



BIO 302:

APRIL 3, 2014

WEEK 11, LECTURE 2:
SYSTEMIC TREATMENT OF CANCER:
DRUGS, BIOLOGICALS AND IMMUNOTHERAPIES

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

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)

The Two Core Therapeutic Challenges in Cancer

- multiple clones with different Rx responses
- inter-connected signaling pathways that predispose to Rx-resistance via by-pass pathways



- how to devise therapies that can hit these multiple targets

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**

Design of Cancer Treatments to Hit Multiple Targets

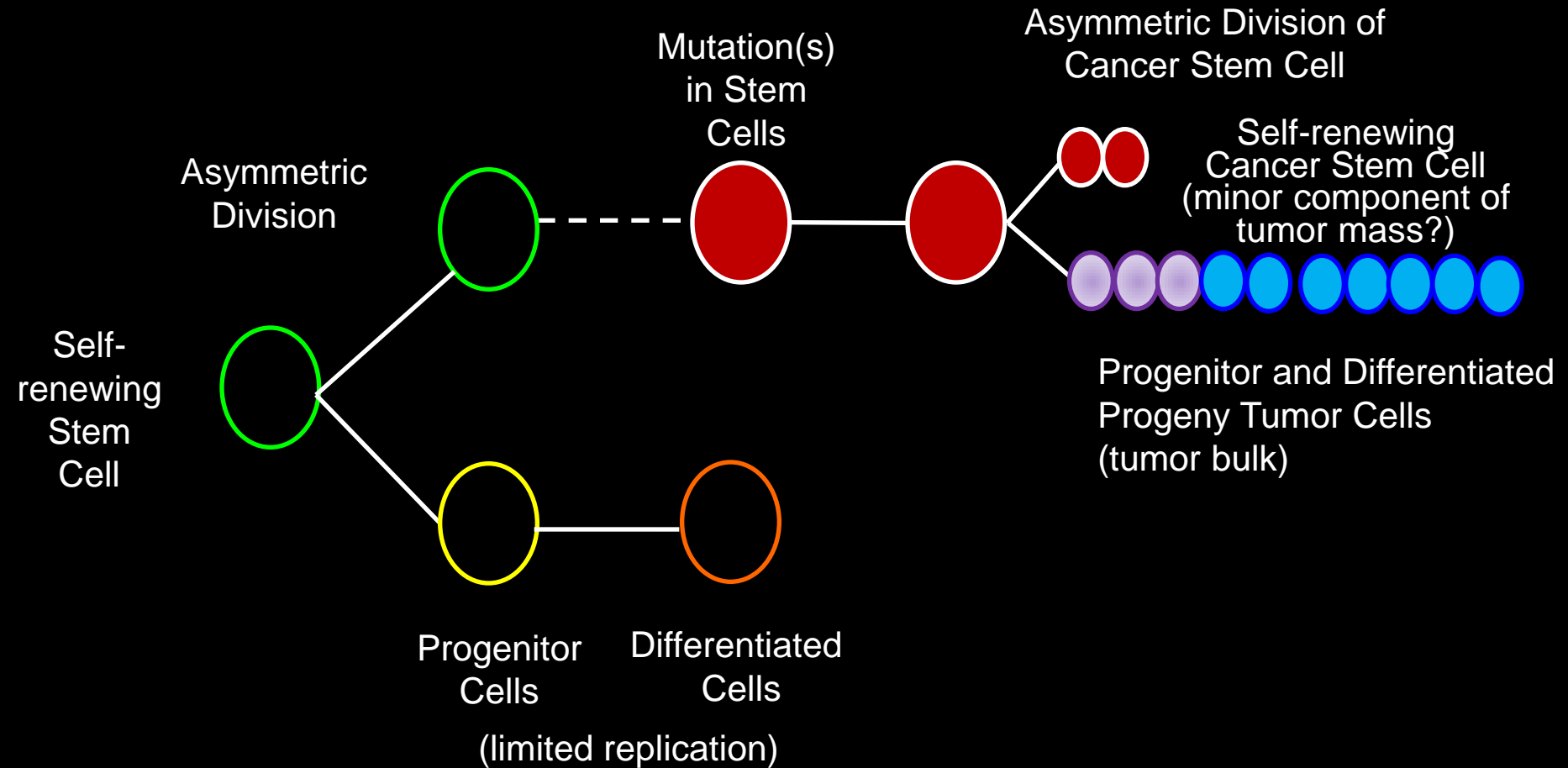
- **multi-drug combinations**
 - **patient tolerance**
 - **cost**
- **may delay emergence of clone(s) with Rx-resistance to one or more drugs in combination**

but

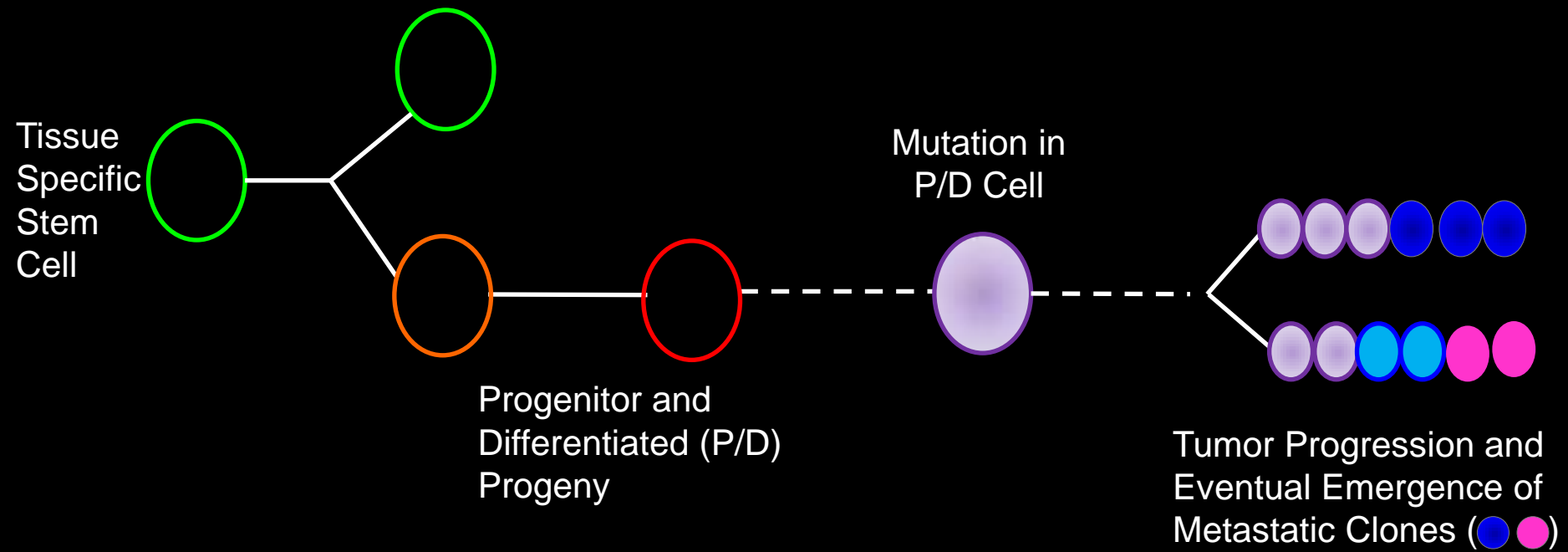
- **high probability that such Rx-resistant variants will eventually emerge**
 - **Rx as selection pressure to generate these ‘escape’ clones**

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

Cancer Arises from Mutations in Stem Cells



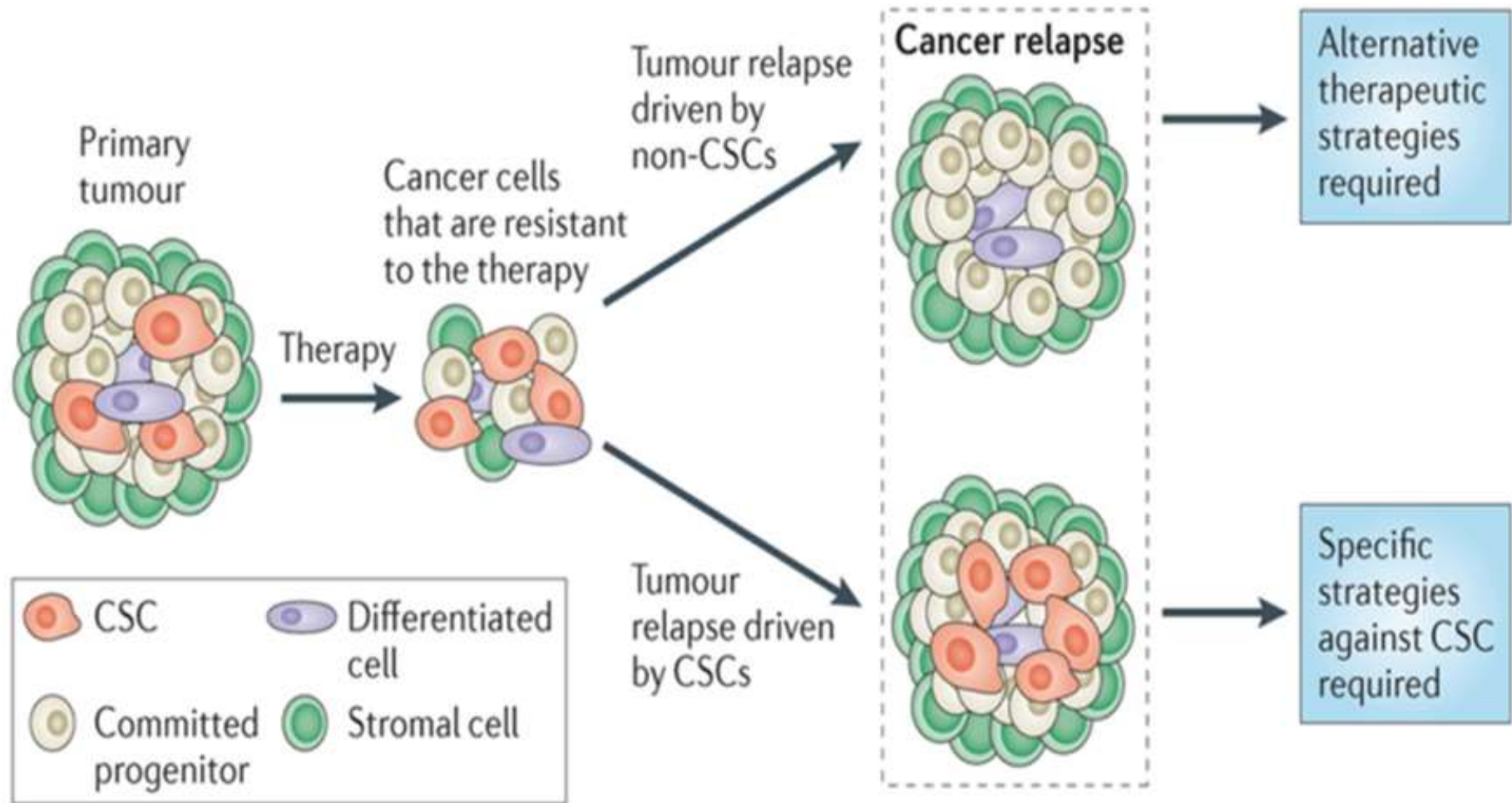
All Initiated Cells Have Potential for Unchecked Replication and Progression to Malignancy



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 progenitor/differentiated (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 Most Important 'Known Unknowns' in Current Approaches to Cancer Treatment

**Are Current Targeted Treatments Attacking Both
Stem Cells and Progenitor/Differentiated Cells or
Largely Only the Latter?**

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

The Problem and The Challenge

- **how to hit multiple tumor clones?**
- **how to hit multiple tumor clones at multiple sites of metastatic disease?**
- **how to hit each new variant clone that may emerge as an escape variant driven by the selection pressure of treatment?**

The Problem and The Challenge

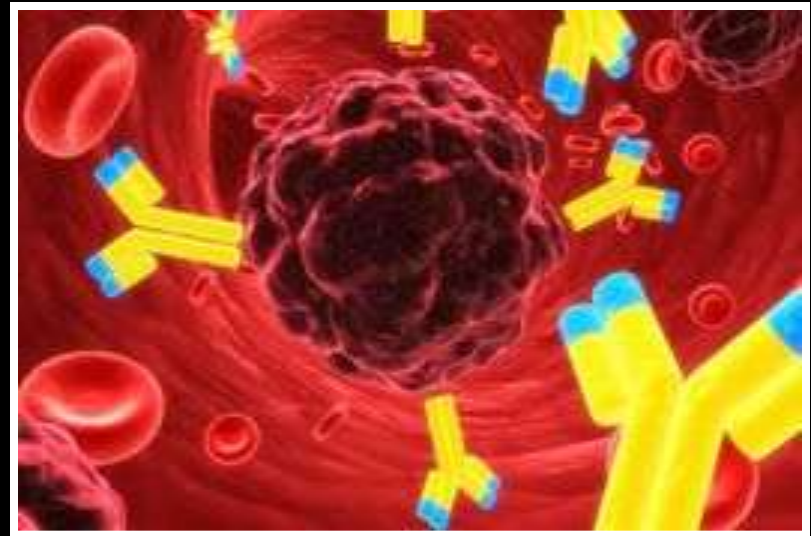
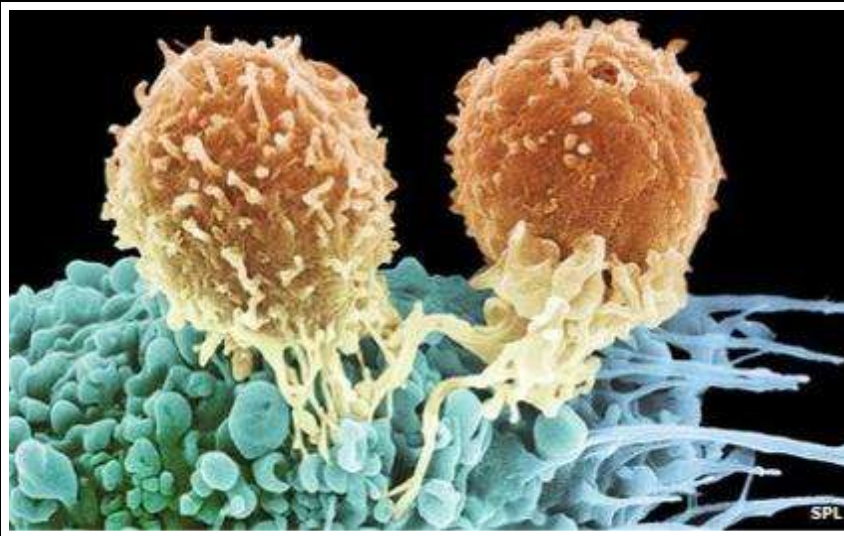
- **moving from limited narrow spectrum ‘chemo’ strategies to device new ways to attack every clone**
- **harnessing the cognate (detection) and destruction (killing) capabilities of the body’s immune system**

The Problem and The Challenge

- **harnessing the cognate (detection) and destruction (killing) capabilities of the body's immune system**
 - **how do cancers escape immune surveillance?**

Immunoavoidance by Tumor Cells

- “stealthy” tumor cell strategies that reduce detection and/or killing by body’s immune defenses



Immunoavoidance 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**

Immunoavoidance by Tumor Cells

- **“stealthy” tumor cell strategies that reduce detection and/or killing by body’s immune defenses**
- **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

Immunotherapies for Cancer

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

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

innate immunity

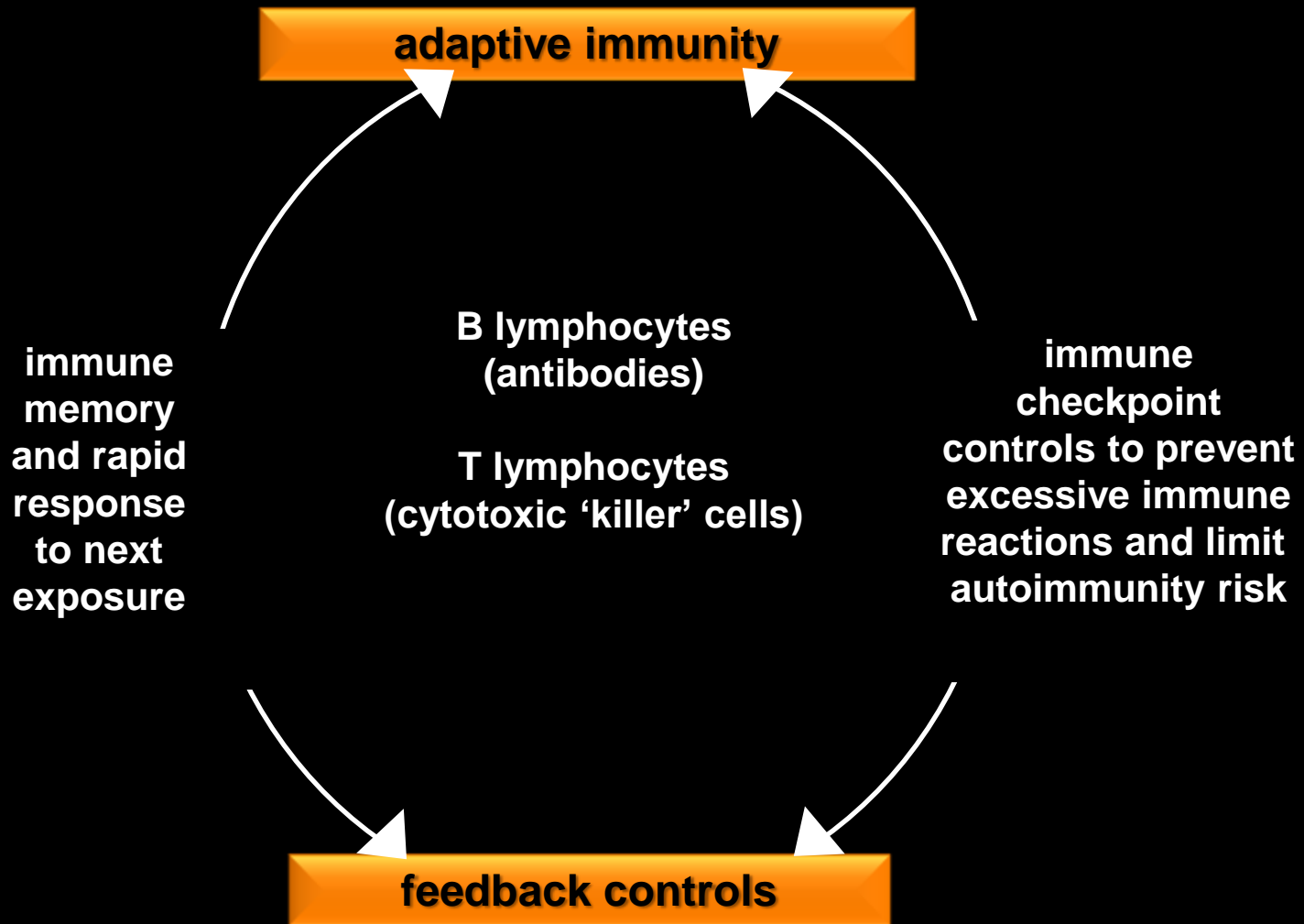
- rapid early detection of non-self presence
- AMPs: altered molecular pattern (AMP) recognition receptors



adaptive immunity

- first wave response
 - PMNs, macrophages, natural killer (NK) cells
- recruitment of antigen-presenting cells (APCs, dendritic cells)
- antigen-processing by APCs and presentation to lymphocytes to initiate adaptive response

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



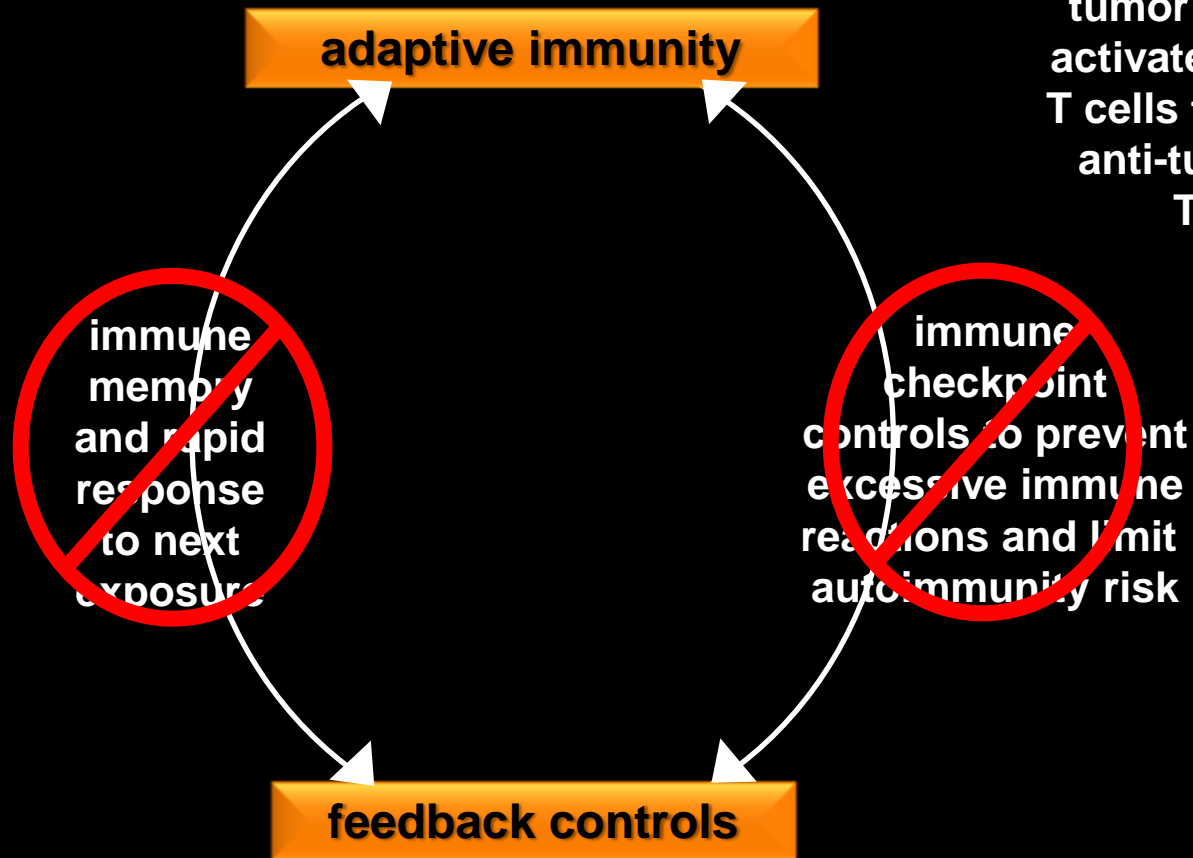
Immuno-evasion by Tumor Cells

stealth

antigen-deletion
variant tumor cell
clones go
undetected

hijacking

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



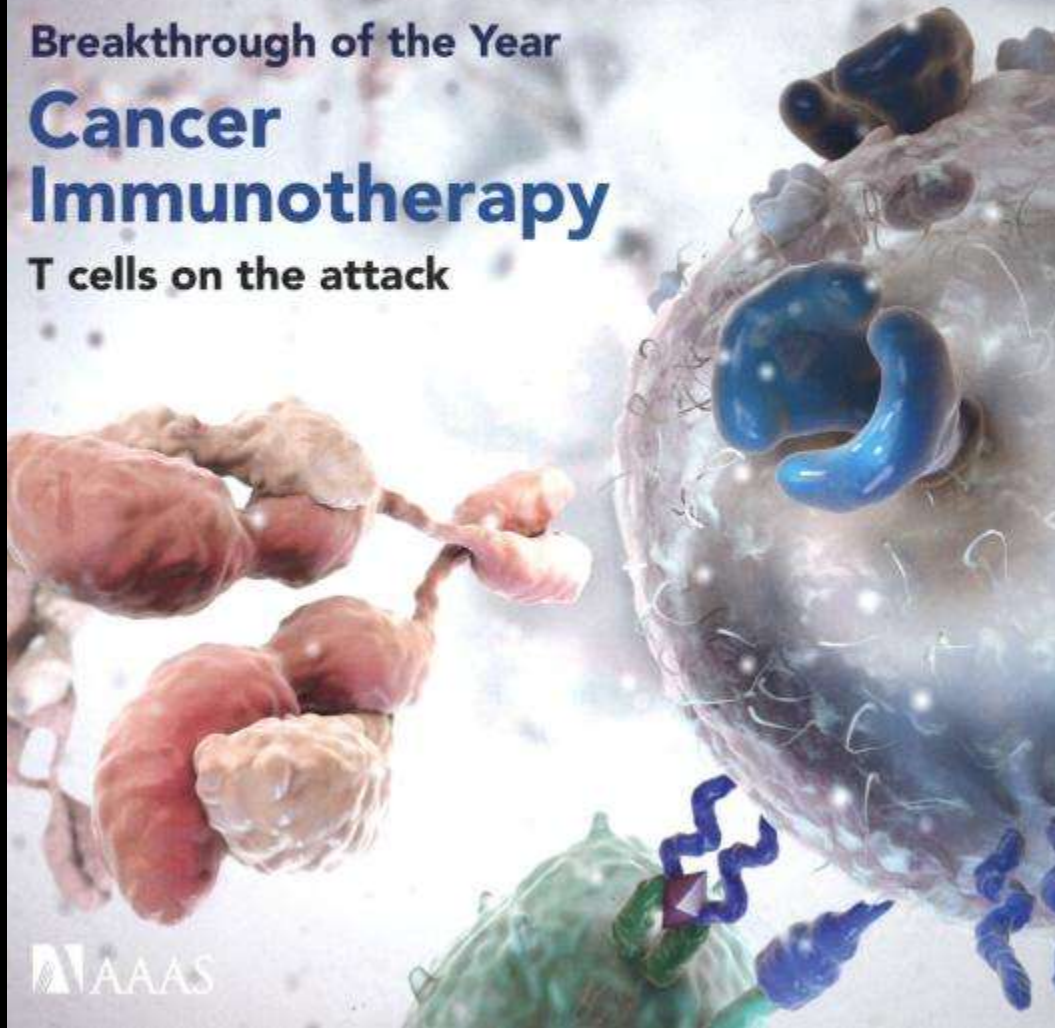
Science

20 December 2013 | \$10

Breakthrough of the Year

Cancer Immunotherapy

T cells on the attack

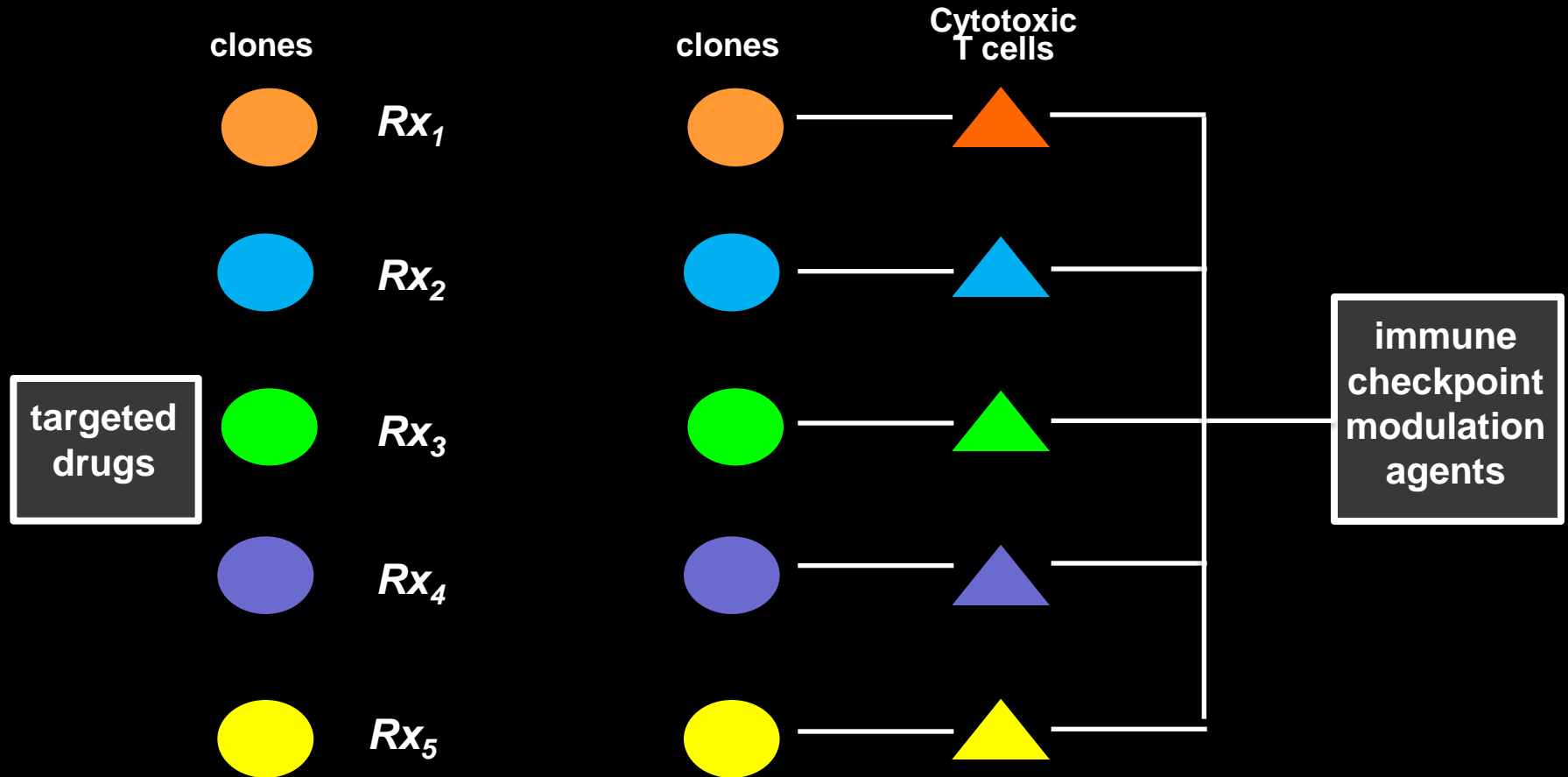


AAAS

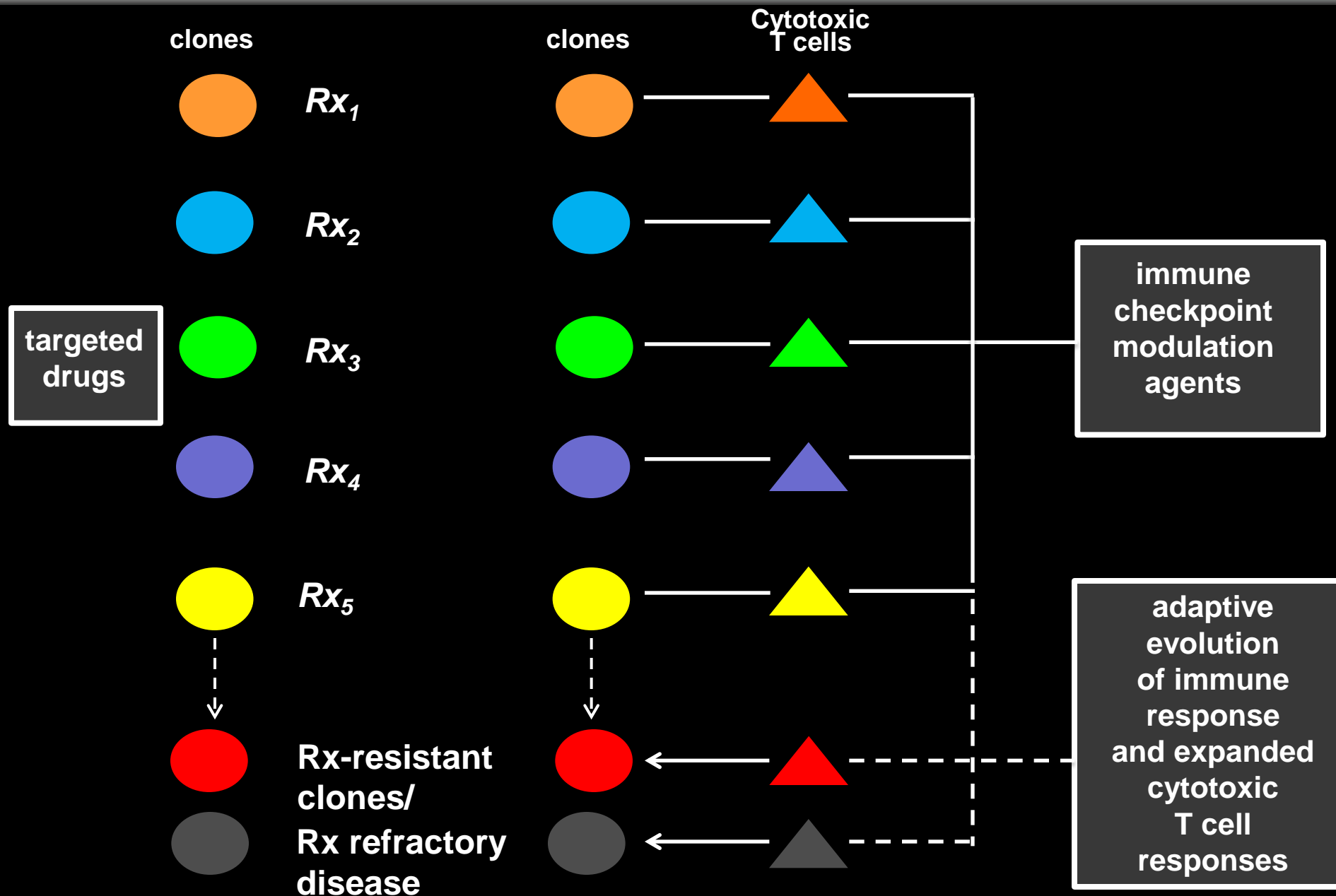
New Therapeutic Strategies to Circumvent Tumor-Mediated Suppression of Anti-Tumor Immune Responses

- **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



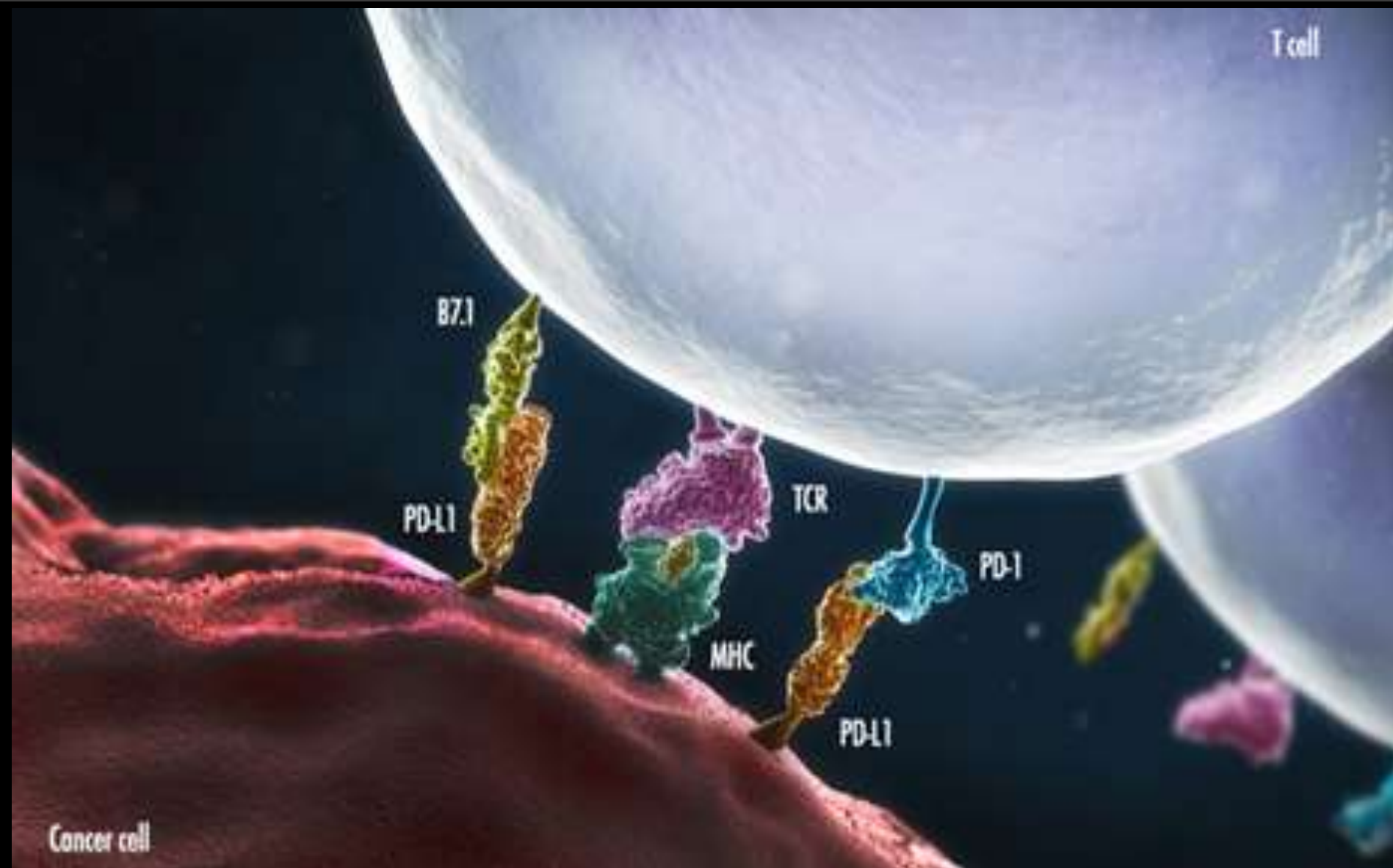
The Promise of Immune Checkpoint Modulation Versus The Drug Resistance Problem in Targeted Therapy



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; lambrolizumab, Merck)**

Expression of PD-L1 (Ligand) and Activation of Regulatory T Cells via PD-1 Receptor



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**

Activated (Immune) Cell Therapy (ACT) for Cancer

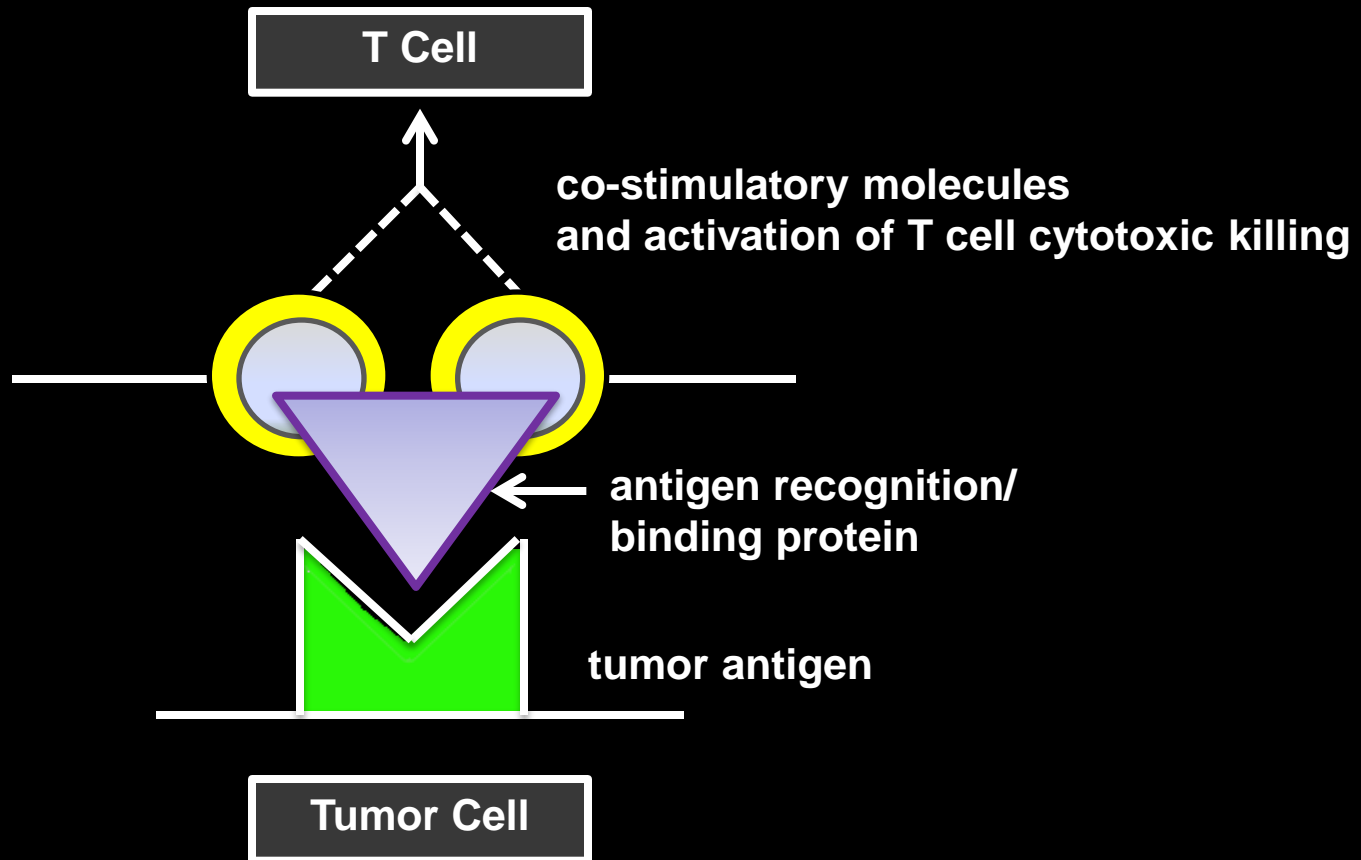
tumor-infiltrating lymphocyte (TIL) therapy

- collect, expand and re-infuse killer T cells from individual patients
- pre-infusion immunosuppression to facilitate engraftment of infused T cells
- utility to date restricted to melanoma trials
 - ease of access to tumor tissue
- low number of TILs recoverable from blood in other malignancies

Engineering Killer T Cells for Cancer Therapy

- **killer T cells harvested from cancer patients**
- **harvested cells genetically engineered in vitro to express T cell receptor(s) (TCRs) or chimeric antigen receptors (CARs) that recognize tumor antigen(s)**
 - **TCR/CAR genes delivered by viral vectors**
 - **TCRs must be genetically matched to the patients immune type**

Three Component Chimeric Antigen Receptors (CARs)



Engineering Killer T Cells for Cancer Therapy

Chimeric Antigen Receptor Therapy

- design of three component antibody-like proteins to bind to tumor cell surface antigen
- antibody component to identify and bind to cancer cells
- second and third component are activated by binding and stimulate T cell proliferation
- encouraging early clinical data but limited to targeting CD19 antigen on β cell leukemias and lymphomas

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**

Looking at the Full Dimension of Cancer Treatment and Care

Post-Treatment Challenges and Survivor Care in Cancer Treatment

Post-Treatment Challenges and Survivor Care in Cancer

- **physical**
- **emotional**
- **social**
- **economic**

Post-Treatment Challenges and Survivor Care in Cancer

Physical

- bone marrow immunosuppression and risk of infection
- impact on physical appearance, frailty and QOL
- cardiovascular/respiratory problems
- nausea, vomiting, diarrhea and other GI problems
- oral care, swallowing and feeding
- neuropathy
- fatigue
- cognition and concentration

Post-Treatment Challenges and Survivor Care in Cancer

Emotional

- **grief, anger**
- **concern over impact on physical appearance**
- **depression**
- **fear of recurrence**
- **family member risk of cancer**

Post-Treatment Challenges and Survivor Care in Cancer

Social: Economic

- financial debt
- employment
- insurability
- education
- effects on social relationships
- grief and bereavement

HOME ALONE:

*Family Caregivers Providing
Complex Chronic Care*



Susan C. Reinhard, RN, PhD
*Senior Vice President and Director,
AARP Public Policy Institute*

Carol Levine, MA
*Director, Families and Health Care Project,
United Hospital Fund*

Sarah Samis, MPA
*Senior Health Policy Analyst,
United Hospital Fund*



funded by



‘To Have and To Hold’

- **major analysis of 700,000 cancer patients**
- **married cancer patients had 20% reduction in deaths than single, divorced, separated and widowed patients**
- **marriage as surrogate for ‘social support’ system including children**
- **nulliparous US women: future implications**

Ensuring That the Patient's Voice is Heard

- **engaged patients have better outcomes by communicating clear goals and desires for their treatment**
- **goals may change over the course of the illness**
- **patients with advance care planning less likely to chose resuscitation and ventilation and death in an ICU**
- **communication must not be one way (physician to patient) or one-time**

Palliative Cancer Treatment

- **reduce or eliminate symptoms and complications**
- **non-curative intervention**
- **greater emphasis on quality-of-life (QOL)**



Bruja/PacificCoastNews.com

<http://aspenbio.wordpress.com/2011/11/02/cachexia-and-pancreatic-cancer/>

Dying with Dignity

**Discussions on End-of-Life Care:
A Difficult but Overlooked Topic**

Dying with Dignity

disease-related concerns

- pain and physical impairments
- cognitive and communication deficits

psychological and spiritual well being

- emotional functioning
- acceptance of disease
- at peace for imminent death
- concern for surviving family members

Dying with Dignity

autonomy, competency and decision-making

- **performance status**
- **clarity of patient preferences in advanced directive**
- **power of health attorney in place**
- **healthcare provider and/or family pressures for actions that conflict with patients stated desire**
- **explain patient's end-of-life (EOL) preferences and decisions to the patients and family in timely fashion not just at the end**

Advance Directives

- **discussions of death and dying largely avoided in patient management**
- **fewer than half cancer patients who died in 2011 had documented preferences**
 - **end-of-life care, resuscitation**
 - **durable power of attorney for health decisions**
- **when discussed typically in last 30 days of life or even less**
- **less than 15% ambulatory patients with advanced cancer have advanced directives**



ARIZONA ADVANCE DIRECTIVE REGISTRY
GEORGE H POSTE

User ID:

Password:

The person named on the front of this card has an
advance health care directive registered at:

www.azsos.gov/adv_dir/

To access this directive please go to the above site
and enter the User ID and Password.

If you have any questions please call
(602) 542-6187 or toll-free (800) 458-5842.

Ensuring That the Patient's Voice is Heard

- transcending medical paternalism
- greater need for realism and promptness in communicating the challenges to patients and family no matter how difficult
- do not delay to the end
- current advance directive practices often circumvent the spirit of the law
 - tick the box but no meaningful discussion with patient and/or surrogates
 - coding evasion: “discussion with patient/surrogate not possible at this time”
- training of healthcare professionals regarding patient processes and preferences

BIO 302: Cancer Treatment

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 metastatic disease due to locally invasive tumor but no detectable metastases**
 - **only small fraction may need treatment**
 - **lack of diagnostic profiling tools to identify the ‘at risk’ group**

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

- major progress in extending PFS and OS in leukemias and lymphomas
- less impressive gains in Rx efficacy against solid tumors
- over diagnosis/over-treatment of indolent tumors that pose low early metastatic risk
- targeted therapies for solid tumors
 - high cost and highly variable impact on disease progression
 - inevitable emergence of Rx-resistant clones
 - need for new methods for early detection of emergence of Rx-resistant clones

Cancer Treatment

- **are current 'chemo' approaches doomed to inevitable therapeutic failure due to failure to address the complex evolutionary biology of cancer?**
 - **clonal heterogeneity and emergence of drug-resistant clones**
 - **pre-existing drug-resistant clones**
 - **treatment-induced selection of drug-resistant clones**
 - **targeting cancer stem cells**

Cancer Treatment

- is the scale of disruption of molecular signaling networks in tumor clones in metastatic disease too large to be reversed by drugs that act on a single target
 - role of by-pass signaling pathways in generation of drug-resistance
- technical and clinical challenges of hitting multiple targets to limit compensatory by-pass resistance/escape pathways

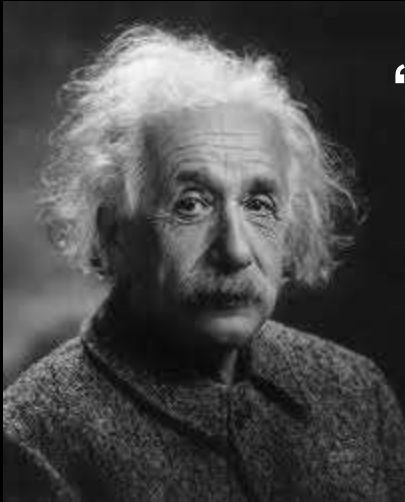
Cancer Treatment

- **clonal heterogeneity and plasticity (redundancy)
molecular signaling networks**
 - the core problem in the design of effective therapies
 - hitting multiple targets in the same signaling pathway
 - hitting multiple signaling pathways to block bypass resistance pathways
 - hitting multiple clones

Cancer Treatment

- **hitting multiple targets**
- **promiscuity in a single Rx (very low probability of success)**
- **multi-drug regimens to hit multiple targets (cost, clinical impact on patients)**
- **any 'chemo' strategy still faces prospect of inevitable emergence of Rx-resistant clones?**

Knowing When to Stop!



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

Albert Einstein

Cancer Treatment

- **urgent need 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**
 - **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?**

Precision Medicine and Cancer Therapy

- **molecular profiling and a new taxonomy for the classification of tumor subtypes**
- **understanding the dynamics of clonal diversification in tumor progression**



- **implications for future discovery efforts for new anti-cancer treatments**
- **need for new clinical trial designs and regulatory policies based on molecular profiling of patients and monitoring of clonal dynamics**

Cancer Treatment

- **molecular profiling and a new taxonomy for the classification of tumor subtypes**
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- **implications for future discovery efforts for new anti-cancer treatments**
- **need for new clinical trial designs and regulatory policies based on molecular profiling of patients and monitoring of clonal dynamics**

Week 14 Lectures 1 & 2