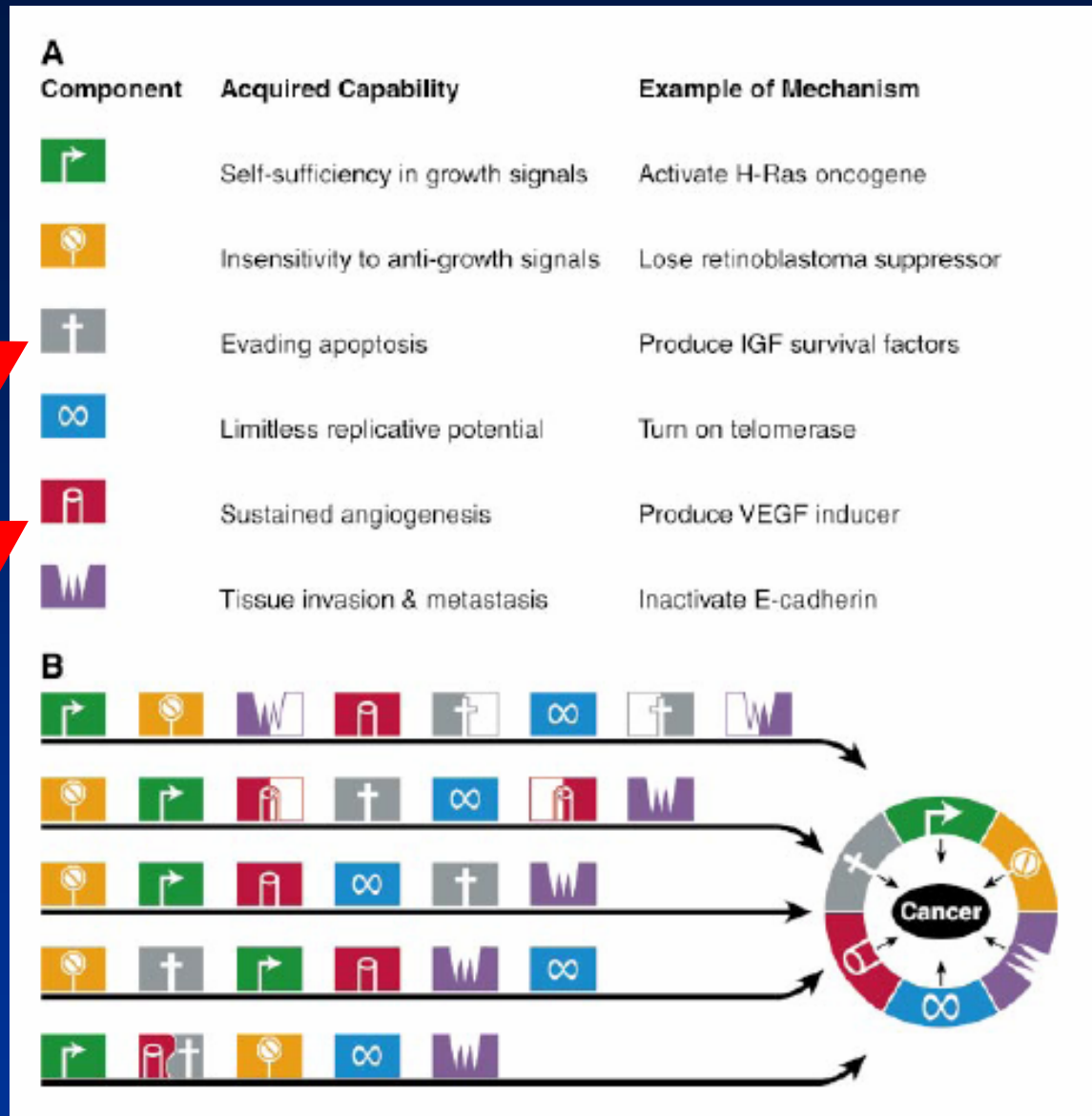


Pardoll, DM. Does the immune system see tumors as foreign or self? *Annu. Rev. Immunol.* 2003;21:807-839.

# Hallmarks of Cancer

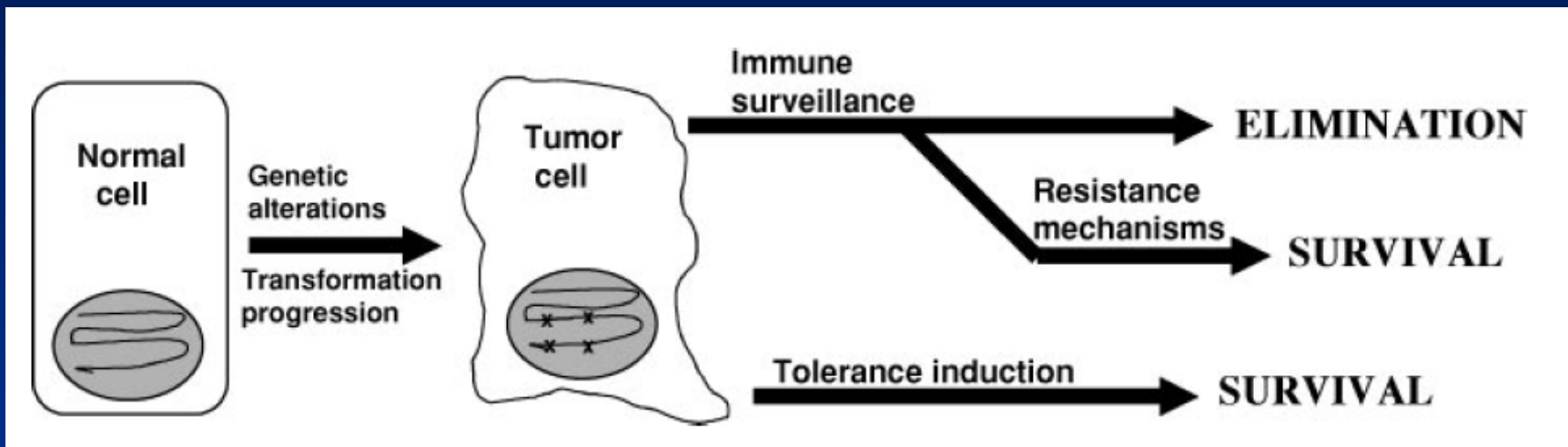
Most cytotoxic chemotherapies

e.g. Avastin (Bevacizumab)



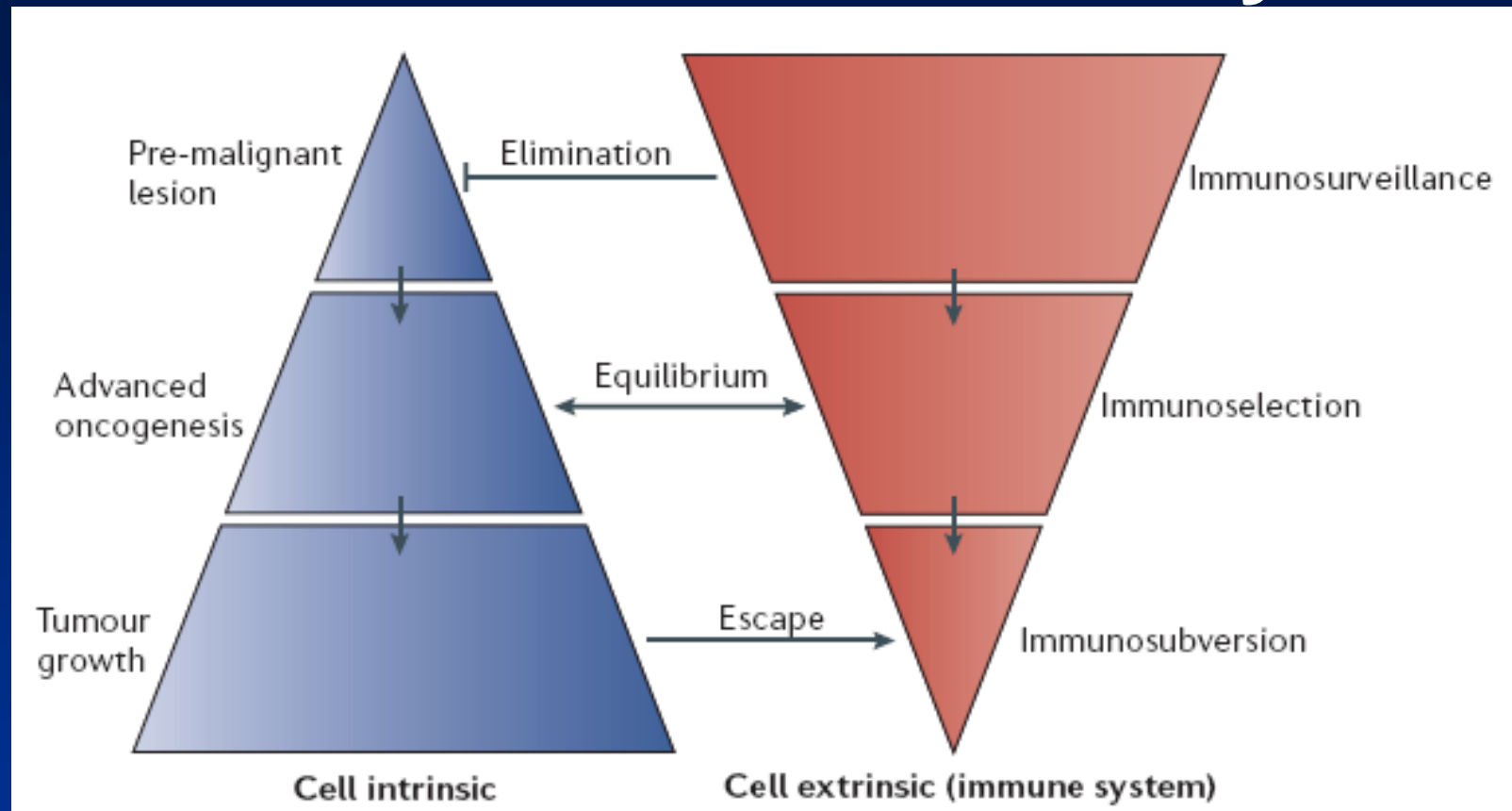
Hanahan D & Weinberg R. The hallmarks of cancer. Cell. 2000;100:57-70.

# Cancer and the Immune System



Pardoll, DM. Does the immune system see tumors as foreign or self? *Annu. Rev. Immunol.* 2003;21:807-839.

# Cancer and the Immune System



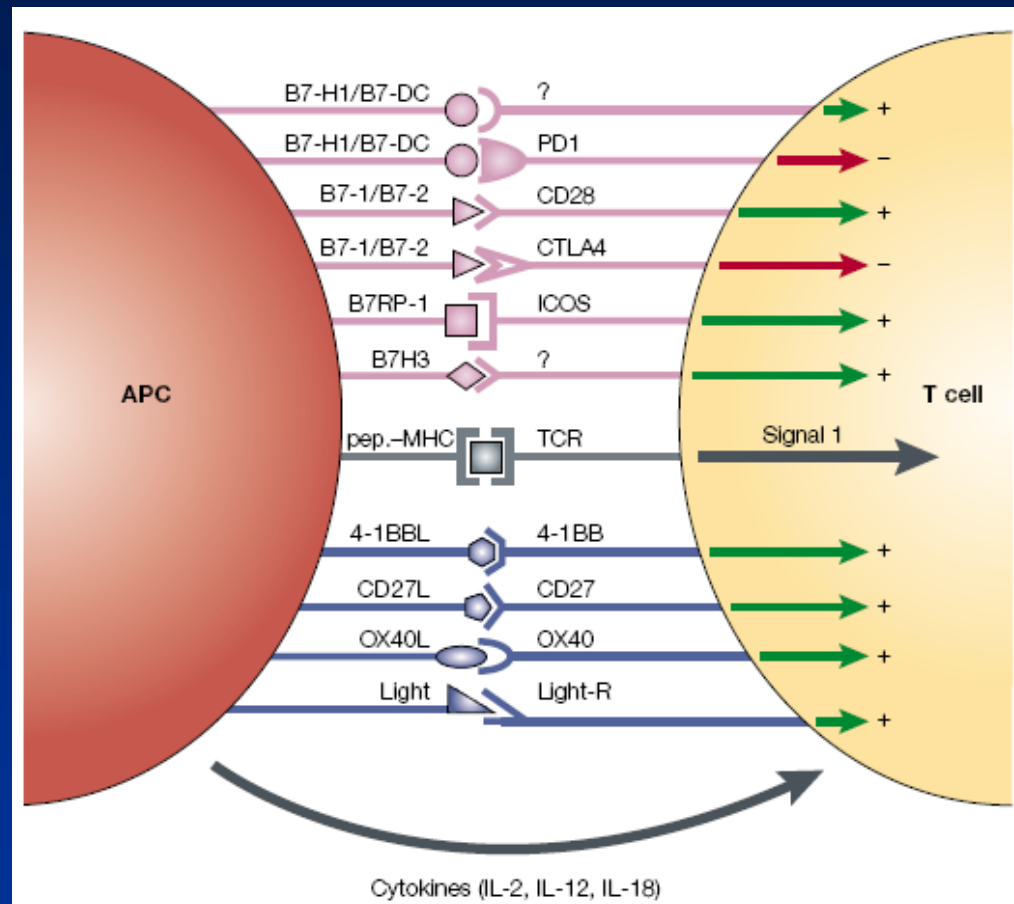
▪Zitvogel L, Tesniere A & Kroemer G. Cancer despite immunosurveillance: immunoselection and immunosubversion. *Nat. Rev. Immunol.* 2006;6:715-727.

▪Koebel CM, Vermi W, Swann JB, Zerafa N, Rodig SJ, Old LJ, Smyth MJ & Schreiber RD. Adaptive immunity maintains occult cancer in an equilibrium state. *Nature.* 2007;450:903-908.

# What Is “Active” Cancer Immunotherapy?

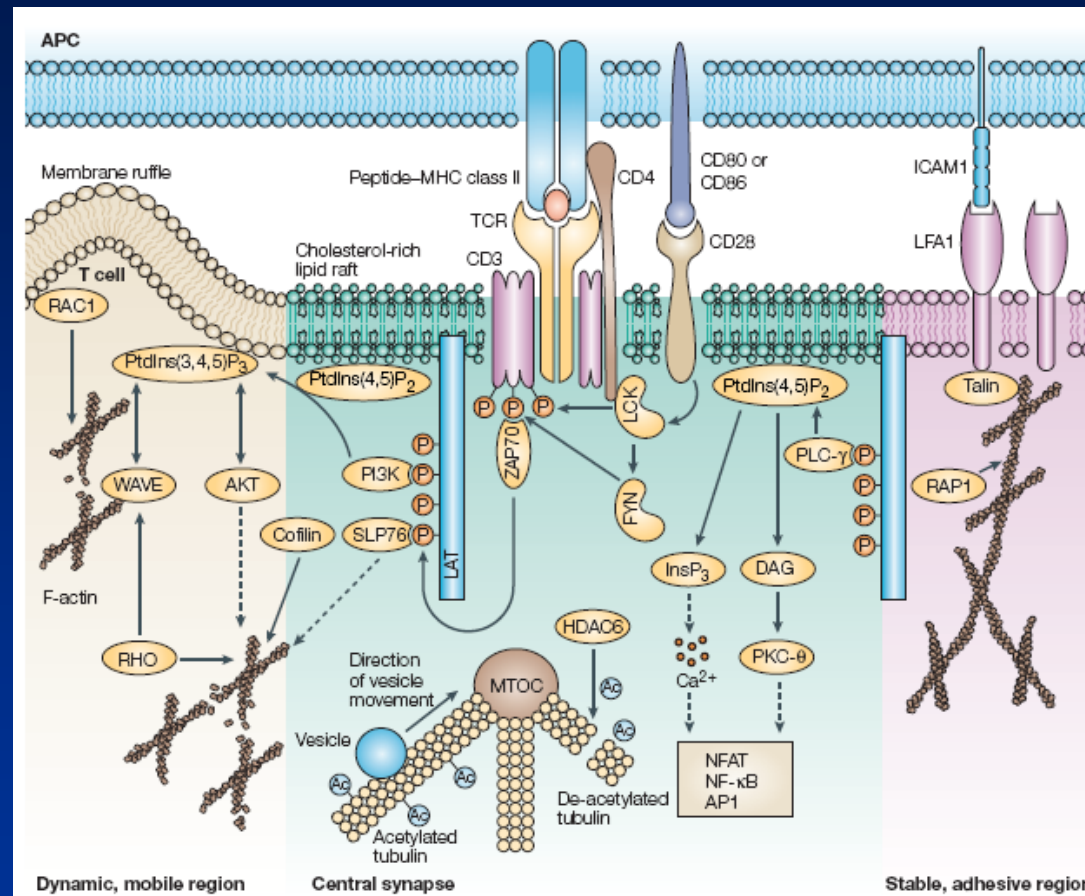
- e.g. Therapeutic cancer vaccines
- Aim: energize the body’s immune system to recognize and attack established tumors that are otherwise ignored by physiologic immune surveillance.
- Potential to combat nearly any type of established tumor

# The immune system is elegantly regulated



Pardoll DM. Spinning molecular immunology into successful immunotherapy. *Nat. Rev. Immunol.* 2002;2:227-238.

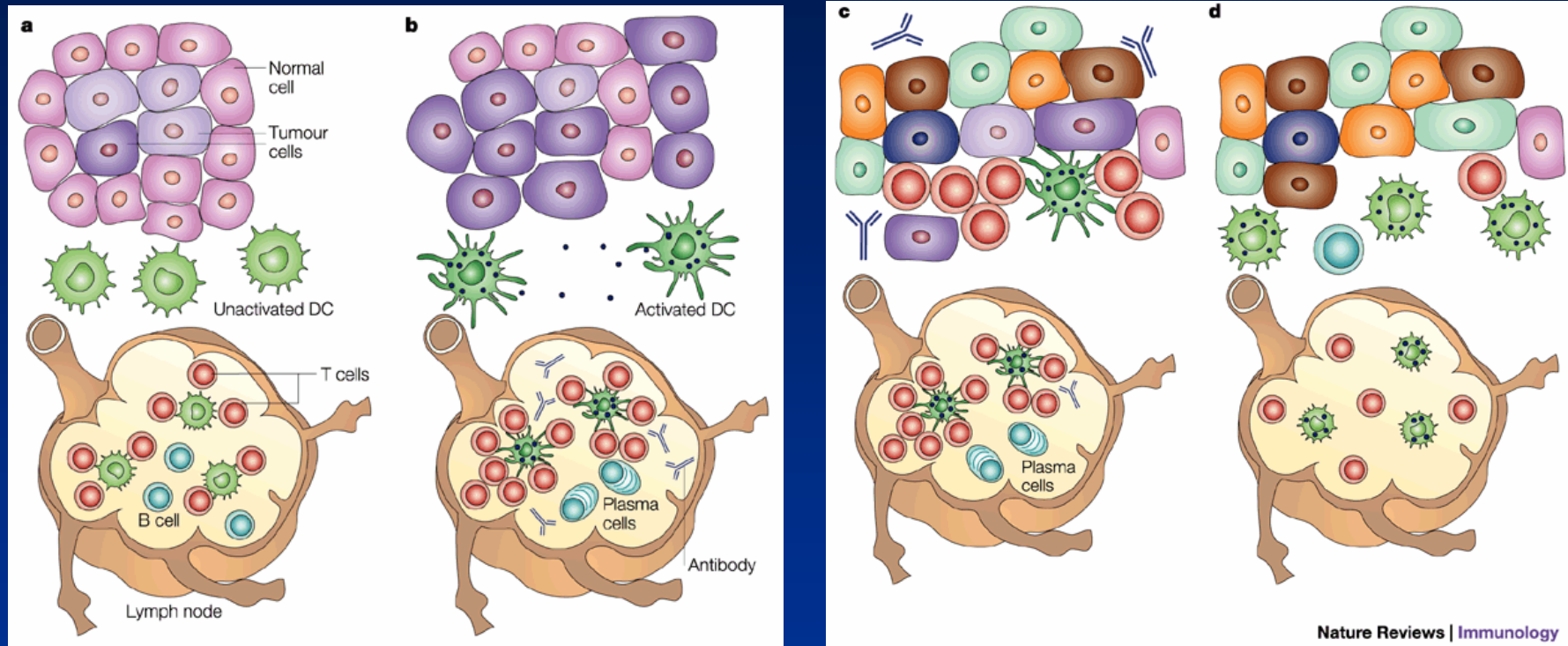
# The immune system is elegantly regulated



Friedl P, den Boer A & Gunzer M. Tuning immune responses: diversity and adaptation of the immunologic synapse. *Nat. Rev. Immunol.* 2005;5:532-545

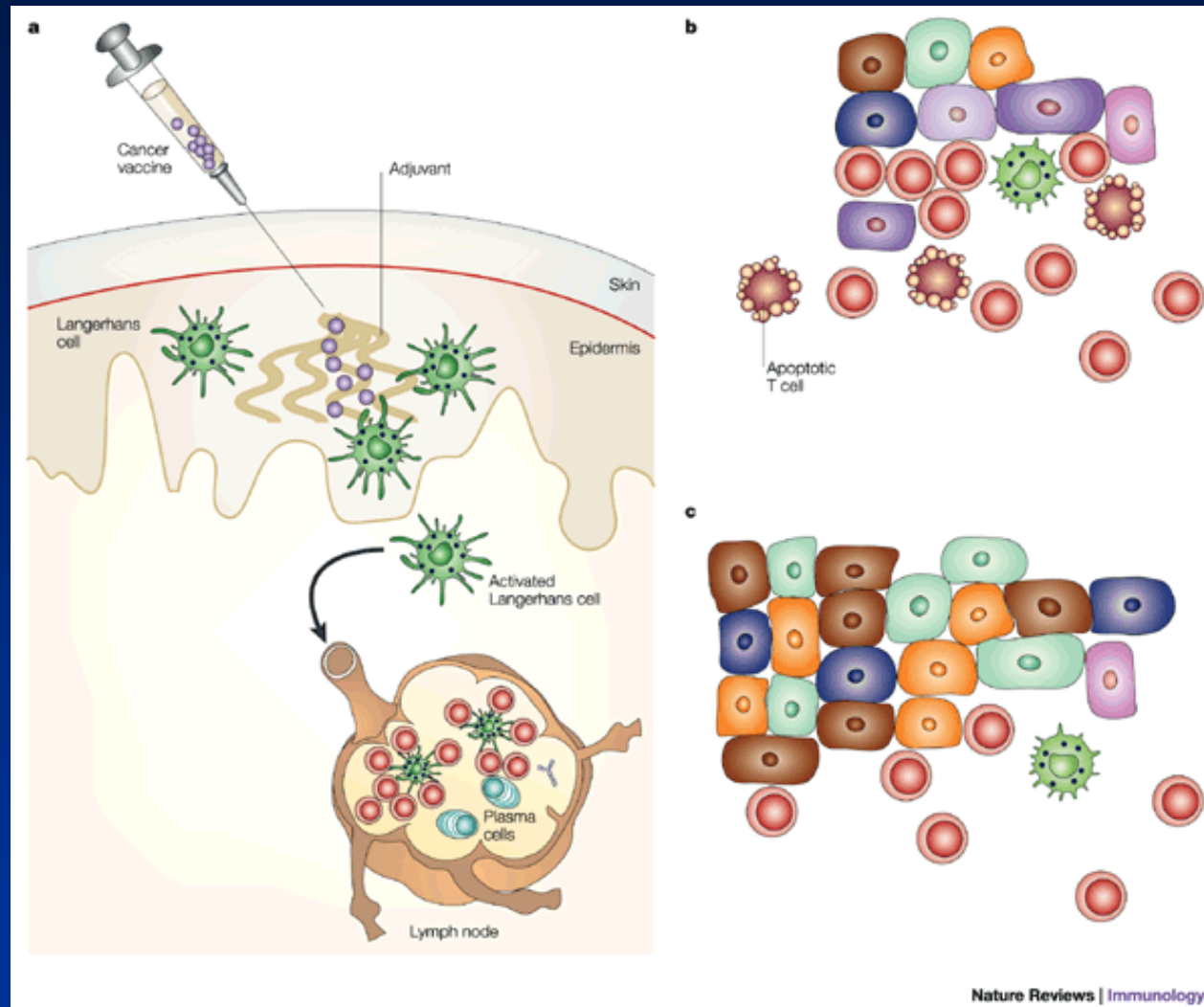
# Cancer and the Immune System

## Without Therapy



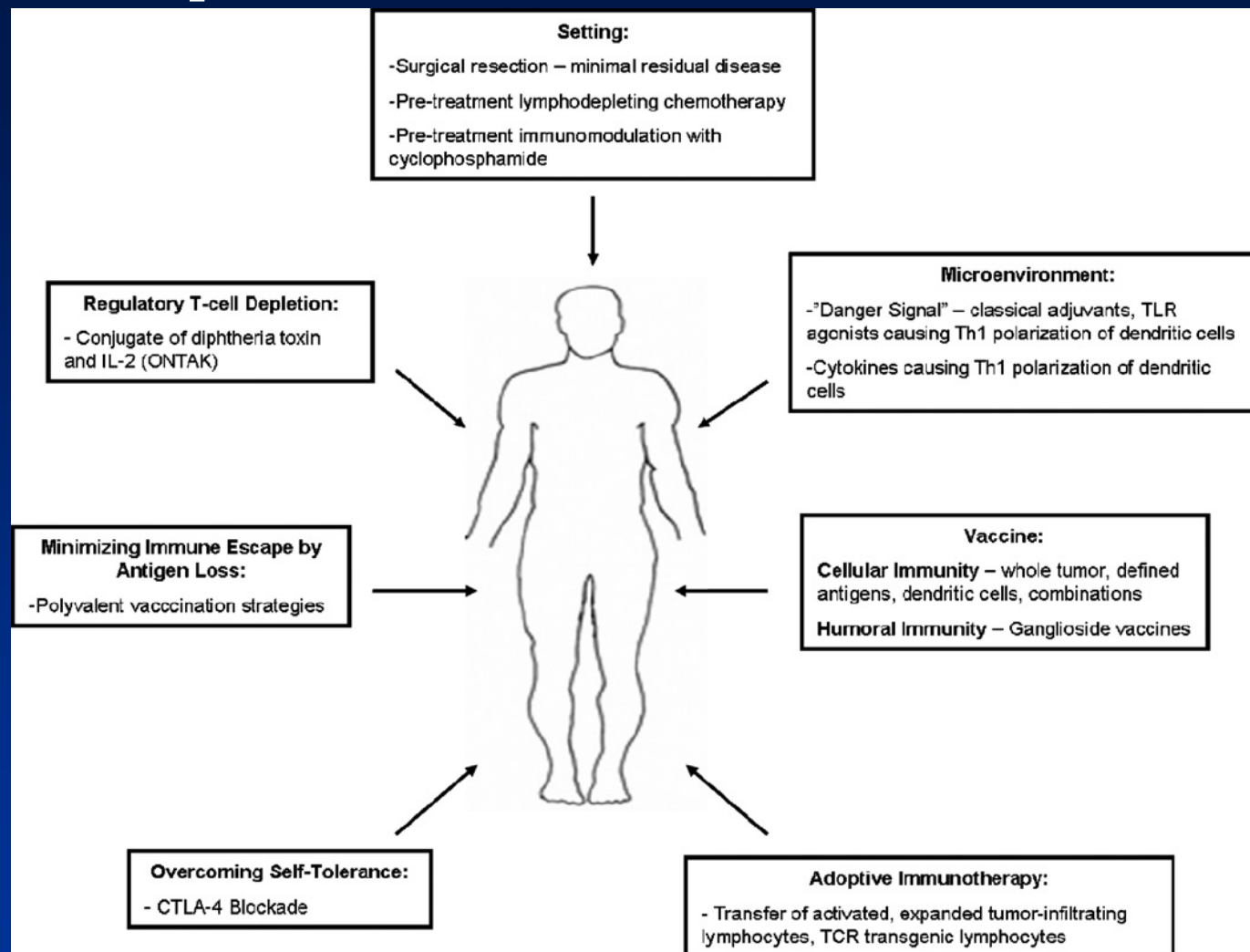
Finn OJ. Cancer vaccines: between the idea and the reality. *Nat. Rev. Immunol.* 2003;3:630-641.

# Therapeutic Cancer Vaccines



Finn OJ. Cancer vaccines: between the idea and the reality. *Nat. Rev. Immunol.* 2003;3:630-641.

# Therapeutic Cancer Vaccines



Terando AM, Faries MB & Morton DL. Vaccine therapy for melanoma: current status and future directions. *Vaccine*. 2007;25S:B4-B16.

# How are cancer vaccines likely to work in practice?

- In combination with other therapeutics
  - Dominant role for combination therapy is not surprising
    - HIV — coronary heart disease — diabetes
- In oncology, combination therapy has long been important, is increasingly common
- This reflects the nature of cancer itself
  - Tumors employ multiple defenses, calling for multifactorial attacks
- Combination therapy is probably even more important for vaccines than for traditional therapy
- In sequence with chemo and other therapeutics
  - Vaccines may make chemo work better
  - Chemo may pave the way for vaccines to work better

# How are cancer vaccines likely to work in practice? (cont.)

- Vaccines may work better against early-stage cancer
  - Cancer treatment can weaken the immune system
  - Cancer itself can weaken the immune system
- Traditional markers of progress may be inadequate
- Most of this has implications for vaccine development and especially FDA regulation

# Economic challenges

- Just a word on economics
  - Financial risk: an oft-solved problem
  - Dealing with intellectual property among multiple firms (combination therapy, diagnostics and biomarkers, etc.)
  - Mounting trials of combination therapy involving more than one firm

# FDA challenges

- Designing clinical trials for combination therapy
- Endpoints for clinical trials
- Adaptive clinical trials
- Bayesian analysis of clinical trial data
- Taking account of patient preferences

# Designing clinical trials for combination therapy

- Traditional trials for FDA approval test a cancer drug against a placebo, standard therapy, or in combination with the standard therapy
- Clinical practice often involves much more combination therapy
- Post-approval drug testing reflects this
- Drugs that undergo traditional testing regimens may fail to reveal that their benefits clearly exceed risks

# Clinical trial endpoints and biomarkers

- Tumor regression and other common endpoints may not be good markers of the effectiveness of therapeutic vaccines
- Vaccines tend to provide mortality benefits even in the absence of significant effectiveness in terms of traditional measures
  - Provenge (recently denied approval) is one of many examples
- Mortality endpoints require longer trials
  - Especially against early-stage cancer
  - Or when rescue therapy keeps death at bay

# Adaptive clinical trials

- How can we take advantage of what we learn during a trial in order to make that trial work better?
- Much discussed at FDA and elsewhere: Critical Path Initiative, etc.
- This is even more pressing for vaccines than for traditional therapeutics

# Bayesian analysis of clinical trial data

- Trials sometimes something really unexpected, such as exceptional response among an identifiable group of patients
- It would be nice to take advantage of that information without having to run another trial
- Reverend Bayes can help
- Again: much discussed

# Taking account of patient preferences

- FDA can take advantage of the tendency for vaccines to be less toxic than traditional therapies
- FDA staff face potent incentives to be “too cautious,” because Type 1 errors (“public errors” in which an approved drug reveals serious problems) are punished far more than Type 2 errors (“private errors” in which a useful drug is approved too slowly or not at all)
- Patient preferences for trade-offs between expected risks and benefits may differ from those of FDA staff and advisory committees

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