Principles of Tumour Immunology

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Disclosure Slide

• I have previously received speaker’s honorarium and travel support from BMS, Merck Sharp & Dohme, Boehringer Ingelheim, Arcus Biosciences.
Talk Outline

1. The Cancer Immunity Cycle
   - Cellular and humoral responses to tumor-associated antigens (TAA) & tumor neoantigens

2. Immunosurveillance of cancer
Cells of the immune system

INNATE IMMUNITY (rapid response)
- Macrophage (primary white blood cell)
- Natural Killer Cell (ILCs)
- Dendritic cell
- Neutrophil
- Eosinophil
- Basophil

ADAPTIVE IMMUNITY (slow response)
- B Cell
- T Cell (γδ, MAIT)
- Natural Killer T Cell
- Antibodies
- CD4+ T Cell
- CD8+ T Cell

ILCs – innate lymphoid cells
MAITs – Mucosal associated invariant T cells
γδ T cells – gamma delta T cells
Hallmarks of Cancer (2017)
The Cancer-Immunity Cycle – 7 steps to generate an effective anti-tumor response

1. Release of cancer cell antigens (cancer cell death)
2. Cancer antigen presentation (dendritic cells/ APCs)
3. Priming and activation (APCs & T cells)
4. Trafficking of T cells to tumors (CTLs)
5. Infiltration of T cells into tumors (CTLs, endothelial cells)
6. Recognition of cancer cells by T cells (CTLs, cancer cells)
7. Killing of cancer cells (Immune and cancer cells)
Not all cell death is the same
(at activating an anti-tumour immune response)
Requirements for immunogenic cell death

The Cancer-Immunity Cycle

1. Release of cancer cell antigens (cancer cell death)
2. Cancer antigen presentation (dendritic cells/APCs)
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Cell-mediated and humoral immune responses to tumour
Tumour-specific and tumour-associated antigens

(Neoantigens)

Tumor-specific antigen – antigen expressed on tumor cells but not on normal cells.

Tumor-associated antigen – antigen expressed on tumor cells but also found on normal cells, often in smaller amounts.

Presentation of mutant peptide from mutated cellular protein

Reactivation of embryonic genes not normally expressed in the differentiated cell

Overexpression of normal self protein by a tumor cell changes density of self-peptide presentation, allowing recognition by T cells
Cell-mediated and humoral immune responses to tumour

Dendritic cells

(IFNs)

Tumor

APC

Naïve CD8+ T cell

MHC class I

cellular immune response

production of interferons, cytokines and chemokines

Th1

IL-2

IFN-γ

Th2

IL-4

IL-5

IL-13

B cell

antibodies against

humoral immune response

Memory

Cell-mediated and humoral immune responses to tumour

Dendritic cells

(IFNs)
Activation of tumour specific T cells by APCs

Complexes of tumor antigens and heat-shock proteins are taken up by dendritic cells and presented to T cells.

Dying tumor cell

endocytosis or membrane fusion

Dendritic cell

CD4

CD8

TCR with the right specificity

Figure 16.17 The Immune System, 3rd ed. (© Garland Science 2009)
Requirements for effective priming of T cells

Signal # 1: Antigen presentation
Signal # 2: Co-stimulation
Signal # 3: Inflammatory cytokines

APC
MHC molecule
CD80/86
Antigenic peptide
T cell receptor (TCR)
CD28

T cell
IFN-α/β
IL-12
IL-1
Mutational load correlates with frequency of tumour neoantigens... & response

Estimate of the neoantigen repertoire in human cancer

Synder A et al., NEJM 2014
van Allen et al., Science, 2015, Hugo W et al., Cell 2016
Ton N. Schumacher, and Robert D. Schreiber
Science 2015;348:69-74
Cell-mediated and **humoral** immune responses to tumour
T cell-independent and T cell-dependent B cell activation

- **T cell-independent B cell activation**
  - B cells
  - BCR
  - IgM secretion

- **T cell-dependent B cell activation**
  - B cells
  - MHC-II
  - TCR
  - Th cell
  - Cytokines
  - IgG secretion
  - T cell activation by antigen presenting cells
  - Antigen uptake
Antibody mechanism of action

- Antibody-Dependent Cell-Mediated Cytotoxicity (ADCC)
- Antibody-Dependent Cellular Phagocytosis (ADCP)

Biolegend
ADCC - the underlying mechanism for the clinical efficacy of therapeutic anti-cancer antibodies.

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Target</th>
<th>FDA-approved indication</th>
<th>Approval in Europe*</th>
<th>Mechanisms of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trastuzumab (Herceptin; Genentech): humanized IgG1</td>
<td>ERBB2</td>
<td>ERBB2-positive breast cancer, as a single agent or in combination with chemotherapy for adjuvant or palliative treatment. ERBB2-positive gastric or gastro-esophageal junction carcinoma as first-line treatment in combination with cisplatin and capecitabine or 5-fluorouracil.</td>
<td>Similar</td>
<td>Inhibition of ERBB2 signaling and ADCC</td>
</tr>
<tr>
<td>Rituximab (Mabthera; Roche): chimeric human-murine IgG1</td>
<td>CD20</td>
<td>For the treatment of CD20-positive B cell NHL and CLL, and for maintenance therapy for untreated follicular CD20-positive NHL.</td>
<td>Similar</td>
<td>ADCC, direct induction of apoptosis and CDC</td>
</tr>
<tr>
<td>Bevacizumab (Avastin; Genentech/Roche): humanized IgG1</td>
<td>VEGF</td>
<td>For first-line and second-line treatment of metastatic colon cancer, in conjunction with 5-fluorouracil-based chemotherapy; for first-line treatment of advanced NSCLC, in combination with carboplatin and paclitaxel, in patients who have not yet received chemotherapy; as a single agent in adult patients with glioblastoma whose tumor has progressed after initial treatment, and in conjunction with IFNα to treat metastatic kidney cancer.</td>
<td>Similar</td>
<td>Inhibition of VEGF signaling</td>
</tr>
<tr>
<td>Cetuximab (Erbitux; Bristol-Myers Squibb): chimeric human-murine IgG1</td>
<td>EGFR</td>
<td>In combination with radiation therapy for the initial treatment of locally or regionally advanced SCCHN; as a single agent for patients with SCCHN for whom prior platinum-based therapy has failed; and palliative treatment of pretreated metastatic EGFR-positive colorectal cancer.</td>
<td>Similar</td>
<td>Inhibition of EGFR signaling and ADCC</td>
</tr>
<tr>
<td>Alemtuzumab (Campath; Genzyme): humanized IgG1</td>
<td>CD52</td>
<td>As a single agent for the treatment of B cell chronic lymphocytic leukemia.</td>
<td>Similar</td>
<td>Direct induction of apoptosis and CDC</td>
</tr>
<tr>
<td>Cilumimab (Arzerra; Genmab): human IgG1</td>
<td>CD20</td>
<td>Treatment of patients with CLL refractory to fludarabine and alemtuzumab.</td>
<td>Similar</td>
<td>ADCC and CDC</td>
</tr>
</tbody>
</table>

Table Adapted from Nature Reviews
Antibody engineering can further improve the therapeutic index of antibodies
The Cancer-Immunity Cycle

1. Release of cancer cell antigens (cancer cell death)
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7. Killing of cancer cells (Immune and cancer cells)
When the Cancer Immunity Cycle is completed....
Immunosurveillance of cancer
(Cancer Immunoditing)
3Es

- Normal
  - Carcinogens
  - Chronic inflammation
  - Inherited genetic mutations
  - Radiation
  - Viral infection
  - Loss of polarity
  - Loss of ECM contact

- Transformed
  - MICA/B, ULBP (human)
  - Tumor antigen
  - RAE1, H60 (mouse)

- Elimination (Cancer immune surveillance)
  - Innate and adaptive immunity
  - IFN-γ
  - Perforin
  - TRAIL
  - IFN-α/β
  - NKG2D

- Equilibrium (Cancer persistence)
  - Genetic instability and/or immune selection
  - Chronic inflammation

- Escape (Cancer progression)
  - sMICA/B
  - IL-23
  - Galectin-1
  - TGF-β
  - IL-10
  - Gangliosides

- KILL
- BATTLE
- LOSE

Teng et al., JLB 2008; Schreiber..Smyth. Science 2011
Teng et al., Cancer Res 2012, Teng et al., JCI 2015
TO THE EDITOR: We report a case of fatal melanoma that had been transferred in a donated kidney and that occurred 16 years after surgery for primary melanoma in the donor. A woman with polycystic disease received a renal transplant in May 1998. The graft functioned well. In November 1999, routine mammography showed a nodule in the left breast, and a biopsy specimen was obtained. Primary breast cancer was diagnosed. Pain and swelling then developed over the renal transplant, and two subcutaneous nodules were found. Biopsy confirmed the presence of secondary melanoma. No primary melanoma was identified. The pathological features of the breast specimen were reviewed, immunocytochemistry was performed, and secondary melanoma was diagnosed. Immunosuppression was stopped, the nodules were excised, and the patient underwent a trial of interferon, which was stopped because of toxicity. She died of metastatic melanoma in March 2000. In May 2000, a man presented with a palpable lump over a kidney, also donated in May 1998. The function of the graft had been good. Renal biopsy showed secondary melanoma, and again no primary tumor was identified.

The transplant registry showed that both of these patients had received a kidney from the same donor, who had died from a presumed subarachnoid hemorrhage. Autopsy had not been performed. The pa-
Changes in genomic landscape of human tumors = evidence for immunoediting

- Analysis of 18 TCGA tumour types shows genomic correlates of immune cytolytic activity
- Number of predicted MHC Class I-associated neoantigens correlated with cytolytic activity.
- Lower than expected in colorectal and other tumours, suggesting immune-mediated elimination
- Infiltrated tumours are enriched for probable escape lesions with mutations CASP8, HLA, B2M which mediates resistance to cytolytic activity

Rooney et al., Cell 2015
Immune contexture correlates with clinical outcome

Immune contexture associated with good prognosis in CRC

Chemokine
- ↑CXCL9
- ↑CX3CL1
- ↑CXCL10
- ↑CCL2
- ↑CCL5
- ↑CXCL13

Adhesion
- ↑MADCAM1
- ↑ICAM1
- ↑VCAM1

Cytotoxic
- ↑Granzymes
- ↑Perforin
- ↑Granulysin

T<sub>H</sub>1
- ↑T-bet
- ↑IRF1
- ↑STAT1

T<sub>FH</sub>
- ↑IL21

B cells

Tumor margin
- ↑CD3+, CD8+, CD45RO+ T cells

Immunoscore

Location, density, functional orientation of cells

Galon et al., 2006 Science, Pages et al., 2005 NEJM, Fridman et al., 2012 NRC, Bindea et al., 2013 Immunity
Evolution of Metastases in Space and Time under Immune Selection

Mihaela Angelova, Bernhard Mlecnik, Angela Vasaturo, Gabriela Bindea, Tessa Fredriksen, Lucie Lafontaine, Bénédicte Buttard, Erwan Morgand, Daniela Bruni, Anne Jouret-Mourin, Catherine Hubert, Alex Kartheuser, Yves Humbert, Michele Ceccarelli, Najeeb Syed, Francesco M. Marincola, Davide Bedognetti, Marc Van den Eynde, and Jérôme Galon.

A

P210

Lung metastases
Liver metastases

Primary colorectal cancer

M8

a

b

M7
tum.
nec.
b1
b2
b3
b4

Lung metastases
Liver metastases
Peritoneal metastases

Primary colorectal cancer

M10

P45

Localization
Primary tumor (PT)
Colon
Metastases
Liver
Lung
Peritoneum

Center of the tumor (CT)
Invasive margin (IM)
Hot Spot (HS)

E

P210
P45

Mutations: VarScan2 + Mutect
Unique counts per sample
Shared mutations
Among PT and metastases
Among metastases
1. Immune escape mechanisms

- Tumor alteration
  - Ploidy
  - Tumor escape
    - Immunoediting
    - Genomics
    - mIMH

- IL15
- LOH
- HLA
- LOH

- Adaptive immunity
  - Immune escape
  - PD-L1
  - FoxP3

- Immunomics

- Immunoscore Editing
  - Lo-No
  - Hi-No
  - Hi-Yes

2. Evolvogram under immune pressure

- Unedited tumor clones
- Immunoedited tumor clones

- Clonal evolution
1. Immune escape mechanisms

- Tumor alteration
  - Ploidy
- Tumor escape
  - Adaptive immunity
    - IL15
    - LOH
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- Immunogenicity
  - HLA
  - LOH
  - PD-L1
  - FoxP3
- Immunoediting
  - mIMH
- Genomics

2. Evolvogram under immune pressure

- Unedited tumor clones
  - CD3+ Ki67+
  - CD45RO+
- Immunoedited tumor clones

3. Predictive factors of recurrence

- Metastasis size
- Distance CD3:CK⁺Ki67⁺
- Immunoscore
- Immunoediting
- Time to Recurrence
Cancer immunoediting and response to immunotherapy

A. Elimination
- Normal Tissue
- Cytokines: IFNs, IL-12, TNF perforin
- Molecules: NKG2D, DNAM-1, TRAIL

B. Equilibrium
- IL-12
- IFNγ
- IL-23
- Tumour Dormancy (Not clinically apparent)

C. Escape
- IL-23
- Progressing Tumour (Clinically apparent)
- Secondary Escape (Acquired Resistance)

Immunotherapy
- Positive immunotherapeutic effect
- Negative immunotherapeutic effect

Immunosuppressive cell types:
- TAM, MDSC, Treg

Cytokine dysregulation:
- TGFβ↑, IL-12↓, IL-2↓, IL-15↓, IL-10↑

Metabolite dysregulation:
- Adenosine↓, Tryptophan↓

Chemokine dysregulation:
- TGFβ↑, CCL4↓, CCL2↑

Carcinogens
- Radiation
- Viral infections
- Chronic inflammation
- Inherited genetic mutations

Cytokines:
- IFNs, IL-12, TNF perforin

Molecules:
- NKG2D, DNAM-1, TRAIL

Tumour Dormancy
- (Not clinically apparent)

Progressing Tumour
- (Clinically apparent)

Primary resistance

On-treatment Equilibrium

On-treatment Elimination
- (Complete response)

A. Elimination
- Carcinogens
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B. Equilibrium
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- Inherited genetic mutations

Cytokines:
- IFNs, IL-12, TNF perforin

Molecules:
- NKG2D, DNAM-1, TRAIL

Tumour Dormancy
- (Not clinically apparent)

Progressing Tumour
- (Clinically apparent)

Primary resistance

On-treatment Equilibrium

On-treatment Elimination
- (Complete response)
Summary

- 7 major steps are required to generate an effective anti-tumour T cell response
Summary

• Cancer immunoediting exist in humans
• It proceeds through three phases; elimination, equilibrium and escape
• Cancer immunoediting occurs during the natural progression of tumours but can also occur in patients treated with cancer immunotherapies.
• To achieve tumour elimination, it will be essential to optimally combine therapies to promote immune activation and T-cell priming, attack immunosuppressive TME pathways, and sustain T-cells within tumour tissue.
Thank you
The four nodes to target for inducing maximal anti-tumour immunity

**Node 1: Elimination of immune suppression**
- PGE₂
- TGF-β
- Immature dendritic cell
- Arginase-1
- HIF-1α
- VEGF
- CCL2
- IDO
- IL-10
- Tie2
- IL-13
- CSF1
- IL-23

**Node 2: Immunogenic cancer cell death**
- NKG2A KIR
- CTLA-4
- PD-1
- LAG-3
- TIM-3
- BTLA
- VISTA
- PD-1H
- TIGIT
- CD96
- Inhibitory
- TRAIL-R agonists
- Oncogene inhibitors
- HDAC inhibitors
- Chemokines to attract CTL and T₃₁
- Vaccines to generate CTL and T₃₁
- Proteasome inhibitors
- p53 rescue

**Node 3: Enhanced APC function/adjuvanticity**
- SIRPα antagonists
- CD40 agonists
- GM-CSF
- STING activator
- Type I IFN

**Node 4: Enhanced T/macroage effector activity**
- ICOS
- CD28
- CD137
- OX40
- GITR
- CD27
- CD30
- HVEM
- DNAM-1
- CD28H

Smyth et al., NRCO 2016
Engagement of checkpoint receptors represents a major mechanism of tumour-induced immunosuppression.

Checkpoint receptors: Brakes to limit overzealous T cell activation

About 20 interactions regulate T cell immune response

Checkpoint blockade can unleash endogenous anti-tumour response

Improved Survival with Ipilimumab in Patients with Metastatic Melanoma

Safety, Activity, and Immune Correlates of Anti–PD-1 Antibody in Cancer

Nivolumab plus Ipilimumab in Advanced Melanoma

Nivolumab and Ipilimumab versus Ipilimumab in Untreated Melanoma

ORR – 10% 2010

ORR – 31% 2012

ORR – 53% 2013

ORR – 61% 2015
Anti-PD-1 to be used as standard of care and in combination immunotherapies

**ORR – 33.7% vs 11.9%**

**ORR – 31.7% vs 10.6%**

**ORR – 20% vs 9%**

**ORR – 44.8% vs 27.8%**
Cancer immunotherapy-based combination studies underway in 2016

Chen & Mellman Nature 2017
Tumour microenvironment can be stratified into 4 types based on TILs and PD-L1 expression in tumours.
Summary

• Anti-PD-1/PD-L1 - will become the immunotherapeutic backbone of future cancer treatments

• Cancers can be divided into four type
  – absence or presence of TILs and PD-L1 expression

• Efficient anti-tumour strategies must focus on hitting different targets concurrently

• Key nodes to target in combination treatment
  – abrogating immune suppression
  – inducing immunogenic cancer-cell death,
  – enhancing antigen presentation/adjuvanticity
  – inducing activation and survival of immune-effector cells
Summary

• Exome-sequencing data can be mined to
  – identify unique neoantigen profile of tumours
  – guide future personalized vaccine design for use in combination treatments

• A large proportion of patients have ‘immune ignorant’ (cold) tumours,
  – predicted to have a poor prognosis regardless of any current intervention
  – novel therapies have to be developed (Oncolytic virus, STING agonist, CAR-T).
Moving Forward...
Key issues in cancer immunotherapy

1) Identifying biomarkers to predict what cancers and pts will respond to anti-PD-1/PD-L1
2) How do we increase the proportion of patients who respond to anti-PD-1/PD-L1?
3) What therapies do we use to treat cancers with microenvironments that are resistant to anti-PD-1/PD-L1 monotherapy?
4) What do we do for patients who develop acquired resistance to anti-PD-1 therapies?
5) What is the optimal scheduling for administration of combination immunotherapy?
6) How to assess the therapeutic index (anti-tumour efficacy/irAEs) of combination immunotherapies?
Improving the tail of the curve....
Identifying biomarkers to predict patients who will respond to anti-PD-1/PD-L1
Tumour microenvironment can be stratified into 4 types based on TILs and PD-L1 expression in tumours.

- **Type I**: TIL+ PD-L1+ (38%)
- **Type II**: TIL- PD-L1+ (41%)
- **Type III**: TIL- PD-L1- (41%)
- **Type IV**: TIL+ PD-L1- (20%)

Melanoma

Taube et al. Sci Transl Med 2012, CCR 2014
**Association of anti-PD-L1 response and tumour-infiltrating immune cell PD-L1 expression**

**LETTER**

doi:10.1038/nature14011

**Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients**

Roy S. Herbst¹, Jean-Charles Soria², Marcin Kowaratz³, Gregg D. Fine⁴, Omid Hamid⁵, Michael S. Gordon⁶, Jeffery A. Sosman⁶, David F. McDermott⁷, John D. Powderly⁸, Scott N. Gettinger⁹, Hollbrook E. K. Kohr¹⁰, Leora Horn¹¹, Donald P. Lawrence¹², Sandra Rost³, Maya Leabman³, Yuanyuan Xiao¹³, Ahmad Mokatrin¹¹, Hartmut Koeppen¹¹, Priti S. Hegde¹³, Ira Mellman¹³, Daniel S. Chen¹³ & F. Stephen Hodi¹²

**Nature, 2014**

<table>
<thead>
<tr>
<th>Indication</th>
<th>n</th>
<th>Percentage of PD-L1 positive (IC)</th>
<th>Percentage of PD-L1 positive (TC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSCLC</td>
<td>184</td>
<td>26</td>
<td>24</td>
</tr>
<tr>
<td>RCC</td>
<td>88</td>
<td>25</td>
<td>10</td>
</tr>
<tr>
<td>Melanoma</td>
<td>58</td>
<td>36</td>
<td>5</td>
</tr>
<tr>
<td>HNSCC</td>
<td>101</td>
<td>28</td>
<td>19</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>141</td>
<td>18</td>
<td>5</td>
</tr>
<tr>
<td>CRC</td>
<td>77</td>
<td>35</td>
<td>1</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>83</td>
<td>12</td>
<td>4</td>
</tr>
</tbody>
</table>

**Nature, 2014**

![Image of PD-L1 expression](image-url)
Cancers with type I TME containing CD8\(^+\) T cells and PD-L1 most likely to respond to anti-PD-1/PD-L1

Level of PD-1 expression
Ngiow et al., Cancer Res 2015

PDL2 expression?

Factors that influence the cancer–immune set point
From bed-side

To bed-side

Clinical research

Ex vivo/
In vitro research

To bench

Experimental
Mouse research

From bench
What therapies do we use to treat cancers with TME that are resistant to anti-PD-1/PD-L1 monotherapy?
- T-VEC + anti-CTLA-4
- Chemotherapy or targeted therapy + anti-PD-1
- Type I IFN (poly-ic) + anti-PD-1 (Bald et al., Cancer Discovery 2014)
- Microbiota (Zitvogel L et al, Gajewski T el, Science 2015)
- Engineering FcR engaging variants of IgG (Ravetch Cancer Cell 2016)
- Scheduling (Neoadjuvant/adjuvant)
- CAR-T + anti-PD-1

anti-CD40 + anti-IL-23
anti-CD40 + anti-CSFR1
T-cell inflamed phenotype gene expression signatures to predict clinical benefit from pembrolizumab across 5 cancer types

<table>
<thead>
<tr>
<th>Signature</th>
<th>OR N = 107</th>
<th>PFS N = 109</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFN-(\gamma) (6 gene)</td>
<td>0.010</td>
<td>0.003</td>
</tr>
<tr>
<td>Expanded-immune (18 gene)</td>
<td>0.028</td>
<td>0.009</td>
</tr>
</tbody>
</table>

*aFrom logistic or Cox regression for OR and PFS, respectively; both regression models included terms adjusting for cancer type.*
Evidence for immunoediting in human tumours

- Analysis of 18 TCGA tumour types shows genomic correlates of immune cytolytic activity
- Multiple tumour types demonstrate strong link between mutation load and local immunity
- Number of predicted MHC Class I-associated neoantigens correlated with cytolytic activity. Lower than expected in colorectal and other tumours, suggesting immune-mediated elimination
- Infiltrated tumours are enriched for probable escape lesions affecting CASP8, HLA, B2M

Rooney et al., Cell 2015
Integrative Analyses of Colorectal Cancer Show Immunoscore Is a Stronger Predictor of Patient Survival Than Microsatellite Instability

- MSI and a subgroup of MSS patients have high intratumoral adaptive immune gene expression
- Functional effector anti-frameshift mutation CTLs kill tumor cells in MSI patients
- Genetic evidence of immunoediting in human CRC, in particular for MSI patients
- Immunoscore gives an indicator of tumor recurrence and survival beyond MSI staging
Priming of naïve T cells by pathogen-activated dendritic cells

- T Cell activation requires 3 signals:
  - Signal 1: Peptide/MHC::TCR
  - Signal 2: Costimulation (CD40::CD40L → CD80/86::CD28)
  - Signal 3: Cytokines for determination of activity

http://www.nature.com/nm/journal/v19/n1/fig_tab/nm201002501t.html
# Tumor associated antigens and tumor specific antigens

<table>
<thead>
<tr>
<th>Normal host cell displaying multiple MHC-associated self antigens</th>
<th>Tumor cells expressing different types of tumor antigens</th>
<th>EXAMPLES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal self proteins</td>
<td>Product of oncogene or mutated tumor suppressor gene</td>
<td>Oncogene products: mutated RAS, BCR/ABL fusion proteins</td>
</tr>
<tr>
<td>No T cell response</td>
<td>Mutated self protein</td>
<td>Tumor suppressor gene products: mutated p53 protein</td>
</tr>
<tr>
<td>MHC Class I</td>
<td>Overexpressed or abnormally expressed self protein</td>
<td>Various mutant proteins in carcinogen, or radiation, induced animal tumors; various mutated proteins in melanomas</td>
</tr>
<tr>
<td></td>
<td>Virus antigen-specific</td>
<td>Overexpressed: tyrosinase, gp100, MART in melanomas</td>
</tr>
<tr>
<td></td>
<td>CD8+ CTL</td>
<td>Aberrantly expressed: cancer-testis antigens (MAGE, BAGE)</td>
</tr>
<tr>
<td></td>
<td>Oncogenic virus</td>
<td>Human papilloma virus E6, E7 proteins in cervical carcinoma; EBNA proteins in EBV-induced lymphoma</td>
</tr>
</tbody>
</table>

![Diagram of Tumor associated antigens and tumor specific antigens](https://www.slideshare.net/csbrprasad/neoplasia-robbins-path-13540987)
Table 1. Classification of tumour-associated antigens that are recognised by T cells [3].

<table>
<thead>
<tr>
<th>Classification of tumour antigen</th>
<th>Mechanism of immune activation</th>
<th>Example</th>
</tr>
</thead>
</table>
| Cancer-testis antigens                 | Normal expression found in spermatocytes in testis (occasionally placenta), which is an immune-privileged site. Therefore, expression elsewhere in the body triggers T cell activation. | MAGE (melanoma antigen)  
BAGE (B antigen)  
GAGE (G antigen) |
| Differentiation antigens               | Antigen is expressed by the tumour and the normal tissue from which it arose.                    | CEA – expressed in embryonic tissue and over-expressed in colorectal cancer.  
Gp100 – expressed in melanocytes and melanoma.  
PSA – expressed in normal prostate and over-expressed in prostate cancer. |
| Over-expressed tumour-associated antigens | Level of expression in normal tissue is below the threshold for T cell activation. Over-expression by malignant cells overrides tolerance and triggers T cell activation. | Her2 – over-expressed in breast cancer.  
AFP – over-expressed in hepatocellular cancer and certain germ cell tumours. |
| Tumour-specific antigens               | These arise from genetic mutations or splicing aberrations, generating a protein that is foreign to the host immune system. | Mutant K-RAS in colorectal cancer. |
| Fusion proteins                        | Chromosomal translocation in certain tumours results in fusion of distant genes and expression of an abnormal fusion protein that is foreign to the host immune system. | BCR-ABL in CML and some ALL.  
EML4-ALK in non-small cell lung cancer. |

*CEA*: carcinoembryonic antigen,  
*PSA*: prostate specific antigen,  
*Her2*: human epidermal receptor 2,  
*AFP*: alpha-fetoprotein,  
*BCR-ABL*: break point cluster region-Abelson,  
*EML4-ALK*: echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase,  
*CML*: chronic myeloid leukaemia,  
*ALL*: acute lymphoblastic leukaemia.
Activation of tumor specific T cells by AntigenPresenting Cells (APCs)

Complexes of tumor antigens and heat-shock proteins are taken up by dendritic cells and presented to T cells.
Antibody mechanism of action
Targeting CTLA-4 and PD-1 to release the brakes on T cells
The Immune System Delves P and Roitt I, NEJM 2000
The five classes of antibodies, or immunoglobulins (Igs)

Classes of Antibodies

**IgG** antibodies account for 80 percent of all antibodies. IgG antibodies are responsible for resistance against

**IgE** attaches as an individual molecule to the exposed surfaces of basophils and

**IgD** is an individual molecule on the surfaces of B cells, where it can bind antigens in the extracellular fluid. This

**IgM** is the first class antibody secreted after antigen is encountered. Concentration decline, production acceleration, anti-A and anti-B anti
Cancer
Emerging Hallmarks and Enabling Characteristics

Emerging Hallmarks
- Deregulating cellular energetics
- Avoiding immune destruction
- Genome instability and mutation
- Tumor-promoting Inflammation

Enabling Characteristics

Hanahan and Weinberg, Cell 2011
Hallmarks of Cancer (2017)
### Tumor Antigens

Potential tumor rejection antigens have a variety of origins.

<table>
<thead>
<tr>
<th>Class of antigen</th>
<th>Antigen</th>
<th>Nature of antigen</th>
<th>Tumor type</th>
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<th>Tumor type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Differentiation</td>
<td>Tyrosinase</td>
<td>Enzyme in pathway of melanin synthesis</td>
<td>Melanoma</td>
<td>Specific antibody after gene rearrangements in B-cell clone</td>
<td>Lymphoma</td>
</tr>
<tr>
<td>Abnormal gene expression</td>
<td>HER-2/neu</td>
<td>Receptor tyrosine kinase</td>
<td>Breast</td>
<td>Underglycosylated mucin</td>
<td>Ovary</td>
</tr>
<tr>
<td>Abnormal post-translational modification</td>
<td>MUC-1</td>
<td></td>
<td>Breast</td>
<td>Viral transforming gene products</td>
<td>Pancreas</td>
</tr>
<tr>
<td>Oncoviral protein</td>
<td></td>
<td></td>
<td>Cervical carcinoma</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 14-11 Part 2 of 2 Immunobiology, 6/e, © Garland Science 2005
### TUMOR ANTIGENS

Potential tumor rejection antigens have a variety of origins

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<tr>
<td>Tumor-specific mutated oncogene or tumor suppressor</td>
<td>Cyclin-dependent kinase 4</td>
<td>Cell-cycle regulator</td>
<td>Melanoma</td>
</tr>
<tr>
<td></td>
<td>β-Catenin</td>
<td>Relay in signal transduction pathway</td>
<td>Melanoma</td>
</tr>
<tr>
<td>Germ cell</td>
<td>Caspase-8</td>
<td>Regulator of apoptosis</td>
<td>Squamous cell carcinoma</td>
</tr>
<tr>
<td></td>
<td>MAGE-1 MAGE-3</td>
<td>Normal testicular proteins</td>
<td>Melanoma Breast Glioma</td>
</tr>
</tbody>
</table>
The many flavours of CD4+ T cells
Conceptual Developments in Cancer Immunology

1 Cancer immunoediting
2 Tumour Neoantigen
3 Immune Reaction
4 Combination mAb-based therapy
5 Tumour induced Immune suppression
Sources of slide

- Charles Janeway’s Immunobiology text book
- Peer-reviewed articles (Pubmed)
- Online slides (URL listed)
Types of professional Antigen Presenting Cells (APCs)

Professional APCs

DCs and macrophages

- Phagocytic
- Express receptors for apoptotic cells, DAMPs and PAMPs
- Localize to tissues
- Localize to T cell zone of lymph nodes following activation (DCs)
- Constitutively express high levels of MHC class II molecules and antigen processing machinery
- Express co-stimulatory molecules following activation

B cells

- Internalize antigens via BCRs
- Constitutively express MHC class II molecules and antigen processing machinery
- Express co-stimulatory molecules following activation

Cells can die in different ways

**Programmed Cell Death**

- Apoptosis
  - Autophagic Cell Death
    - Anoikis
    - Cornification ("keratinization")
  - Pyroptosis (casp-1)
- Necroptosis (RIPK1/3)
  - Necrotic Cell Death
    - "accidents": lack of energy, physical damage, chemical damage

**DAMPs, PAMPs, tumour antigens**
Effector responses of NK cells are regulated by inhibitory and activating receptors

![Diagram showing the regulation of NK cell responses](image)

- **Missing-self**
  - Target
  - NK cells
  - Release of Cytokines
  - Cytolysis

- **Normal**
  - MHC-I
  - Inhibitory receptor
  - Activation receptor

- **Induced-self**
  - Release of Cytokines
  - Cytolysis
Major inhibitory and activating receptors on NK cells and their cognate ligands on targets

Chan et al., 2014 Cell Death Differentiation
Antibody mechanism of action