Immunotherapy of cancer
Some historical background

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History of cancer immunotherapy before the immune checkpoint inhibitors

- Coley's toxin (1863)
- Virchow: Immune infiltrates (1898)
- Burnet: Immune-surveillance (1957)
- Rosenberg: IL-2 and LAK cells (1976)
- Morales: BCG (1985)
- Lejeune: Isolated limb perfusion (1992)
- Slaman: Trastuzumab (1998)
- Bendani: Anti-idiotypic vaccination (1999)
Coley’s toxin

Complete remission of a sarcoma in a patient after 2 episodes of erysipelas caused by streptococcus pyogenes

William Coley, 1893
Coley’s toxin

• Induction of erysipelas by direct inoculation with streptococci

• Coley’s toxin: Heat inactivated mixture of streptoccoci and serratia
  About 900 patients treated, most inoperable sarcoma, 10% response rate. Treatment associated high fever

Fig. 3. First patient Coley treated by deliberate induction of erysipelas (Coley, 1896a). Large lesion on neck broke down and disappeared under treatment; see text for description. Patient remained well for 8 years, then died of recurrence (Coley, 1909).
Coley’s Active Career (1890-1936)

1890

1891
1894

1909

1931

1936

Vaccine used improperly to treat unselected patient population; isolated, but dramatic response in ovarian carcinoma.

1962

1965

1975
1978

Vaccine used concomitantly with chemotherapy to treat lymphoma patients; only modest effects.

1981

1988
1989
1990

Coley repeatedly calls attention to sarcomas as being comparatively sensitive to his treatment.

Vaccine of undetermined origin used unsuccessfully to treat melanoma and sarcoma patients, half of which were inappropriately selected.

Carswell et al. use a murine sarcoma in the discovery of TNF.

Berendt et al. use sarcomas to illustrate the importance of tumor immunogenicity to the curative effects of endotoxin.

Demetri et al. empirically select sarcomas for treatment with TNF and γ-interferon.
Isolated Limb Perfusion With High-Dose Tumor Necrosis Factor-α in Combination With Interferon-γ and Melphalan for Nonresectable Extremity Soft Tissue Sarcomas: A Multicenter Trial


Conclusion: ILP with TNF, IFN, and melphalan is a safe and highly effective induction biochemotherapy procedure that can achieve limb salvage in patients with nonresectable extremity STS. TNF is an active anticancer drug in humans in the setting of ILP.

Immunotherapy with BCG

- **Raymond Pearl, Amer J Hyg 1929:** Lower incidence of cancer in patients with TB
- **Lloyd Old, Nature 1959:** Mice infected with BCG have resistance to transplantable tumors
- **Burton Zbar, JNCI 1971:** Suppression of tumor growth in mice at the site of infection with BCG
- **George Mathé, 1968:** Adjuvant BCG in children with acute lymphoblastic leukemia
- **Donald Morton, Surgery 1970:** Intralesional treatment of melanoma metastases with BCG
- **Alvaro Morales, J Urol 1976:** Intracavitary bacillus Calmette-Guerin in the treatment of superficial bladder tumors
Immune Surveillance of Tumours

- *Paul Ehrlich 1909*: the immune system might repress a potential overwhelming frequency of carcinomas
Immune Surveillance of Tumours

• *Lewis Thomas 1957*: “… the primary function of cellular immunity is in fact not to promote allograft rejection but rather to protect from neoplastic disease, thereby maintaining tissue homoestasis in complex multicellular organisms”

• *1982 Lewis Thomas*: “the greatest trouble with the idea of immunosurveillance is that it cannot be shown to exist in experimental animals”
Immune Surveillance of Tumours

Sir Macfarlane Burnet, 1964

“...in animals, ..., inheritable genetic changes must be common in somatic cells and a proportion of these changes will represent a step toward malignancy.

It is an evolutionary necessity that there should be some mechanism for eliminating or inactivating such potentially dangerous mutant cells and it is postulated that this mechanism is of immunological character.”
IFN-gamma and lymphocytes prevent primary tumour development and shape tumour immunogenicity

Sponaneous carcinomas in immundeficient mice

RAG2\(^{-/-}\): no B and no T cells;

STAT1\(^{-/-}\): No IFN-y signaling

Shankaran, …, Old, Schreiber, Nature 2001
Vaccines against cancer-associated antigens


- “The demonstration of molecular remissions, analysis of cytotoxic T lymphocytes against autologous tumor targets, and addition of granulocyte-monocyte colony-stimulating factor to the vaccine formulation provide principles relevant to the design of future clinical trials of other cancer vaccines administered in a minimal residual disease setting”
Vaccination with patient-specific tumor-derived antigen in first remission improves disease-free survival in follicular lymphoma.
MAGRIT, a double-blind, randomized, placebo-controlled phase III study to assess the efficacy of the recMAGE-A3 + AS15 as adjuvant therapy in resected MAGE-A3-positive NSCLC
Cytokines in immunotherapy: the example of IL2

- *Steven Rosenberg, NEJM 1985*: Observations on the systemic administration of autologous lymphokine-activated killer cells and recombinant interleukin-2 to patients with metastatic cancer
Table 2. Toxicity of Therapy with LAK Cells and Interleukin-2

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malaise</td>
<td>25</td>
</tr>
<tr>
<td>Fever</td>
<td>22</td>
</tr>
<tr>
<td>Chills</td>
<td>19</td>
</tr>
<tr>
<td>Nausea or vomiting</td>
<td>21</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>18</td>
</tr>
<tr>
<td>Confusion</td>
<td>8</td>
</tr>
<tr>
<td>Weight gain (&gt;10%)</td>
<td>16</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>20</td>
</tr>
<tr>
<td>Erythema or rash</td>
<td>17</td>
</tr>
<tr>
<td>Pruritus</td>
<td>16</td>
</tr>
<tr>
<td>Glossitis</td>
<td>14</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>13</td>
</tr>
<tr>
<td>Serum creatinine &gt;2 mg/dl</td>
<td>12</td>
</tr>
<tr>
<td>Serum bilirubin &gt;2 mg/dl</td>
<td>16</td>
</tr>
<tr>
<td>Eosinophilia &gt;5%</td>
<td>24</td>
</tr>
<tr>
<td>Anemia requiring transfusion</td>
<td>24</td>
</tr>
<tr>
<td>Thrombocytopenia (&lt;50,000/mm³)</td>
<td>11</td>
</tr>
</tbody>
</table>

Rosenberg, NEJM 1985
Tolerance and effectiveness of recombinant interleukin-2 (r-met Hu IL-2 [ala-125]) and lymphokine-activated killer cells in patients with metastatic solid tumors.

- 26 patients with metastatic solid tumors, including 14 renal cell carcinomas, seven melanomas, three extragonadal germ cell tumors refractory to chemotherapy and two colon carcinomas
- Capillary leak syndrome with hypotension and impaired renal function and CNS toxicity were the major reasons for dose modification
- Partial responses were documented in three renal cell carcinomas and one melanoma. The median response duration was 5.5 (range 1-6) months.

Stahel, Eur J Cancer Clin Oncol 1989
High-Dose Recombinant Interleukin 2 Therapy for Patients With Metastatic Melanoma: Analysis of 270 Patients Treated Between 1985 and 1993

- 270 patients treated, RR 16% including 6% CRs
- 12 patients (28% of responding patients) remain disease free
- 6 patients died as related to treatment

Atkins, JCO 1999

- 259 patients treated, RR 20%, including 23 (9%) with CR
- 19 pts remain disease-free
- 2 pts with treatment related mortality

Klapper, Cancer 2008
Monoclonal antibodies in cancer therapy


17/37 responses in relapsed B-cell lymphoma
Monoclonal antibodies in cancer therapy


“The use of rhuMAb HER2 in combination with CDDP in patients with HER2/neu-overexpressing metastatic breast cancer results in objective clinical response rates higher than those reported previously for CDDP alone, or rhuMAb HER2 alone. In addition, the combination results in no apparent increase in toxicity.”
CTLA-4 and PD-1

• Brunet, ..., Golstein, Nature 1978: A new member of the immunoglobuline superfamily – CTLA-4

• Ishida, ..., Honjo, EMBO Journal, 1992: Induced expression of PD-1, a novel member of the immunoglobulin gene superfamily, upon programmed cell death
Immune checkpoint inhibition

- **Stephen Hodi, PNAS 2003:**
  Biologic activity of cytotoxic T lymphocyte-associated antigen-4 antibody blockade in previously vaccinated metastatic melanoma and ovarian carcinoma patients.

  MDX-CTLA4 stimulated extensive tumor necrosis with lymphocyte and granulocyte infiltrates in 3 of 3 metastatic melanoma patients...

(A) Reticular erythematous rash. (B) Perivascular lymphocyte infiltrate extending into epidermis with interface dermatitis. (C) CD4+ T cells apposed to dying melanocytes. (D) CD8+ T cells apposed to dying melanocytes.
Immune checkpoint inhibition

- **Judy Brahmer, …, Suzanne Topalian**
  *JCO 1010: Phase I study of single agent anti programmed death-1 in refractory solid tumors*

Objective responses in a patient with renal cell carcinoma (A) and melanoma (B)
Immunotherapeutic approaches

**Immunotherapy**

- **Active**
  - Acts directly on immune system
  - Enhancing Immune Cell Function
    - Coley’ toxin
    - TNFα
    - IL-2
  - Therapeutic Vaccines
    - Anti-idiotype
    - B-cell vaccine
    - MAGRIT
    - Private antigens
  - Immune Checkpoint Inhibitors
    - CTLA-4
    - PD-1
    - PD-L1 antibodies

- **Passive (Adoptive)**
  - Targets the tumor; may utilise immune system
  - Antitumor mAbs
    - Rituximab
    - Trastuzumab
  - Adoptive
    - LAK cells
    - CARs