Cancer immunotherapy: an update
General principles

• The immune system recognizes and reacts against cancers

• The immune response against tumors is often dominated by regulation or tolerance
  – Evasion of host immunity is one of the hallmarks of cancer

• Some immune responses promote cancer growth

• Defining the immune response against cancers will help in developing new immunotherapies
T cell responses to tumors
Cross-presentation of tumor antigens
Immune phenotypes that predict better survival

Analysis of 124 published articles on correlation of T cell subsets and prognosis of 20 cancer types

Types of tumor antigens

• Most tumor antigens that elicit immune responses are neoantigens
  – Not present normally, so no tolerance
  – Produced by mutated genes that may be involved in oncogenesis (driver mutations) or reflect genomic instability (passenger mutations)
  – In tumors caused by oncogenic viruses (HPV, EBV), neoantigens are encoded by viral DNA

• Some are unmutated proteins (tyrosinase, cancer-testis antigens)
  – Derepressed (epigenetic changes), over-expressed
Identification of tumor neoantigens

1. Obtain tumor material
2. Identify tumor-specific mutations within expressed genes
3. Filter in silico
   - Filter by MS analysis
4. Assess T cell recognition

Next gen sequencing and/or RNA-seq

Identification of HLA-binding peptides

MHC-peptide multimer and/or functional assays
Immune responses that promote tumor growth

The history of cancer immunotherapy: from empirical approaches to rational, science-based therapies
Harnessing the immune system to combat cancer

Cancer vaccines

Antigen presentation

Tumor cell

T cell

Adoptive cellular therapy

Blockade of checkpoint molecules

Dendritic cell

Vanneman and Dranoff, Nat Rev Can, 2012
Chimeric antigen receptors

- Remarkable success in B cell acute leukemia (targeting CD19); up to 90% complete remission
- Risk of cytokine storm
- Outgrowth of antigen-loss variants of tumors?

Development of chimeric antigen receptors

First Generation CAR
- Targeting Element (scFv)
- VH and VL domains
- Linker
- Hinge
- CD3ζ (Essential signaling domain)

Second Generation CAR
- Targeting Element (scFv)
- VH and VL domains
- Linker
- One Costimulation Domain (4-1BB or CD28)
- CD3ζ

Third Generation CAR
- Targeting Element (scFv)
- VH and VL domains
- Linker
- Two Costimulation Domains (CD27, CD28, ICOS, 4-1BB, OX40)
- CD3ζ
Limitations and challenges of CAR-T cell therapy

• Cytokine storm – many T cells respond to target antigen
  – Requires anti-inflammatory therapy (anti-IL-6R)
  – Risk of long-term damage (especially brain)
• Unclear how well it will work against solid tumors
  – Problem of T cells entering tumor site
• Will tumors lose target antigen and develop resistance?
• Technical and regulatory challenges of producing genetically modified CAR-T cells for each patient
  – Prospect of gene-edited “universal” CAR-T cells?
Limitations and challenges of CAR-T cell therapy -- 2

- Exhaustion of transferred T cells
  - Use CRISPR gene editing to delete PD-1 from T cells
  - Increased risk of autoimmune reactions from endogenous TCRs
  - Use CRISPR to delete TCRs
  - Result is PD-1- T cells expressing tumor-specific CAR
Dendritic cell vaccination

Active T cell immunity enhanced by dendritic cell vaccines

Dendritic cells pulsed with tumor antigens → Vaccinate with tumor-antigen pulsed dendritic cell → Tumor antigen presentation to patient’s tumor-specific T cells → CD8+ T cell activation → Activation of tumor-specific T cells and killing of tumor cells
Blocking CTLA-4 promotes tumor rejection: CTLA-4 limits immune responses to tumors

Administration of antibody that blocks CTLA-4 in tumor-bearing mouse leads to tumor regression
Checkpoint blockade: Removing the brakes on the immune response

Anti-CTLA-4 antibody is approved for tumor immunotherapy (enhancing immune responses against tumors).

Even more impressive results with anti-PD-1 in cancer patients.
Checkpoint blockade for cancer immunotherapy

**Priming phase**
- Lymph node
- NO COSTIMULATION
- CD8+ T cell
- Tumor peptide-MHC
- CTLA-4
- B7
- CD28
- TCR

**Effector phase**
- Tumor tissue
- Activated CD8+ CTL
- Peptide-MHC
- Anti-PD-1
- PD-1 ligand
- TCR
- Cytotoxic granules
- Killing of tumor cell
Why do tumors engage CTLA-4 and PD-1?

- **CTLA-4**: tumor induces low levels of B7 costimulation $\rightarrow$ preferential engagement of the high-affinity receptor CTLA-4

- **PD-1**: tumors may express PD-L1

- Remains incompletely understood
  - These mechanisms do not easily account for all tumors
Is checkpoint blockade more effective than vaccination for tumor therapy?

- Tumor vaccines have been tried for many years with limited success

- Immune evasion is a hallmark of cancer
  - Multiple regulatory mechanisms

- Vaccines have to overcome regulation
  - Tumor vaccines are the only examples of therapeutic (not prophylactic) vaccines
  - Vaccination after tumor detection means regulatory mechanisms are already active
Targeting inhibitory receptors for cancer immunotherapy

• Blocking inhibitory receptors induces tumor regression
  – Partial or complete responses in up to 40%
  – Biomarkers for therapeutic responses?

• May be more effective than vaccination
  – Vaccines have to overcome tumor-induced regulation/tolerance

• Adverse effects (inflammatory autoimmune reactions)
  – Typically manageable (risk-benefit analysis)
Combination strategies for cancer immunotherapy

- Combinations of checkpoint blockers, or bispecific antibodies targeting two checkpoints
  - Already done with CTLA-4 and PD-1

- Checkpoint blockade (anti-PD1 or -CTLA-4) + vaccination (DCs presenting tumor antigen)

- Checkpoint blockade + agonist antibody specific for activating receptor

- Checkpoint blockade + kinase inhibitor to target oncogene
Checkpoint blockade: prospects and challenges

- Exploiting combinations of checkpoints
  - Poor biology underlying choice of combinations to block
  - Difficult to reliably produce agonistic antibodies

- Typically, 20-40% response rates; risk of developing resistance?
Checkpoint blockade: prospects and challenges

• Exploiting combinations of checkpoints
• Typically, 20-40% response rates; risk of developing resistance?

• Possible biomarkers of response vs resistance:
  - Nature of cellular infiltrate around tumor
  - Expression of ligands for inhibitory receptors (e.g. PD-L1) on tumor or DCs
  - Frequency of neoantigens (HLA-binding mutated peptides) in tumors from different patients
  - Frequency of tumor-specific “exhausted” T cells