ASU Complex Adaptive Systems
ARIZONA STATE UNIVERSITY

BIO 302:
APRIL 2, 2015

WEEK 11, LECTURE 2:
SYSTEMIC TREATMENT OF CANCER: PHARMACOLOGIC, BIOLOGICAL AND IMMUNOTHERAPEUTIC TREATMENTS

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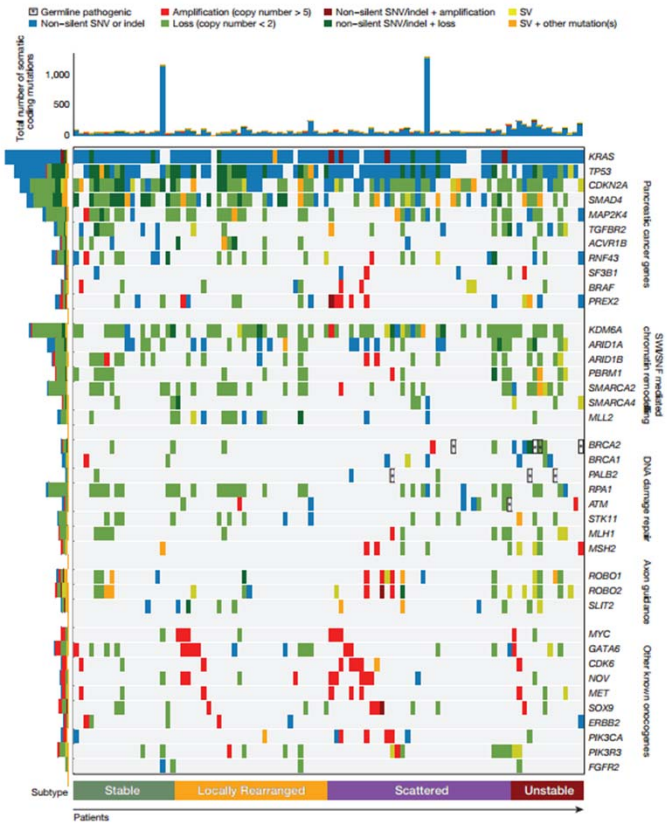
Tumor Cell Heterogeneity: The Omnipresent and Greatest Challenge in Cancer Therapy

Mutations in Key Genes and Pathways in 100 Pancreatic Ductal Adenocarcinomas



From: N. Waddell et al. (2015) Nature 518, 495

Cancer Rx: Ugly Realities

- in the majority of cancers the efficacy of single therapies is either short-lived or completely ineffective
- mutations that confer Rx resistance may pre-exist prior to treatment (intrinsic resistance) or arise as de novo mutations conferring selective survival during treatment (acquired resistance)
- mutations are typically present in multiple pathways and intrinsic and/or acquired mutations in non-targeted pathways will enable 'by-pass' signaling circuits to ensure tumor cell survival and create a domino (cascading) effect and broadening resistance spectrum

Challenges in Cancer Therapy

- heterogenous disease
  - how to select right Rx for right patient
- alterations in multiple molecular targets and pathways
  - how to design rational combination therapies
- ongoing clonal diversification with tumor progression and effect of Rx on clonal evolution
  - how to destroy multiple clones and/or stop clonal evolvability
- selective deregulation of growth controls in cancer cells versus replication still needed for production of normal cells (gut, bone marrow, hair)
  - how to minimize adverse events

The Biological Complexity of Cancer and the Design of Future Treatment Strategies

Formidable Performance Requirements

- hit all clones
- hit all clones in multiple metastases in multiple body locations
- hit all new emergent Rx-resistant clones

Design of Cancer Treatments to Hit Multiple Targets

- single drug that hits multiple clones and multiple signaling pathways
  - pharmacological promiscuity
  - very low probability of technical success

- http://www.tentonhammer.com/columns/gravity-well/having-my-cake-and-eating-it-too

Design of Cancer Treatments to Hit Multiple Targets

- multi-drug combinations
  - patient tolerance
  - cost
- may delay emergence of clone(s) with Rx-resistance to one or more drugs in combination

- high probability that such Rx-resistant variants will eventually emerge

but

  - Rx as selection pressure to generate these 'escape' clones

Are We Targeting the Right Cancer Cell Lineage with Current Cancer Drug Therapy Approaches?

Stem Cells and the Growth Dynamics of Normal Tissues

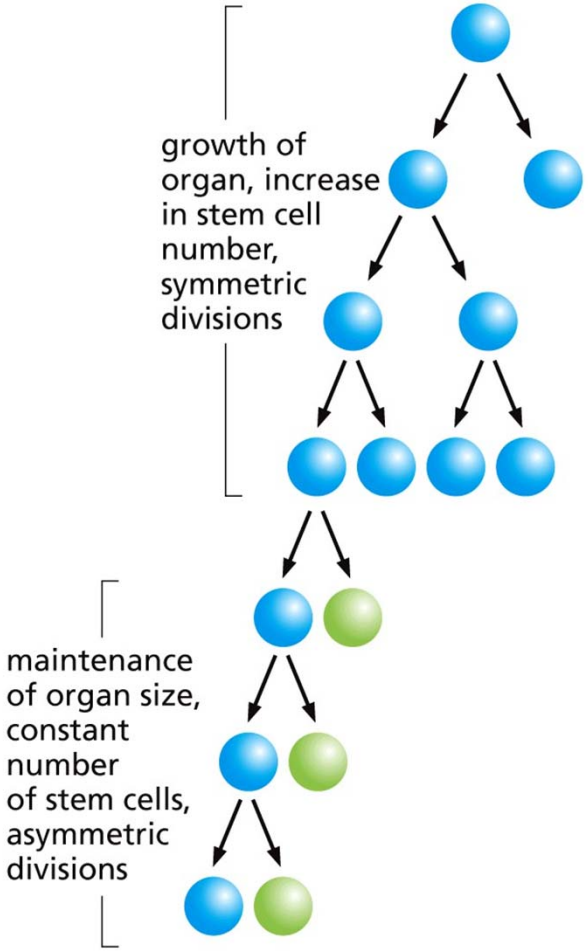
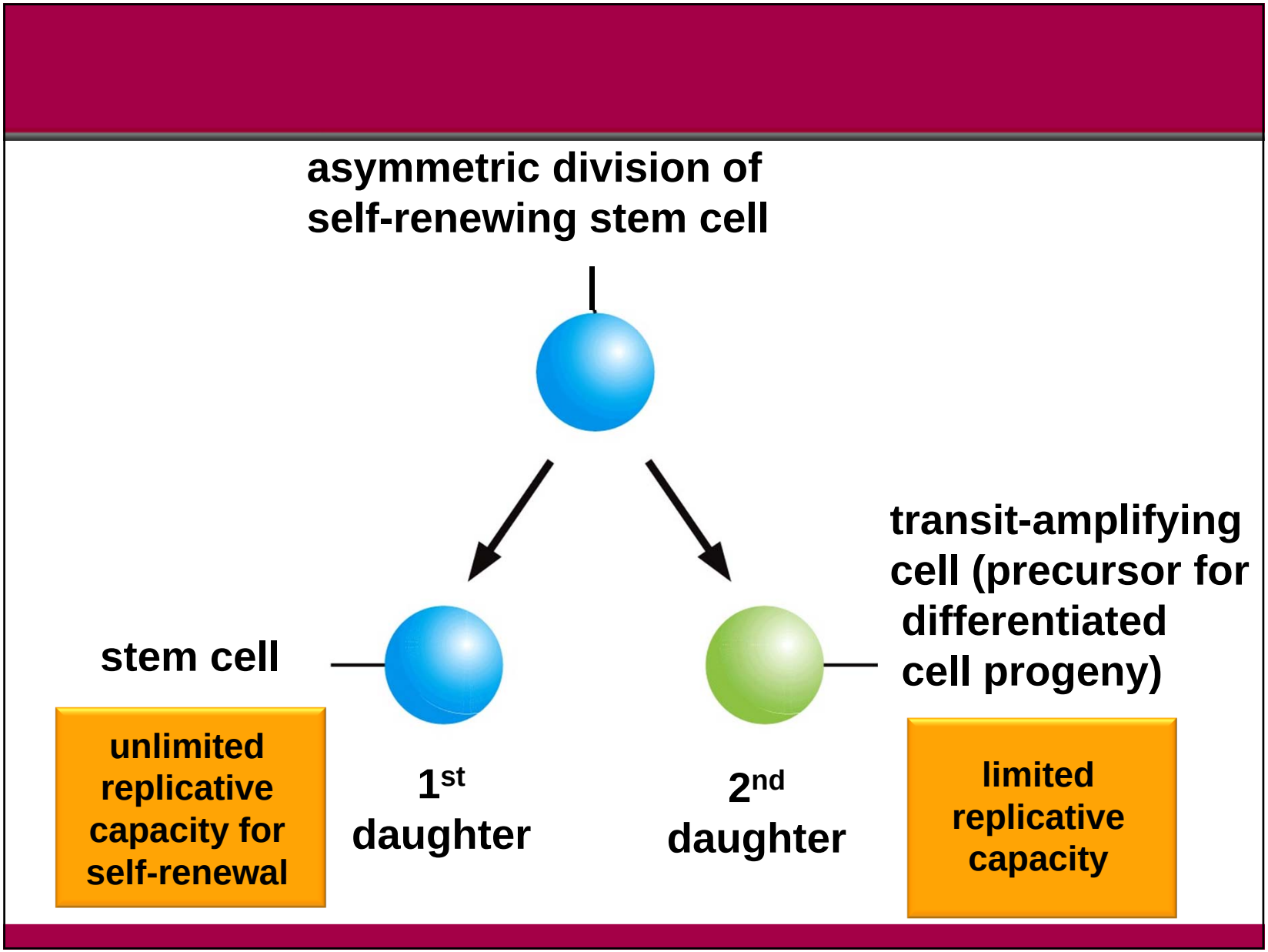
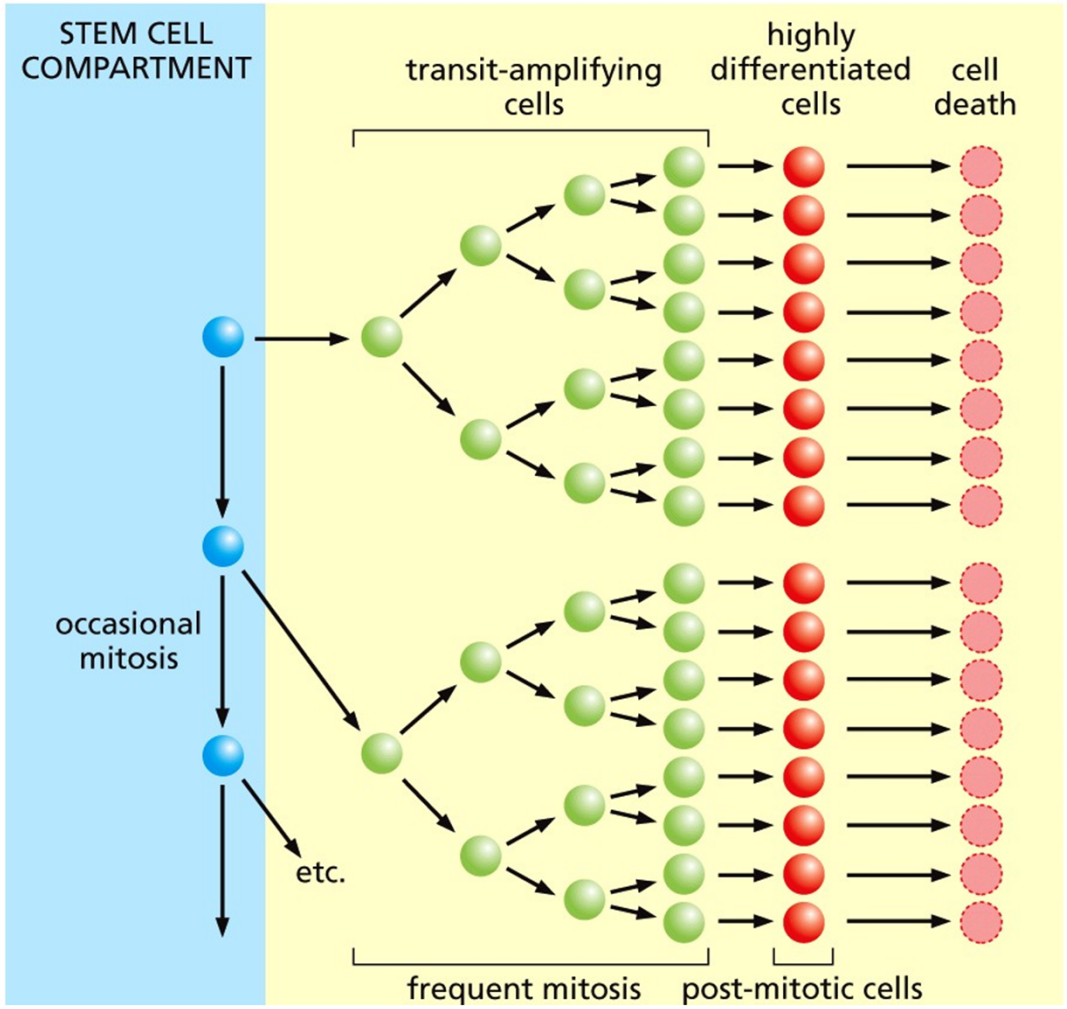


Figure 12.3c The Biology of Cancer (© Garland Science 2014)

- **embryogenesis**
- **organ regeneration (limited in mammals)**

- **post-natal cell turnover in different body tissues/ organs**
- **tissue repair**


asymmetric division of self-renewing stem cell
stem cell
unlimited replicative capacity for self-renewal
1st daughter
2nd daughter
transit-amplifying cell (precursor for differentiated cell progeny)
limited replicative capacity


STEM CELL COMPARTMENT
transit-amplifying cells
highly differentiated cells
cell death
occasional mitosis
etc.
frequent mitosis
post-mitotic cells

Replicative Self-Renewal

normal tissues

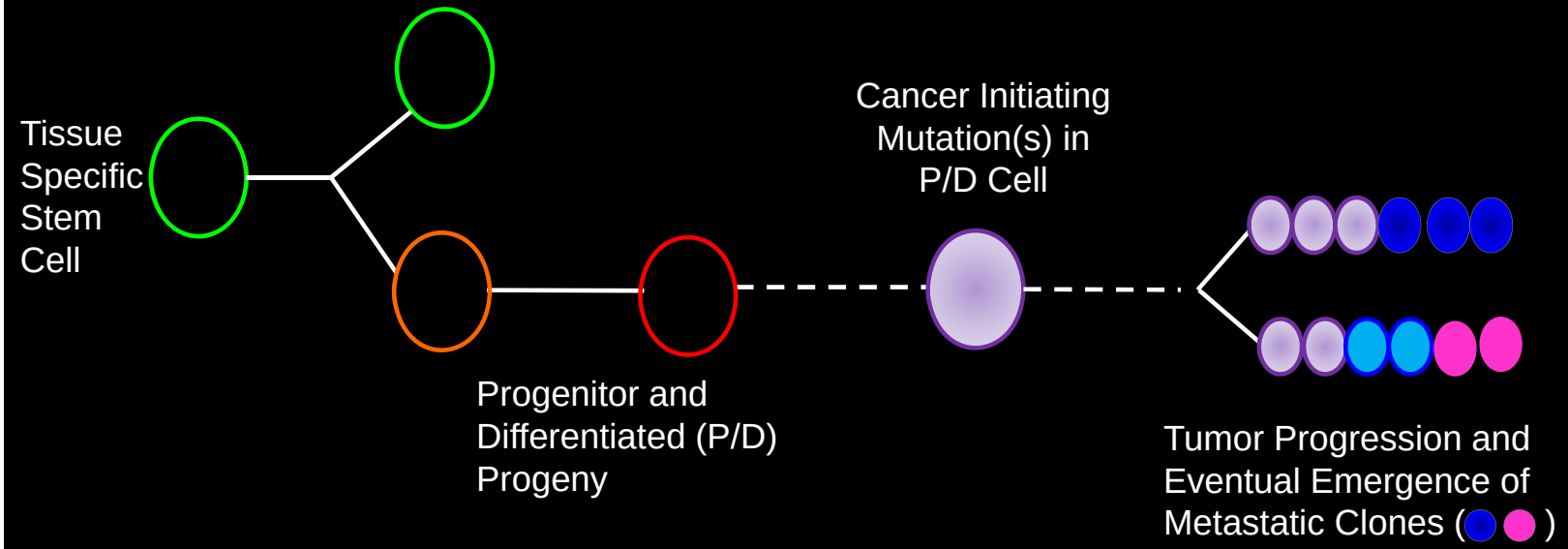
- **stem cells: unlimited but highly controlled division potential**
- **asymmetric division sustains stem cell population and pool of progenitor and differentiation committed cells with limited number of cell divisions (terminal differentiation)**

Replicative Self-Renewal

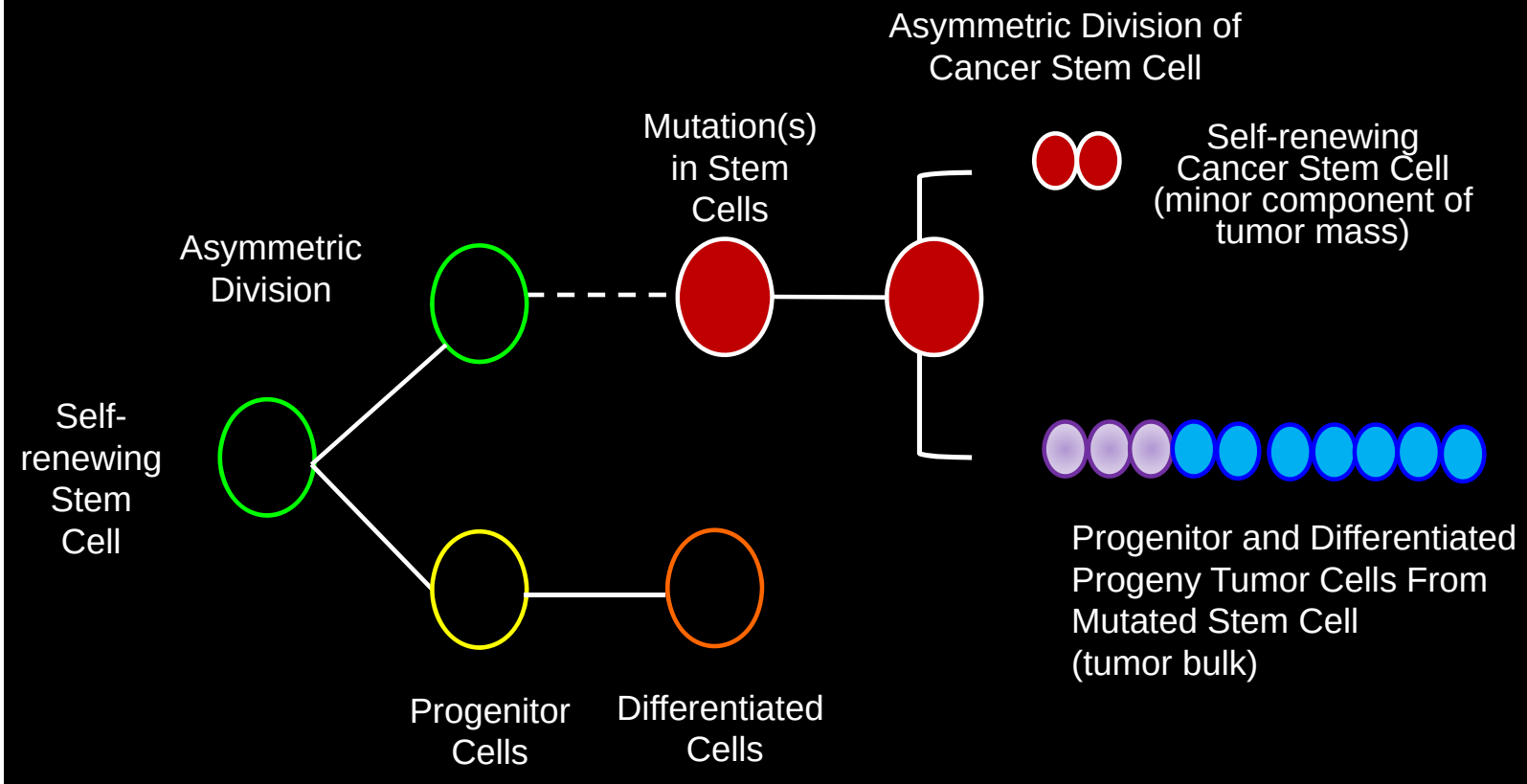
cancer

- loss of control circuits that limit the number of cell divisions as hallmark feature of cancer
- does every cancer cell have potential to generate clones with metastatic ability and unlimited replicative capacity or are only a specific population of stem-like cancer cells (CSCs) endowed with this capability?

All Initiated Cells Have Potential for Unchecked Replication and Progression to Malignancy



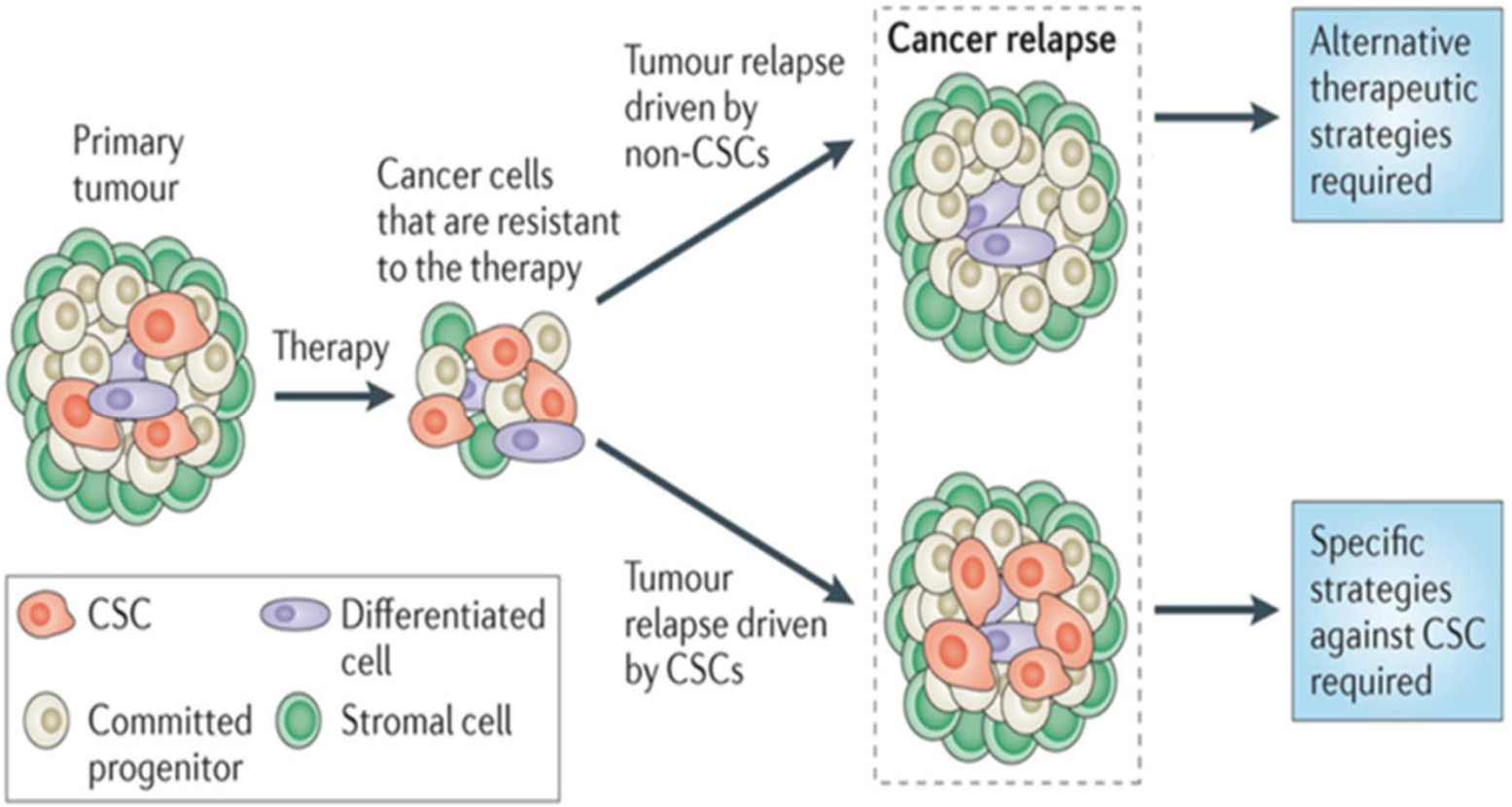
Cancer Originates and is Maintained by Mutations in Tissue Stem Cells



Unknown But Crucial Issues in the Evolution of Drug-Resistance (D^r) Phenotypes in Cancer

- can only stem cells seed metastases with subsequent expansion of the tumor cell population in metastases by proliferation of their P/D progeny?
- do all drug-resistance (D^r) phenotypes arise in stem cells and subsequent expression in their P/D progeny?

Implications of Different Cell-of-Origin Models for Cancer on Therapeutic Strategies



Adapted From: B. Beck and C. Blanpain (2013) Nature Rev. Cancer 13, 734

The Cell-of-Origin in Cancer

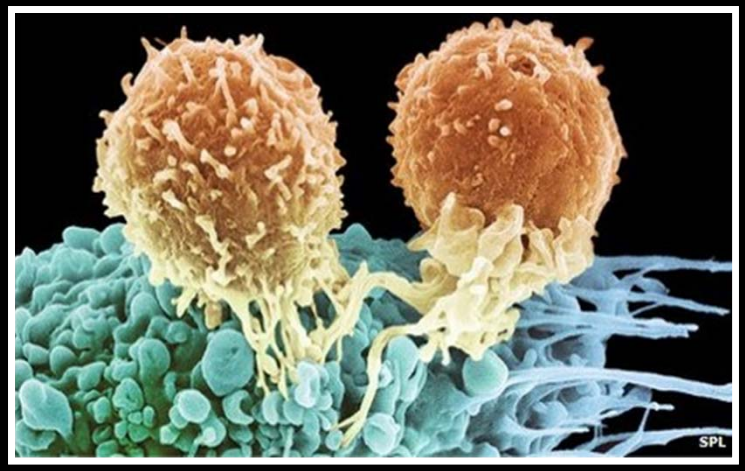
- balance of evidence shifting to cancer stem cell (CSC) model

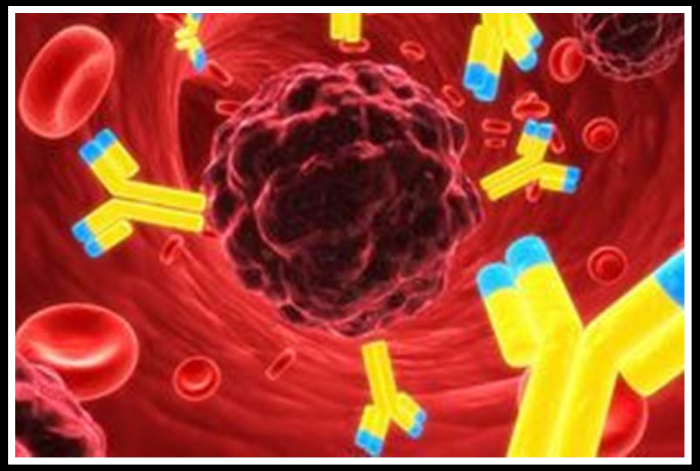
If Stem Cells Are Surviving Unscathed then Therapeutic Failure is Inevitable and New Therapeutic Approaches to Selectively Attack of Stem Cells Are Required

Immunotherapies for Cancer

Immunoevasion by Tumor Cells

- **“stealthy” tumor cell strategies that reduce detection and/or killing by body’s immune defenses, therapeutic monoclonals and anti-cancer vaccines**





Immunoevasion by Tumor Cells

- "stealthy" tumor cell strategies that reduce detection and/or killing by body's immune defenses
- avoiding the immune detection radar
  - loss or masking of abnormal tumor cell surface proteins recognized by antibodies, NK cells and/or killer T lymphocytes
- suppression of the host immune system
  - tumor signaling to activate regulatory T cells (Treg) that suppress action of anti-tumor killer T cells

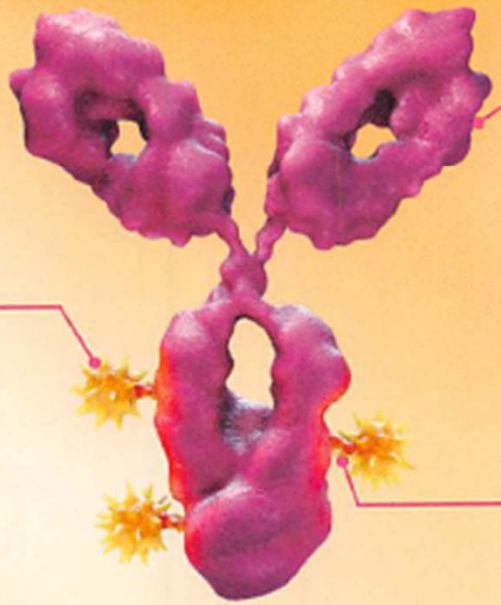
Immunotherapies for Cancer

- non-specific immunotherapies
- monoclonal antibodies (Mabs)
- immune checkpoint modulators
- adoptive (immune) cell transfer (ACT)
- tumor vaccines

The next era of treatment

KADCYLA contains 3 components: the active antibody trastuzumab, the cytotoxic agent DM1, and a stable linker[1-3]

In preclinical studies:



Trastuzumab (monoclonal antibody)
Binds to HER2 at subdomain IV to suppress downstream signaling

DM1* (cytotoxic maytansinoid)
Inhibits tubulin polymerization to induce cell-cycle arrest and cell death

MCC* (stable linker)
Stabilizes KADCYLA in circulation to release DM1 after entering the target cell

Immunotherapy for Cancer

Monoclonal Antibodies (Mabs)

- direct destruction of tumor cells with or without “Rx warhead”
- tagging tumor cells for destruction by immune cells
- blocking tumor cell signaling pathways to halt proliferation (anti-EGFR Mabs)
- blocking host tissue stroma signaling pathways that promote tumor proliferation (anti-angiogenesis Mabs)
- physical access to target tumor cells antigen-deletion clones escape destruction

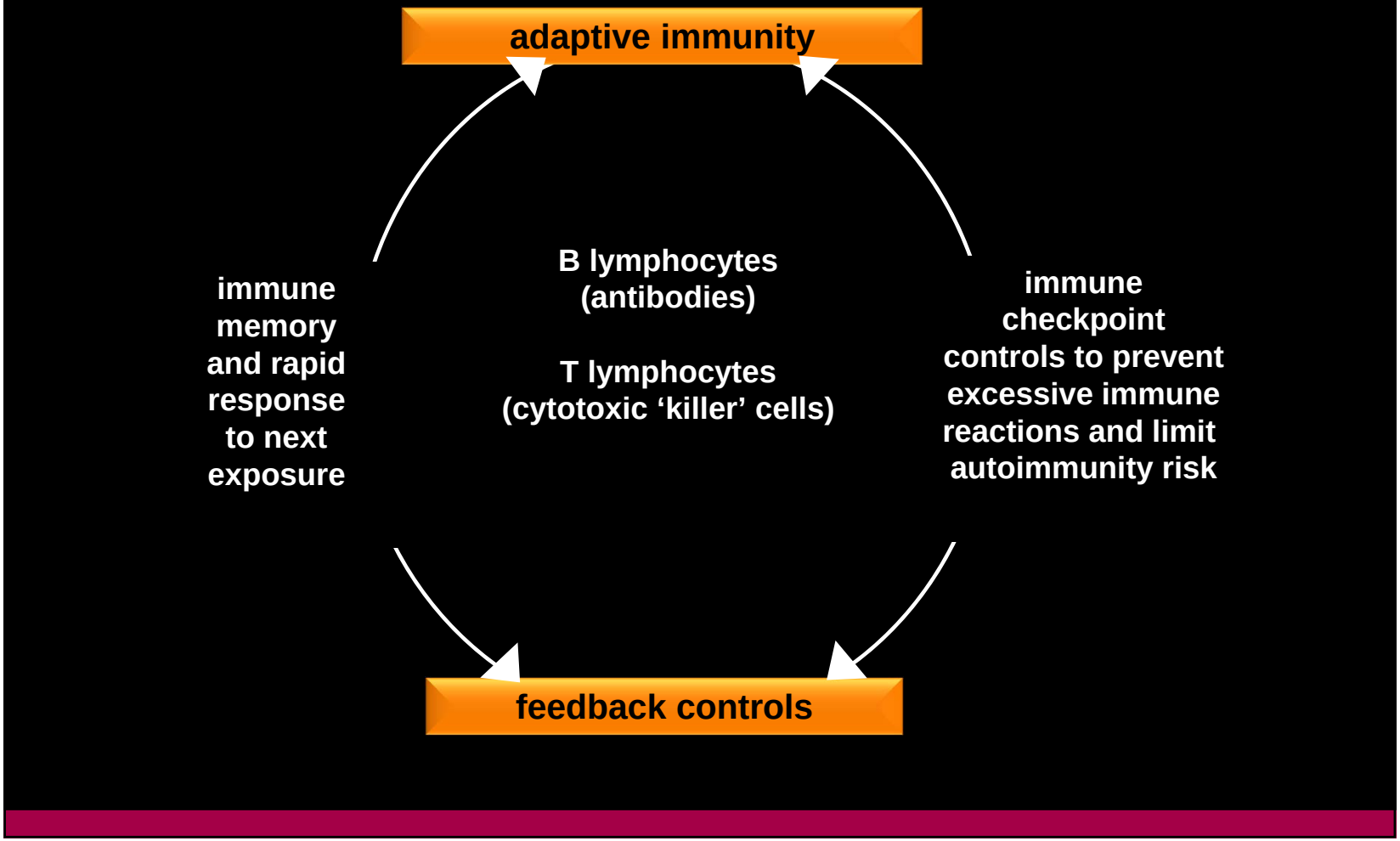
Immunotherapy for Cancer

Vaccines

- far greater technical challenge than most antimicrobial vaccines
- antigenic variation in different tumor cell clones plus inter-patient variation
- how to identify the best combination of antigens as vaccine candidates
- high probability of antigen-negative/deletion variants and tumor relapse
- analogy with the still unsuccessful quest for HIV vaccine
- same problem: massive antigenic heterogeneity due to rapid evolution of new viral quasispecies

Setting the Immune System Free to Combat Cancer

The Immune System: Detection and Response to 'Non-Self' Signals



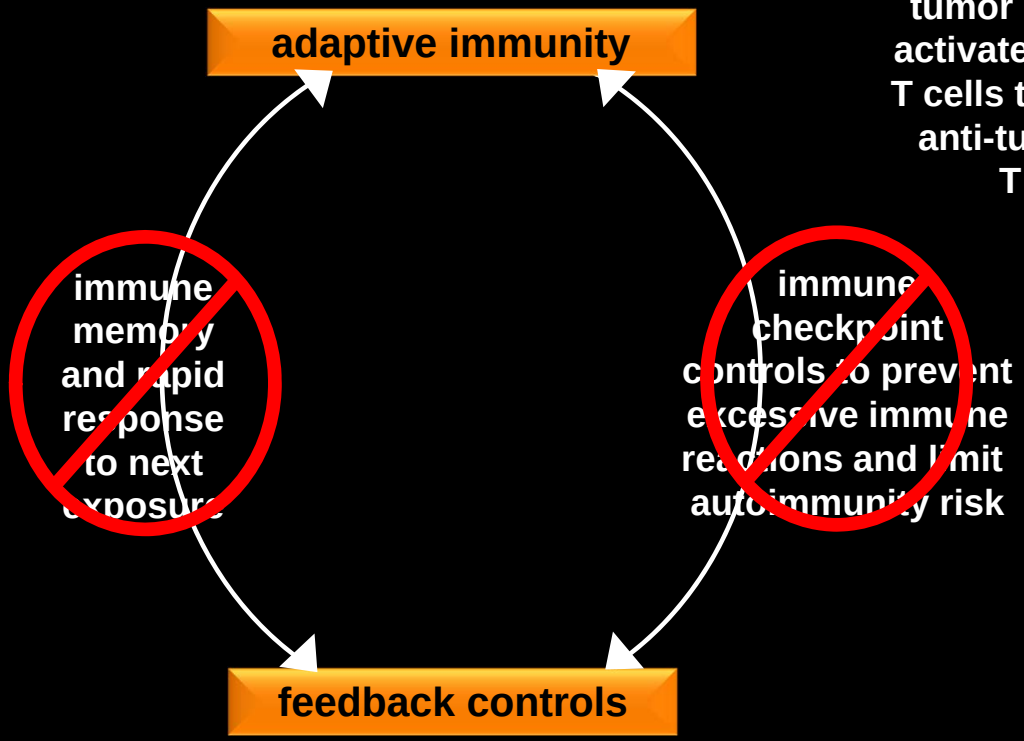
Immunoevasion by Tumor Cells

stealth

antigen-deletion variant tumor cell clones go undetected

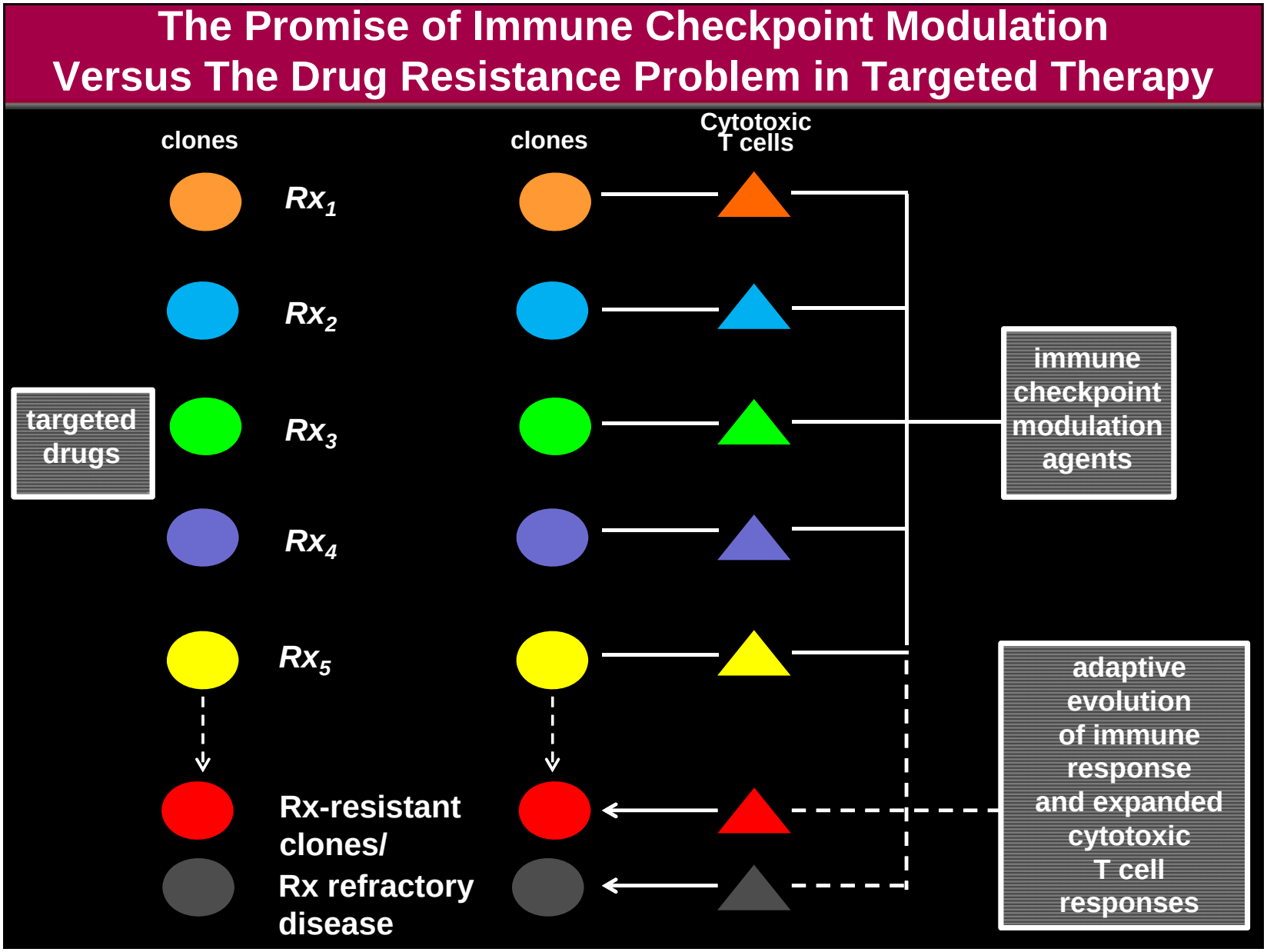
hijacking

tumor molecules activate regulatory T cells to suppress anti-tumor killer T cells

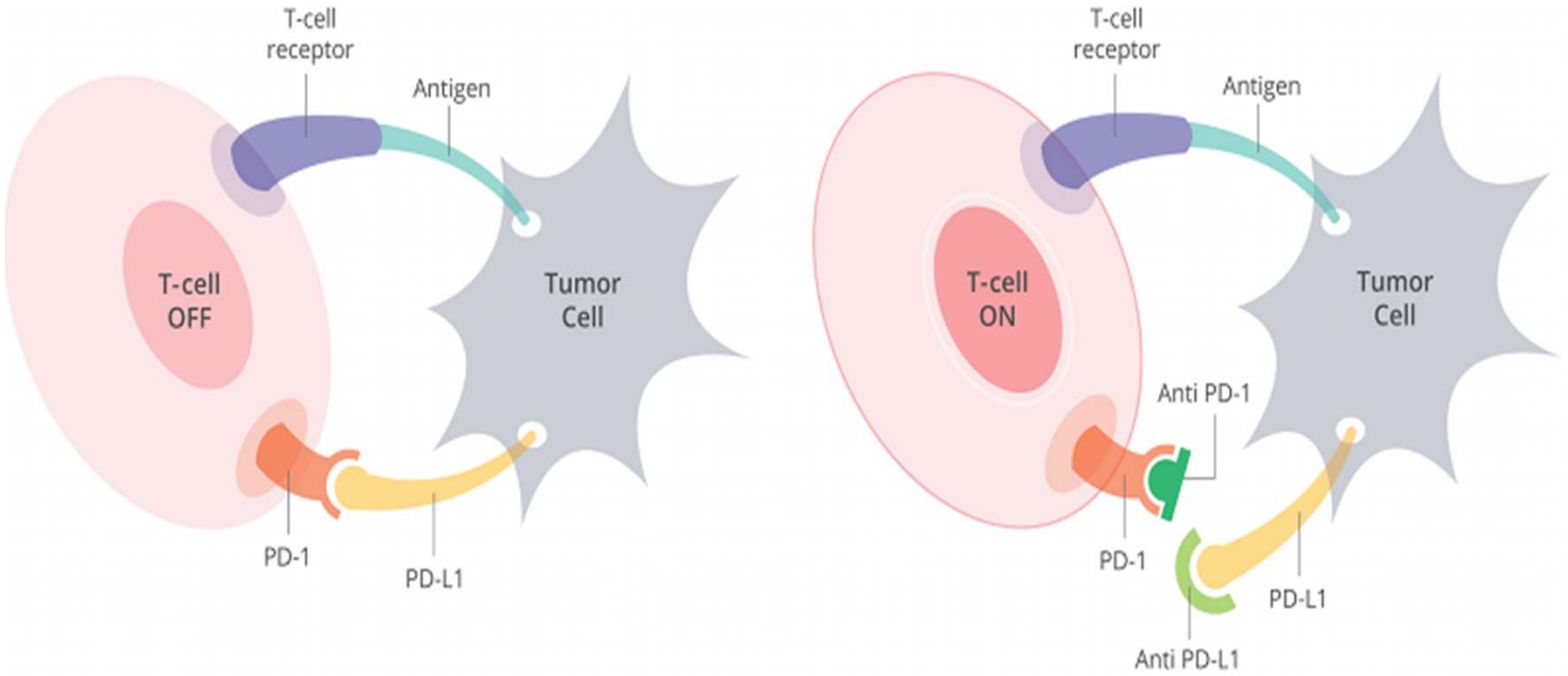


New Therapeutic Strategies to Circumvent Tumor-Mediated Suppression of Anti-Tumor Immune Responses

- circumventing tumor-mediated activation of T regulatory (Treg) cells to limit activity of anti-tumor killer T cells
- immune checkpoint modulation
  - "releasing the brakes" on the immune system
  - "removing the blindfold"
  - "unleashing the killer instinct"

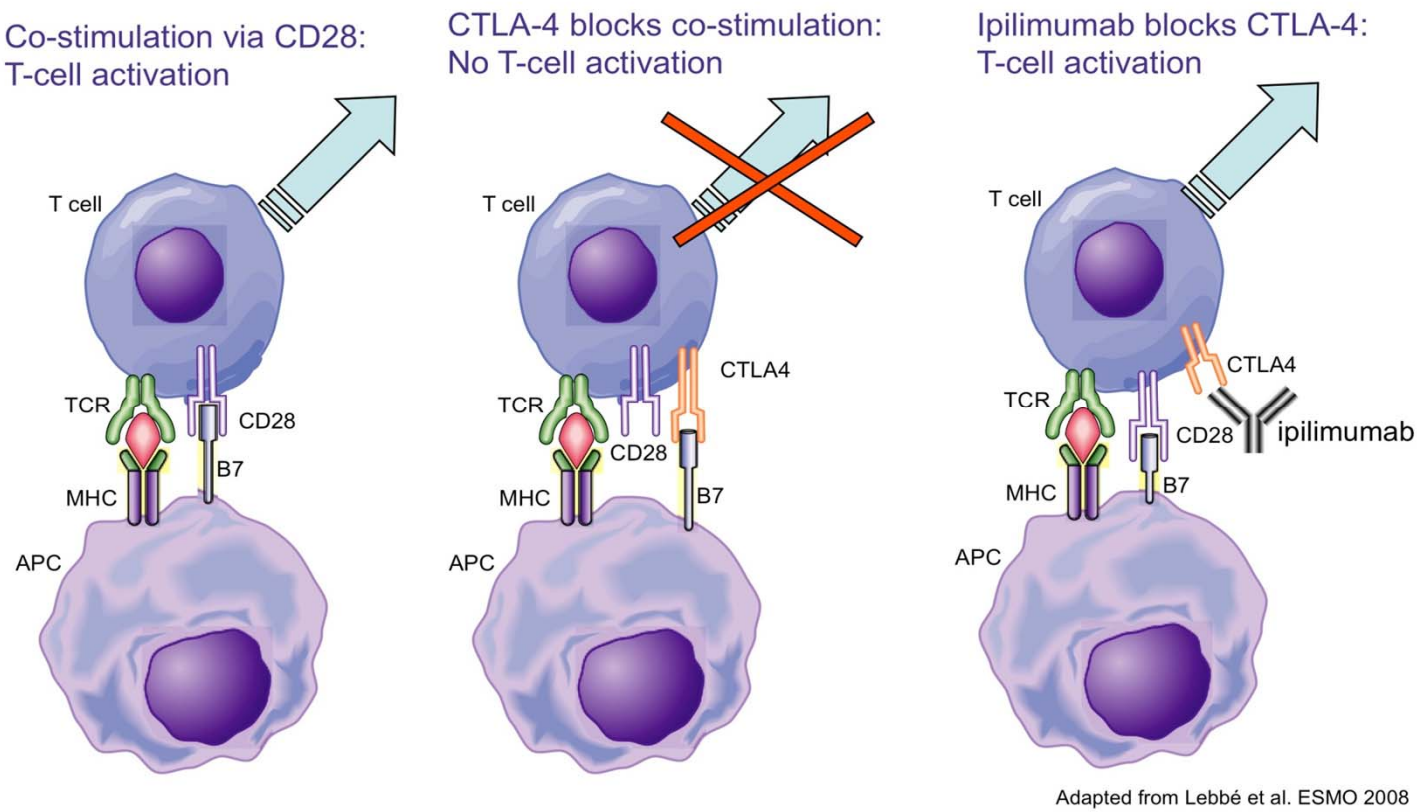

The Promise of Immune Checkpoint Modulation
Versus The Drug Resistance Problem in Targeted Therapy
clones
clones
Cytotoxic T cells
Rx1
Rx2
Rx3
Rx4
Rx5
targeted drugs
immune checkpoint modulation agents
adaptive evolution of immune response and expanded cytotoxic T cell responses
Rx-resistant clones/
Rx refractory disease

Tumor-Mediated Inactivation of T Effector Cells by PDL1 Expression



PD-1 | Smart Patientswww.smartpatients.com800 × 293Search by imagePD-1 Clinical Trials

Ipilimumab Blocks Negative Signaling From CTLA-4



Adapted from Lebbé et al. ESMO 2008

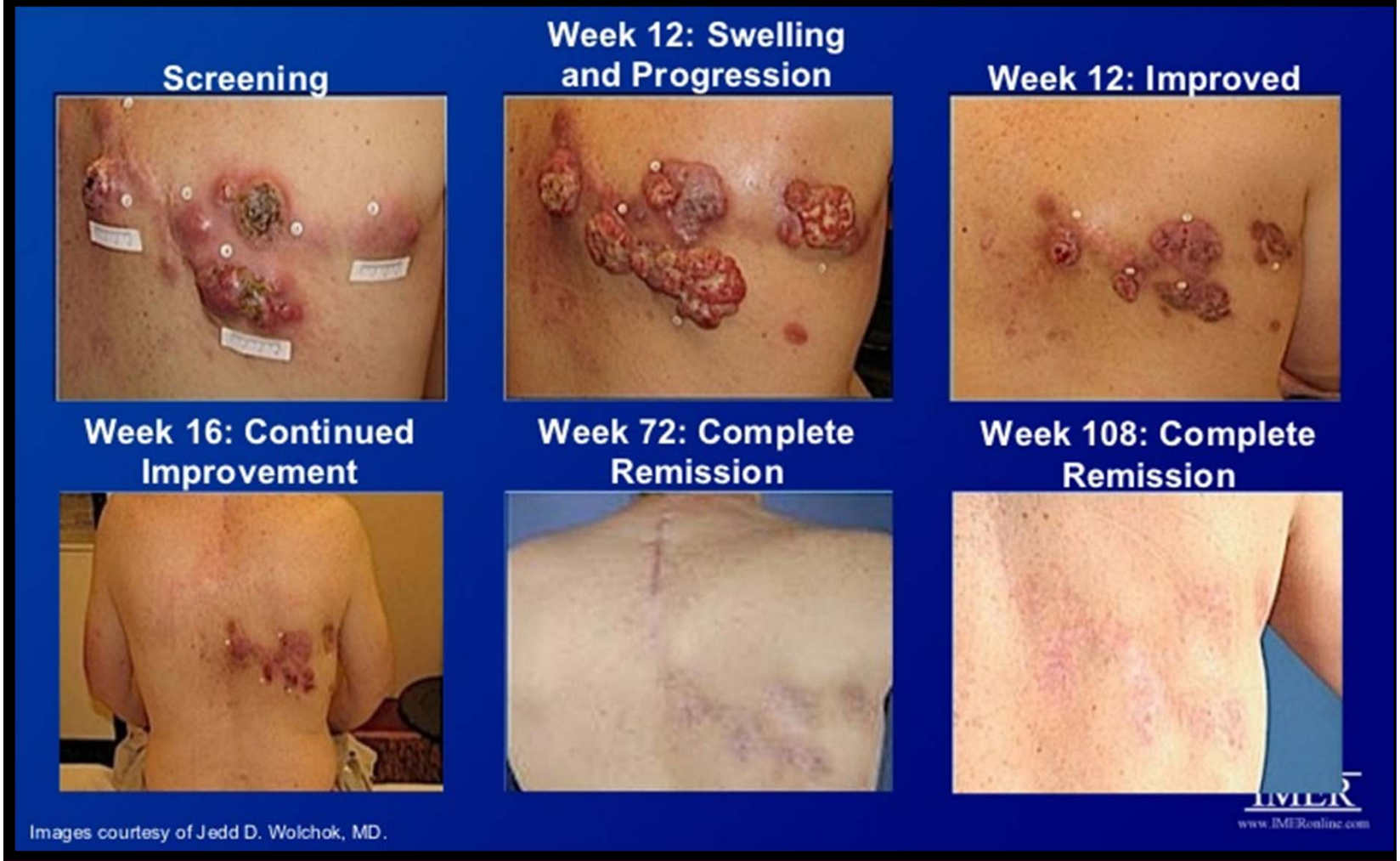
APC, antigen-presenting cell; CTLA-4, cytotoxic T-lymphocyte antigen-4; MHC, major histocompatibility complex; TCR, T-cell receptor.

CTLA-4 | GRACE :: Lung Cancercancergrace.org2999 × 2249Search by image

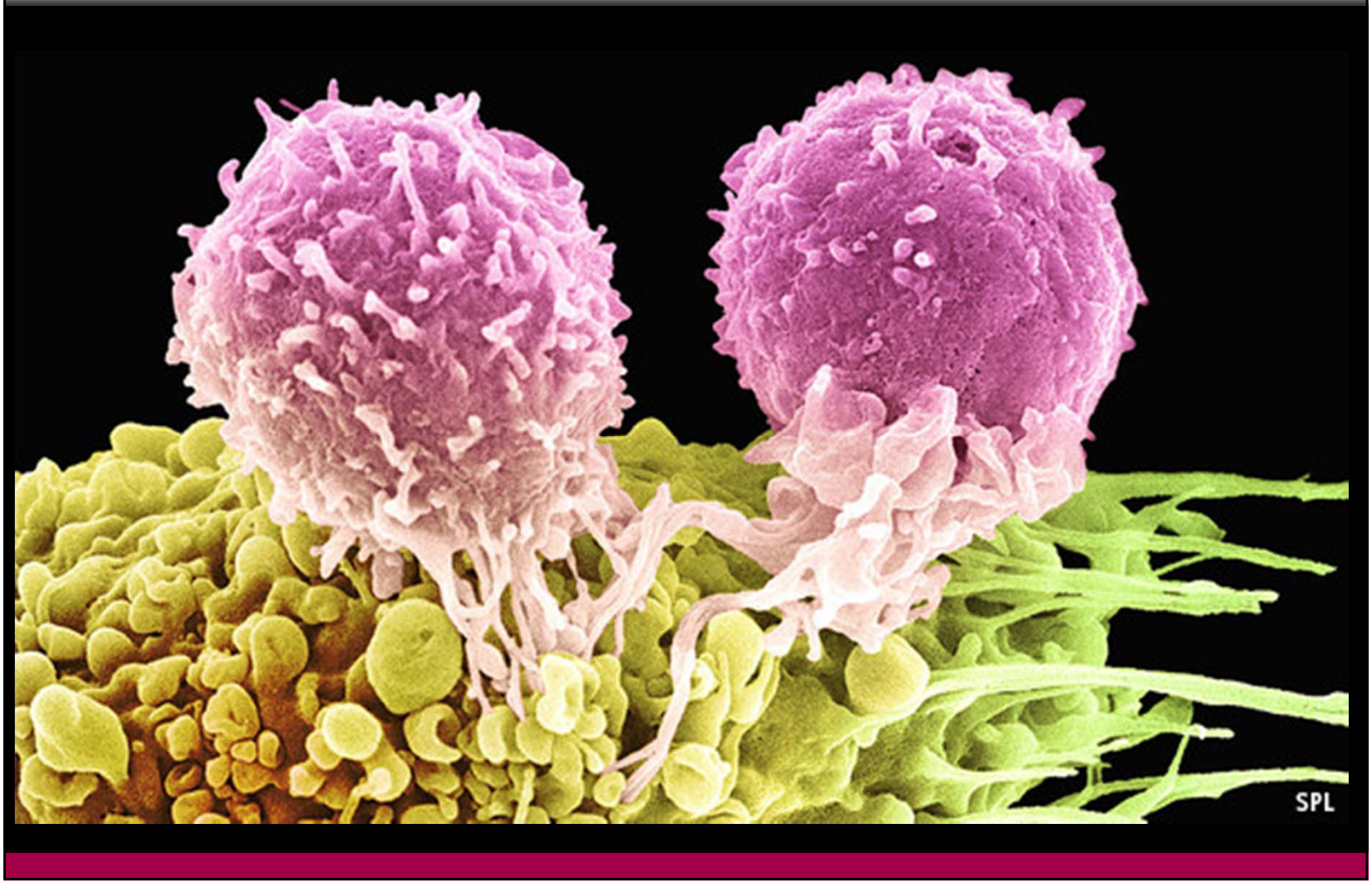
The Promise of Immune Checkpoint Modulation Drugs

- novel concept to circumvent tumor-mediated suppression of anti-tumor T cell responses
- production of CTLA-4 and PD-1 by tumor cells stimulates regulatory T cells to suppress killer T cells
- circumvention of checkpoint block
  - anti-CTLA-4 monoclonal antibodies (ipilimumab; Yervoy, Bristol-Myers)
  - anti-PD-1 antibodies (nivolumab, Bristol-Myers; pembrolizumab, Merck)

Unique Kinetics of Response in Patients Treated With Ipilimumab



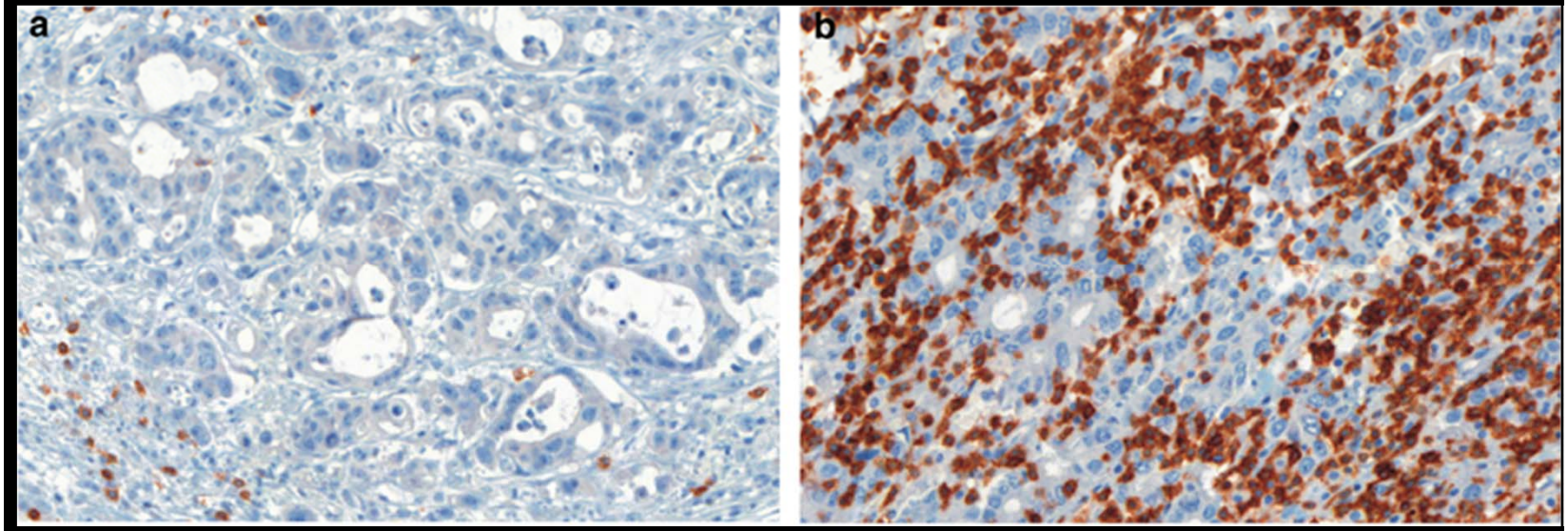
Activated (Immune) Cell Therapy (ACT) and Cancer: "Living Drugs"



Activated (Immune) Cell Therapy (ACT) for Cancer

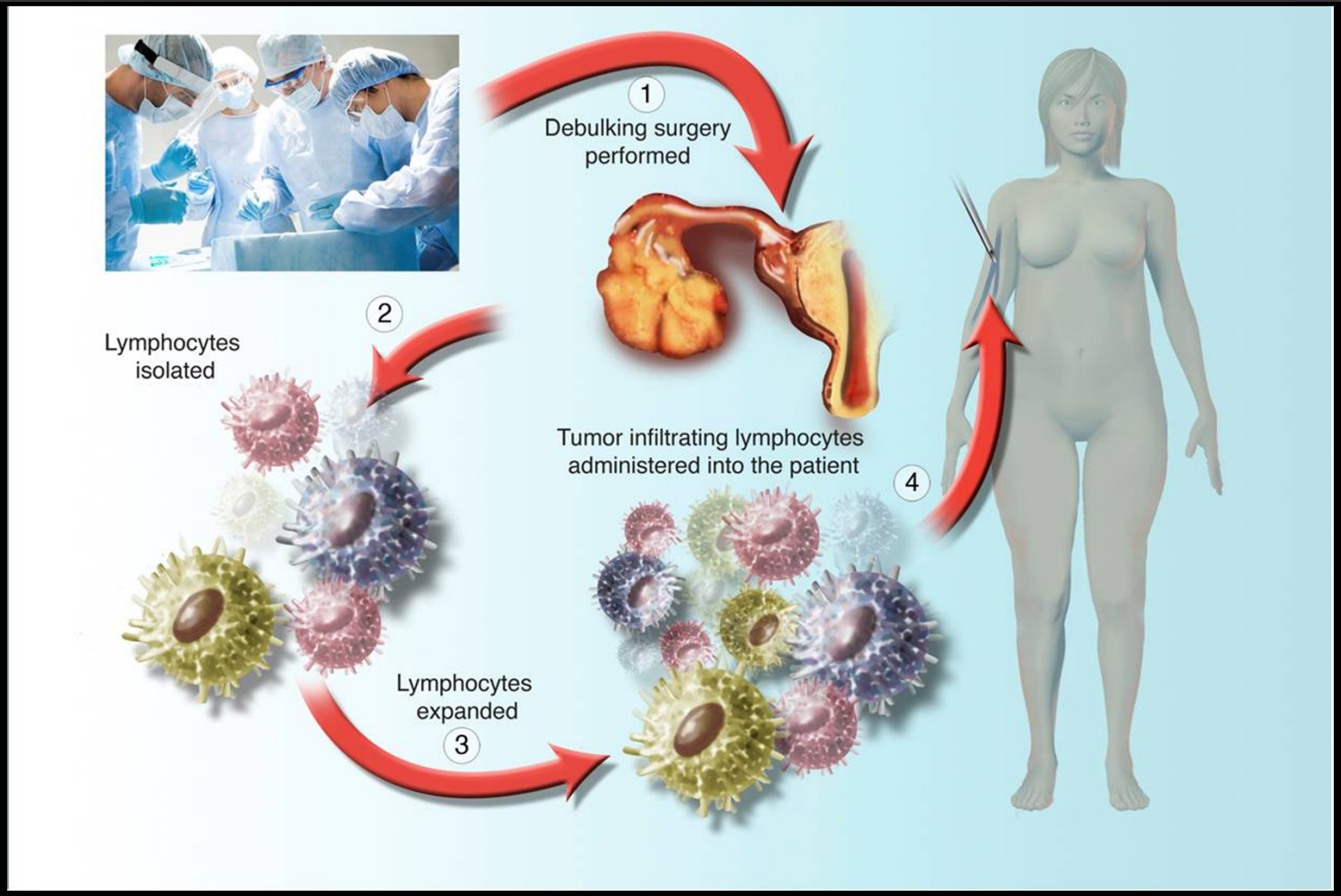
- capture, expand and re-infuse unmodified tumor-infiltrating lymphocytes (TIL)
- genetic engineering of killer lymphocytes with new T cell receptors (TCRs) to enhance tumor cell detection and killing

Tumor Infiltrating Lymphocytes (TIL)

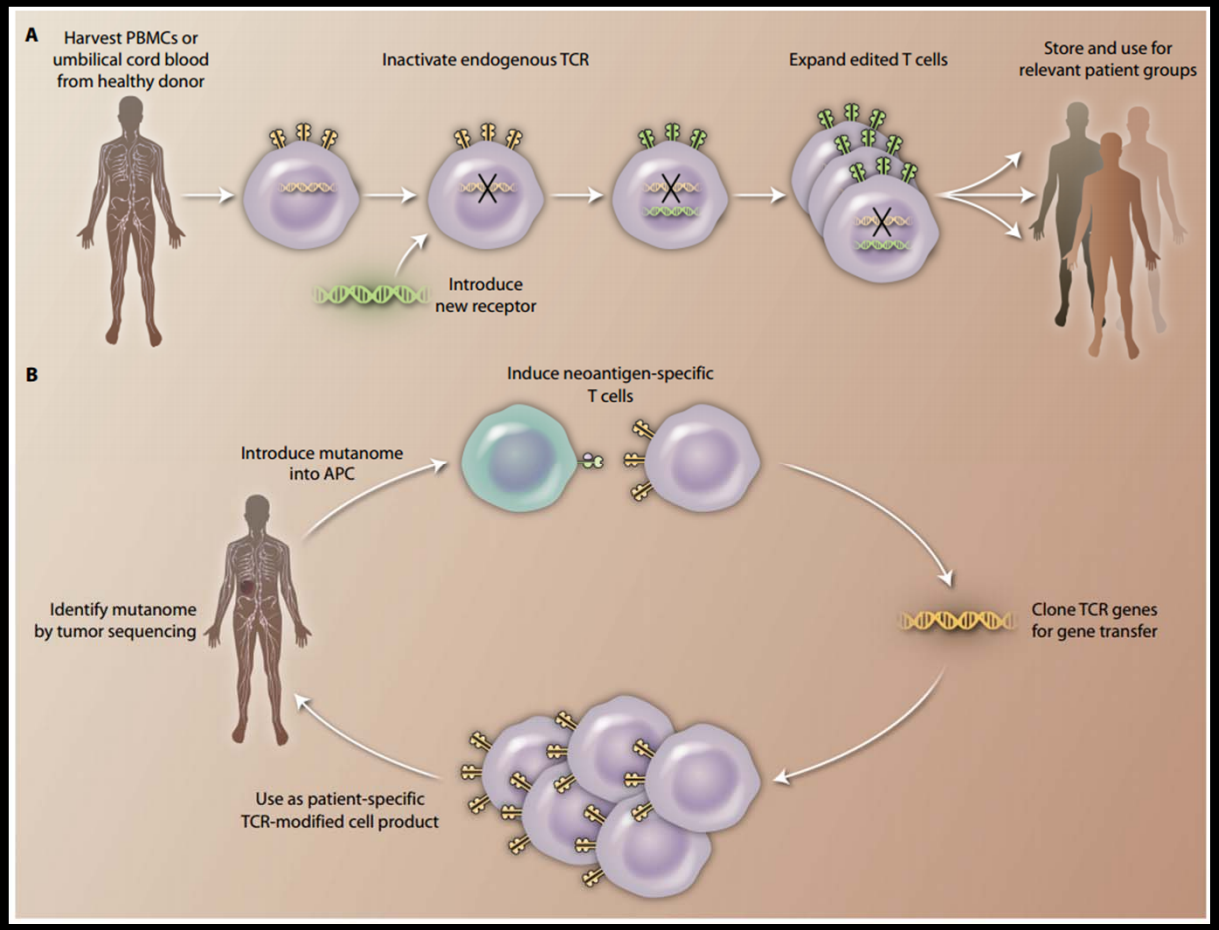


Modern Pathology - Figure 5 for article: Tumor-infiltrating ...www.nature.com

Tumor Infiltrating Lymphocyte (T-cell) Study



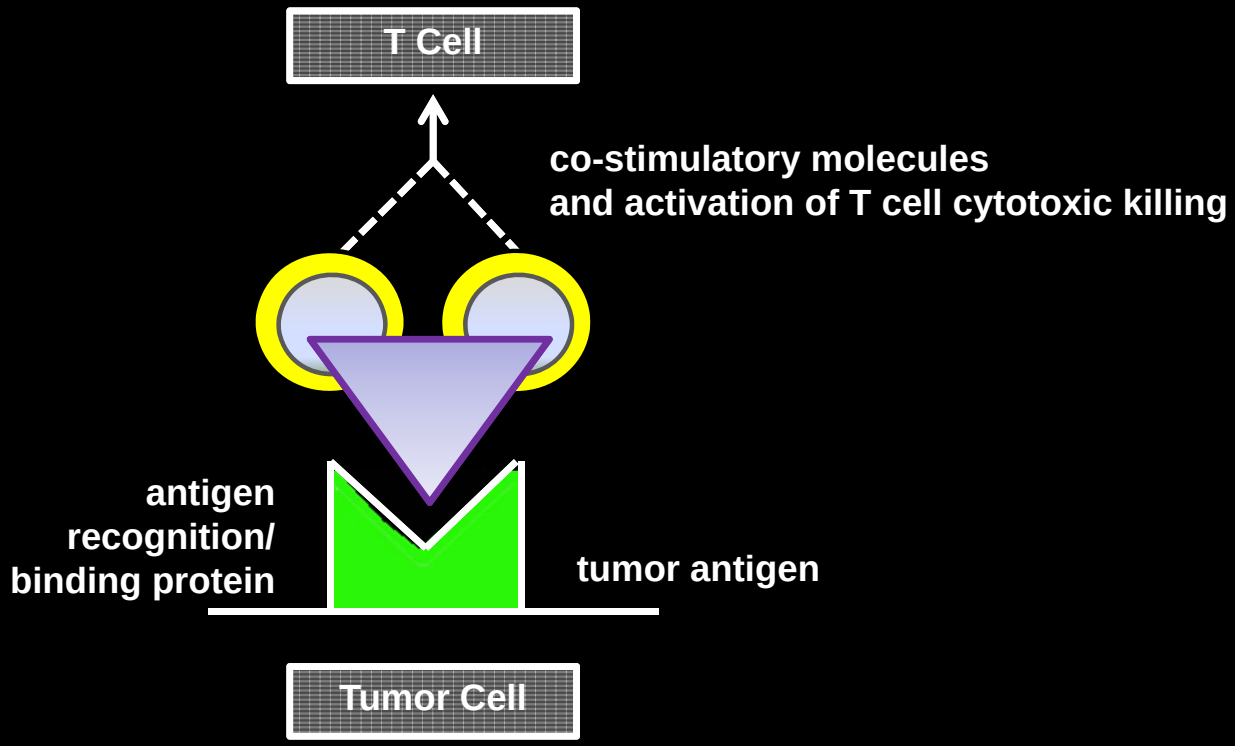
Genetic Engineering of T Cells for Adoptive Cell Therapy (ACT) in Cancer



From: C. H. June et al. (2015) Sci. trans. Med. 280ps7

immunotherapy

Chimeric Antigen Receptors (CARs)



Immunotherapy and Cancer

Challenges

- identification of the right tumor antigen(s) to attack
  - the clonal heterogeneity challenge
- ensuring that the antigen(s) selected for attack are not present on normal host tissues
  - NCI trial fatalities with MAGE-A3 TCR engineered T cell attack on related MAGE-A in brain and Titin in heart
- limiting the immunoevasion mechanisms of the tumor

Milestone Timelines in Evolution of Melanoma Immunotherapy

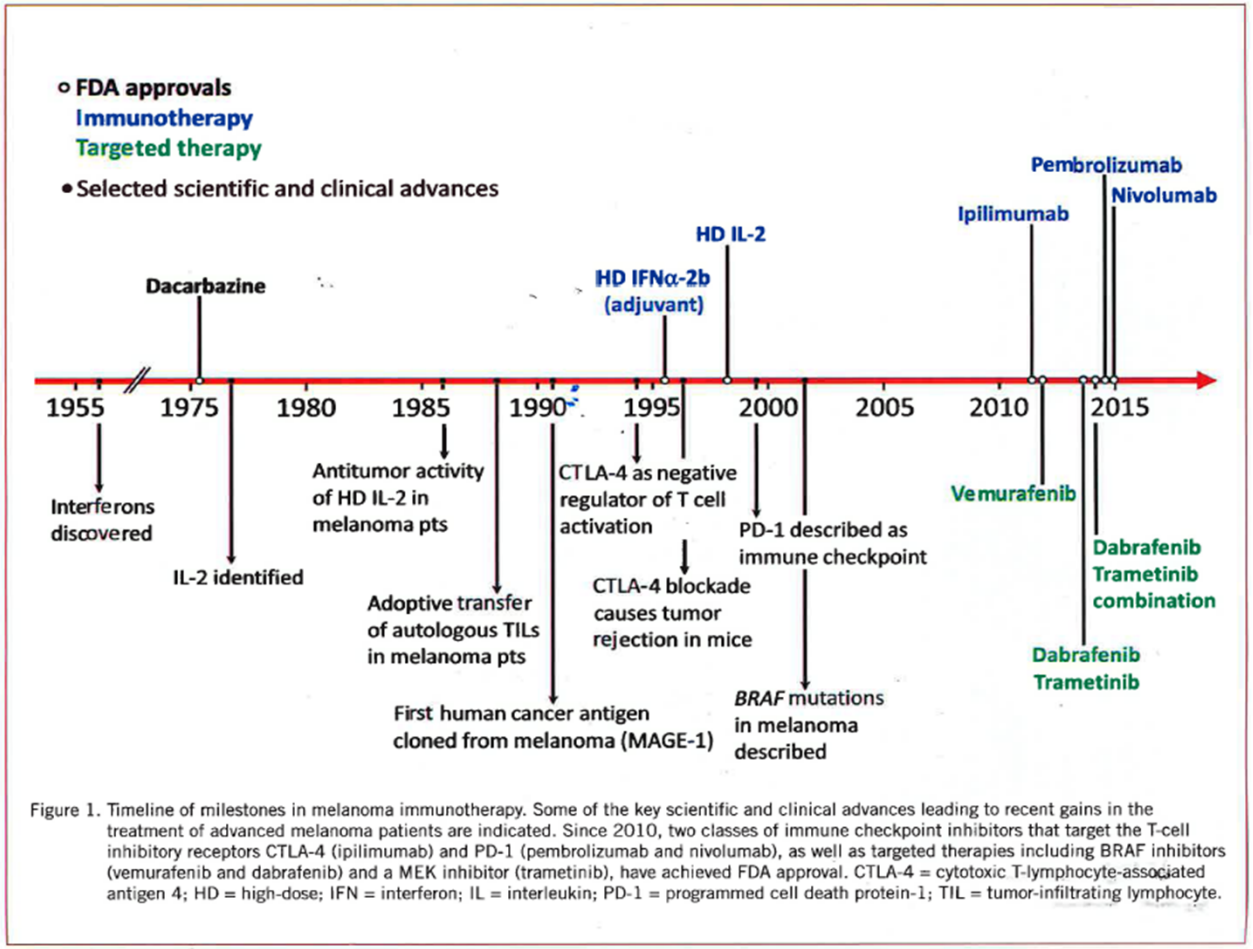


Figure 1. Timeline of milestones in melanoma immunotherapy. Some of the key scientific and clinical advances leading to recent gains in the treatment of advanced melanoma patients are indicated. Since 2010, two classes of immune checkpoint inhibitors that target the T-cell inhibitory receptors CTLA-4 (ipilimumab) and PD-1 (pembrolizumab and nivolumab), as well as targeted therapies including BRAF inhibitors (vemurafenib and dabrafenib) and a MEK inhibitor (trametinib), have achieved FDA approval. CTLA-4 = cytotoxic T-lymphocyte-associated antigen 4; HD = high-dose; IFN = interferon; IL = interleukin; PD-1 = programmed cell death protein-1; TIL = tumor-infiltrating lymphocyte.

From: M. Diamond et al. (2015) Abeloff's Clinical Oncology Issue 2

BIO 302: Cancer Treatment

Summary of Key Issues

The Principal Challenges in Cancer Treatment

- early (pre-metastatic) detection and removal of primary tumor (=cure)
- identification and treatment decisions for patients at-risk of metastic disease due to locally invasive tumor but no detectable metastases
  - only small fraction may need treatment

The Three Most Dangerous Phenotypes in Tumor Cell Clones: metastasis; immunoevasion; and drug resistance

Dynamic Heterogeneity

Emergence and Adaptive Evolution of Different Tumor Clones and Subclones During Tumor Progression

The Principal Challenges in Cancer Treatment

- the heterogeneity challenge
  - genomic instability and rapid evolution of tumor clones with highly variable phenotypes and Rx responses
  - intra-lesion heterogeneity (zonal variation)
  - inter-lesion heterogeneity in same patients
  - inter-patient variation
- the central problem in effective therapy

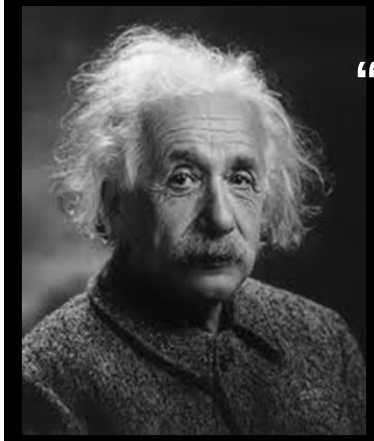
Cancer Treatment

- clonal heterogeneity and plasticity (redundancy) molecular signaling networks
  - the core problem in the design of effective therapies
  - hitting multiple targets
  - different clones
  - different signaling pathways

Mapping the Dynamics of Clonal Diversification in Tumor Progression

- urgent need for new technologies for minimally invasive profiling of the full spectrum of clones present in a patient and changes occurring over time with treatment
- difficult to sample (biopsy) multiple metastases in solid tumors
- the quest to create a 'liquid biopsy' for profiling clonal dynamics for solid tumor profiling from analysis of blood samples
  - exosomes
  - circulating tumor cells
  - cell-free (cf) DNA or miRNAs from tumor cells

Knowing When to Stop!



**"Insanity is doing the same thing
over and over again
and expecting a different result."**

Albert Einstein

Cancer Treatment

- how to design new strategies to hit multiple clones and every new clonal variant that emerges
- the promise of immunotherapy
  - leveraging the detection and destruction capabilities of the host immune system
  - reactivation of immune system following suppression by tumor
  - early stages of assessing in clinical efficacy
  - highly promising early results but long term evaluation needed to assess risk of relapse due to immunoevasion clones
  - value of new combinations of drug and immunotherapies?