ESMO Preceptorship Program: Immuno-Oncology, From the essentials of tumor immunology to clinical application – May 4 2018, Lugano

From basic to tumor immunology for oncologist

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DISCLOSURES
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Personal financial interests
Speaker honoraria: BMS, Astra Zeneca, Roche
Member Scientific Advisory Board: Immatics biotechnologies, Enterome
Grant for research: Roche pRED, Zurich

Non-financial interests
Transgene - Member Scientific Advisory Board
NexImmune - Member Scientific Advisory Board
Editor-in-chief - Journal for Immunotherapy of Cancer
It all started ca. 1895 – NY Hospital

Immuno-Oncology is ~ 120 years old

ORR by 1900 – 20%, tumor type: sarcomas

ORR by 2018 – close to 100% in HM, 20 – 50% in solid tumors

Products – toxins by 1900; CAR T cells and mAbs by 2018
Major Questions

Can the Immune System recognize Cancer?

Can we use the Immune System to fight Cancer?
« It ’s every immunologist ’s dream to use the immune system to cure cancer. It ’s every immunologist’s nightmare that there is not such a thing as an immune response to cancer in humans. »

Steven Rosenberg, 1992
Concept of immunosurveillance
Adaptive immunity can confer long term and effective control of minimal tumor burden.

Low dose carcinogen

~ 20%

α-CD4, α-CD8, α-IFN-γ
The current model of immunoediting: the three Es

**Elimination**

- *Cancer immunosurveillance*
  - Effective antigen processing/presentation
  - Effective activation and function of effector cells
    - e.g. T cell activation without co-inhibitory signals

**Equilibrium**

- *Cancer dormancy*
  - Genetic instability
  - Tumour heterogeneity
  - Immune selection

**Escape**

- *Cancer progression*
  - Tumours avoid elimination through the outgrowth of tumour cells that can suppress, disrupt, or ‘escape’ the immune system
Recognition of tumors by the immune system

What are the tumor targets recognized by T and B cells?
Structure of physiological antigen receptors

B CELL RECEPTOR (BCR)  T CELL RECEPTOR (TCR)

<table>
<thead>
<tr>
<th>T Cell Receptor</th>
<th>Antibody</th>
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<tbody>
<tr>
<td>Membrane</td>
<td>Membrane and soluble</td>
</tr>
<tr>
<td>Two chains</td>
<td>Two H and L chains</td>
</tr>
<tr>
<td>CDR1, 2 and 3</td>
<td>CDR1, 2 and 3</td>
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<tr>
<td>Ligand: MHC/peptide also unrestricted</td>
<td>unrestricted</td>
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<td>Two isotypes: $\alpha\beta$, $\gamma\delta$</td>
<td>Five classes: M, G, A, D, E Several isotopyes, per class</td>
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<td>Low affinity ($10^{-5}$ M)</td>
<td>High affinity ($10^{-9}$ – $10^{-11}$)</td>
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<tr>
<td>No affinity maturation</td>
<td>Affinity maturation</td>
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</tbody>
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CYTOLYTIC CD8 + T LYMPHOCYTES (CTL),

the major effectors of anti-tumor adaptive immunity

- Direct lysis (perforin, GZB)
- IFN-γ, TNF-α, GM-CSF ...
- Fas L
- CD40L