The immunotherapy of cancer: past, present & the next frontier

Ira Mellman
Genentech
South San Francisco, California
William Coley and the birth of cancer immunotherapy

Elie Metchnikoff & Paul Ehrlich won the Nobel Prize 3 months later
Past activities focused on vaccines & cytokines

- Discovery that T cells in cancer patients detected tumor-associated epitopes (Thierry Boon, Brussels)

- Attempts to boost T cell responses with (peptide) vaccines
  - Thousands treated, few clinical responses
  - Poor mechanistic understanding of immunization

- Attempts to boost T cell responses with cytokines (IL-2, interferon)
  - Promising but limited clinical activity in various settings
  - On target toxicity an additional limit to broad use
  - Limited mechanistic understanding

- Cancer immunology & immunotherapy fails to find a home in either immunology or cancer biology
Dawn of the present: Ipilimumab (anti-CTLA4) elicits low frequency but durable responses in metastatic melanoma

Overall Survival

No. at risk

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Hodi et al (2010) NEJM
The sun continues to rise: anti-PD-1 is superior to and better tolerated than anti-CTLA4 (melanoma)

What we have learned: immunosuppression is a rate limiting step to effective anti-tumor immunity*

*for some patients

Chen & Mellman (2013) Immunity
Blocking the PD-L1/PD-1 axis restores, or prevents loss of, T cell activity

- PD-L1/PD-1 interaction inhibits T cell activation, attenuates effector function, maintains immune homeostasis
- Tumors & surrounding cells up-regulate PD-L1 in response to T cell activity
- Blocking PD-L1/PD-1 restores or prevents loss of T effector function
αPD-L1 and αPD-1 exhibit similar early activities despite blocking different secondary interactions.

αPD-1 blocks interaction with both PD-L1 & PD-L2 on myeloid cells.

αPD-L1 blocks PD-L1 interaction with inhibitory B7.1 on T cells.
Broad activity for anti-PD-L1/PD-1 in human cancer

Head & neck cancer
Lung cancer
Liver cancer
Melanoma
Renal cancer
Colorectal cancer
Bladder cancer
Glioblastoma
Breast cancer
Pancreatic
Gastric
Ovarian
Hodgkin lymphoma

Broad activity, but only subset of patients benefit: ~10-30%
Cancer Immunotherapy: present focus

Diagnostic biomarkers to enrich responders to PD-L1/PD-1

- Identify patients most likely to respond to αPD-L1/PD-1
- Identify combinations that extend the depth and breadth of response to PD-L1/PD-1
- Investigate new targets to overcome immunosuppression, enhance T cell expansion
PD-L1 expression predicts clinical response: an imperfect but useful Dx biomarker

Immune cells (ICs)  Tumor cells (TCs)  Tumor and immune cells (TCs and ICs)

Predictive of benefit in bladder cancer (ORR/OS)¹

Predictive of benefit in lung cancer (ORR/PFS/OS)²

WCLC 2015
¹IMvigor 210 (ECC 2015), ²POPLAR (ECC 2015)
PD-L1 expression by tumors can enrich for responses to atezolizumab (anti-PD-L1) in NSCLC and bladder cancer

**Lung cancer (TC + IC)**

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<tr>
<th>Subgroup (% of enrolled patients)</th>
<th>Survival hazard ratio*</th>
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<td>TC3 or IC3 (16%)</td>
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<td>TC2/3 or IC2/3 (37%)</td>
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<td>TC1/2/3 or IC1/2/3 (68%)</td>
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<td>TC0 and IC0 (32%)</td>
<td>0.73</td>
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<td>ITT (N = 287)</td>
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</table>

**Bladder cancer (IC only)**

<table>
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<td>TC3 or IC3 (16%)</td>
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</table>

Median OS Not Reached (95% CI, 9.0-NE)
Median OS 7.6 mo (95% CI, 4.7-NE)

Vansteenkiste et al (2015) ECC
Rosenberg et al (2015) ECC
PD-L2 also correlates with clinical benefit to atezoluzumab (n=238 patients)

OS HR: 0.46 (95%CI: 0.27 – 0.78)
PD-L1

OS HR: 0.39 (95%CI: 0.22 – 0.69)
PD-L2

OS HR: 0.43 (95%CI: 0.24 – 0.76)
PD-1

B7.1
OS HR: 0.44 (95%CI: 0.26 – 0.77)

Schmid et al (2015) ECC; data from Fluidigm panel
The predictive power of PD-L1+ IC’s suggests a special role for infiltrating immune cells in anti-tumor T cell function


- Why can PD-L1 expression by immune infiltrating cells more predictive than PD-L1+ tumor cells?
- Do PD-L1+ myeloid cells, not tumor cells, regulate T cell function at baseline?
- What is the actual mechanism of PD-1-mediated suppression?
PD-1 acts by down-regulating T cell costimulation via CD28, not TCR signaling

- Infiltrating immune cells may provide costimulation to help activate TILs, and then homestatically turn them off
- Importance of B7.1 and its interaction with PD-L1?

**Cancer Immunotherapy: present focus II**

**Combinations**

- Identify patients most likely to respond to αPD-L1/PD-1
- Identify combinations that extend the depth and breadth of response to PD-L1/PD-1
- Investigate new targets to overcome immunosuppression, enhance T cell expansion
Combinations of immunotherapeutics or immunotherapeutics with SOC/targeted therapies

**Hypothetical OS Kaplan Meier curves**

- Agents must be safe in combination with anti-PD-L1
- Targeted/chemo therapy should not interfere with immune response or immunotherapeutic mechanism of action
Combinations may extend the benefit of anti-PDL1 Chemo and targeted therapies

- MEK is not required for T cell killing
- MEK inhibition slows T cell apoptosis in tumors
Chemotherapy as immunotherapy: effect of platins on preclinical efficacy and immunobiology

Camidge et al., 16th World Conference on Lung Cancer, Sept 6-9, 2015 (Denver)
Early data suggests that anti-PD-L1 may combine with chemotherapy in NSCLC (& TNBC)

Includes all patients dosed by 10 Nov 2014; data cut-off: 10 Feb 2015; SLD, sum of longest diameters; ASCO 2015

*PD for reasons other than new lesions
Modulation of tumor immune status by chemotherapy may be transient

CD8 staining images are illustrative
Simultaneous combinations may help to maintain and extend tumor inflamed state.

- **Hypothetical curve**
  - Treatment (e.g., chemotherapy)
  - Response
  - Immunotherapy
  - Maintenance of inflamed state

CD8 staining images are illustrative.
Immune doublets: (1) agonist + PD-L1/PD-1
(2) second negative regulator + PD-L1/PD-1

- anti-OX40
- anti-CTLA4
- anti-CD137

PD-L1/PD-1 as a foundational therapy
Negative regulator anti-TIGIT combines with PD-L1 to produce complete tumor regression in mice

Ipi+nivo combination in melanoma: difficulty in assessing combos where one agent is more active

Marginal PFS benefit in all comers?

No PFS benefit in PD-L1-positive patients?

PFS benefit restricted to PD-L1-negative patients?

Challenges with endpoints in combination trials

- Difficulty in assessing the success of a given combination when one agent is significantly more active than the other.

- The utility of traditional radiographic response criteria for cancer immunotherapy (CIT) may be limited by the non-classical tumor kinetics ("pseudoprogression") observed in some patients with clinical benefit.

- ORR and PFS have underestimated the overall survival (OS) benefit in monotherapy studies with PD1/PDL-1 inhibitors: how do we keep later line cross-over from confounding and prolonging studies?

- Immune modified RECIST may capture of benefit of atypical responses otherwise missed with RECIST 1.1
  - All atezolizumab trials include RECIST 1.1 and imRECIST.
Cancer Immunotherapy present focus III: looking for next generation targets in the same space

Agonists to costimulators
- αOX40
- αCD27
- αCD137
- αCD40
- αGITR

Antagonists of negative regulators, Treg depletors
- αLag-1 (MHCII blocker)
- αKIR (NK cell activator)
- αTim-3 (PS? Galectin? CEACAM?)
- αTIGIT (PVR blocker, CD226 activator)
- NKG2a, IDOi
Current approaches largely address patients with pre-existing immunity

Pre-existing Immunity (20-30%?)

Non-functional immune response

Excluded infiltrate

Immune desert

CD8/IFNγ signature

Response to immunotherapy

Many or most patients may lack pre-existing immunity
Cancer immunotherapy: the next frontier
Exploring the entirety of the cancer immunity cycle

1. Release of cancer cell antigens (Cancer cell death)
2. Cancer antigen presentation (Dendritic cells/APCs)
3. Priming and activation (APCs and T cells)
4. Trafficking of T cells to tumors (CTLs)
5. Infiltration of T cells, through the stroma, and into tumors (CTLs, endothelial cells, stromal cells)
6. Recognition of cancer cells by T cells (CTLs, cancer cells)
7. Killing of cancer cells (CTLs, cancer cells and immune cells)

Excluded infiltrate
- Extracellular matrix
- MDSCs
- Chemokines
- CAFs
- Protease processing
- Angiogenesis

Immune desert

Non-functional response

Blood vessel
Cancer immunotherapy: the next frontier
Capturing patients without pre-existing immunity

1. Release of cancer cell antigens (Cancer cell death)
2. Vaccines (neo-epitope, conserved)
   Induced inflammation (cytokines)
   Chemotherapy, targeted agents
   Oncolytic viruses
   T cell-directed bispecific antibodies
3. Priming and activation (APCs and T cells)
4. Trafficking of T cells to tumors (CTLs)
5. Infiltration of T cells, through the stroma, and into tumors (CTLs, endothelial cells, stromal cells)
6. Recognition of cancer cells by T cells (CTLs, cancer cells)
7. Killing of cancer cells (CTLs, cancer cells and immune cells)

Excluded infiltrate
- Extracellular matrix
- MDSCs, B cells
- Chemokines
- Protease processing
- Angiogenesis

Immune desert

Non-functional response

Induced inflammation (cytokines)
Indication response rates correlate with mutation frequency

Patients with lung cancer have a high rate of somatic mutations

Higher mutation rates have been observed in lung cancer tumors from smokers vs nonsmokers

High mutational rates likely contribute to increased immunogenicity

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Structural analysis suggests that only some mutations will be accessible to T cell receptors.

**Immunogenic?**

**solvent-exposed mutation**

**Non-immunogenic?**

**mutation in MHC groove**

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<tr>
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Promise for an individualized vaccine?: *immunization with antigenic peptides regresses MC-38 tumor growth*

Yadav et al. (2014) Nature
Cancer immunotherapy: the frontier
Environment, microbiome, and patient genetics

- Whole blood: 20ml, 50ml
- Nasal swabs / Stool
- Skin Biopsy
- Clinical data
- Serology

- Microbes
- Adjuvants
- Cytokines
- TCR stim

- Supernatant
- Cell pellets

- Fully recruited: 1000 donors, 5 decades of life, 2 timepoints

- 1000 eCRF
- 15000 FCS files
- 1000 Genotypes
- 750K var / p
- 180.000 Supernatant Tubes
- ≥ 50 var / tube
- ≈ 2000 var / p
- 60.000 RNA profiles
- ≥ 600 var / tube
- ≥ 24000 var / d
- 1000 Enterotypes
- 16S rRNA NGS
- 300 fibroblast lines ➔ iPS
Summary

The past:
- Hampered by a poor understanding of human immunology

The present:
- Realization that normal immune homeostatic mechanisms restrict anti-cancer immunity
- Predominant focus on targets relevant to patients with pre-existing immunity

The frontier:
- Need to expand focus to include targeting stroma and to understand host genetics, the microbiome, and the environment
- Return to our origins to induce immunity in patients who have none
Perspectives

- We are at the beginning of an exciting journey for patients and for scientific investigation.
- Excitement has been driven by clinical data, outpacing the basic science foundation of cancer immunology.
- Investigating cancer immunology by “reverse translating” to the lab from clinical studies is needed to bring benefit to an ever greater number of patients.
- Rapid clinical progress and new response patterns have created a critical need for new approaches to regulatory assessment.
- Although the journey is just beginning, we can see the destination, justifying courageous action to accelerate our arrival time.