IMMUNE THERAPY IN STS: WHERE ARE WE?
And where are we going?

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GSK
Morphotek / Eisai
Pfizer
Lilly / Imclone
Bayer
Sarcoma Alliance for Research through Collaboration (SARC)
Arcus
Gem Pharmaceuticals
Presage Biosciences
Studying immunity (like studying cancer):
Layer upon layer of complexity

These layers are not just independent or dependent: they interact
Boring little lymphocytes ?
More variety than anyone initially appreciated
Two arms of the immune system

Innate Immunity

- Dendritic Cell (DC)
- Monocyte
- Activated Macrophage
- Infected Cells

Natural Killer (NK) Cell

Adaptive Immunity

- Th2 Cell
- Th1 Cell
- CD8+ T cell
- CD4+ T cell
- Naive T Cell

EB

TNF, NO, IL-10, TGFβ

IL-12, IFNγ

Peptide, TCR, MHC

B Cell

IgG Antibodies

T cell subsets

Antigen Presenting Cell

Antigen input

Immune response

Initiation

IFNα/β
IL-12

+ TGFβ

IL-4

Th1

IL-6

IFNα/β
IL-12

Th9

IL-21

IL-12

Th17

IL-23

IL-27

CTL

IL-17

Tfh

IFNγ
TGFβ

Treg

RA

Amplification

IFNγ
TNFα

Th2

IL-4

IL-5

IL-13

Th9

IL-9

IL-17

Exaggeration

Th17

Autoimmunity

Asthma

Allergy

Autoimmunity

Cytokine storm

B cell costimulation

Fibrosis

Tumor

Qualities of stimulated lymphocytes

Dendritic cell classes

Lymph nodes

Spleen
- Plasmacytoid
- DN
- CD4⁺
- CD8⁺
- CD103⁺ (e.g. langerin⁺ dermal)

Migratory
- CD11b⁺ (e.g. classic dermal)
- Langerhans (skin)

Innate protection
- CD4 T cells
- CD8 T cells
- CD4 T cells
- CD8 T cells
- CD4 T cells
- CD8 T cells

The basic immune response: Cancer as a specific example.
Components of an effective immune response against cancer

- Phagocytes / APCs
- T cells
- Tumor antigens
  - Viral
  - Differentiation antigens
  - Novel antigens
- B cells or antibodies – paradoxical effects

...but tumors obviously grow despite all this
Cancer Immunology’s Basic Concept: Immune surveillance of cancer

• If it is possible to *tolerize* the immune system against an antigen, cancer neoantigens must be present that elicit an effective anti-tumor immune response

• If animals and humans can reject tissue grafts, they must have mechanisms to reject cancers

Amendment to immune surveillance: Immunoediting (add some Darwin)

Dunn GP, Old LJ, Schreiber RD. 2004; Immunity 21: 137
Immunotherapy: what is out there?

• **Mifamurtide**: Muramyl tripeptide - nonspecific immunotherapy for osteogenic sarcoma

• Limiting factor: cost

• Could MTP-PE work in other sarcomas?

Meyers PA et al. JCO 2008; 26: 633
Modifying the equilibrium between the immune system & cancer

1. **Vaccines**
   - Specific antigens
   - Whole cells
   - Adjuvants (TLR agonists, viral vectors)

2. **mAb against a specific antigen**
   - Passive immunity – antibody directed cell mediated cytotoxicity (ADCC)

3. **Activated T cells against a specific antigen**
   - CAR-T cells

4. **mAb against immune effectors**
   - Immune checkpoint inhibitors

5. **Stromal effects/effectors**
   - IDO
Examples
Vaccinology: NCI meta-analysis

- 440 patients
  - Melanoma (vast majority of patients)
  - Variety of antigens: MART1, gp100, NYESO1, TRP2, HER2, etc
  - RECIST Response rate: 2.6%

Vaccines: adjuvant + ganglioside vs. adjuvant

- Gangliosides overexpressed in sarcomas even more than melanoma
- OPT821 adjuvant ± GM2/GD2/GD3 vaccine in patients with resected lung metastatic disease from sarcomas
  - n = 136
  - PFS 6.4 mo on both arms

Carvajal RD et al. J Clin Oncol 32:5s, 2014 (abstr 10520)
Set of vaccine targets examined for years: Cancer germ cell antigens (CGAs)

• Near universal expression of least some CGAs in synovial sarcoma
  – Examples: SSX, MAGE, BAGE, LAGE, NY-ESO-1
• Change in gene regulation of large number of X chromosome genes (most are on X)
• Antibodies against NY-ESO-1 are found in cancer patients with NY-ESO-1(+) tumors
• Vaccine strategies against NY-ESO-1 (+) tumors
NY-ESO-1 as model cancer-germ line antigen

**Jungbluth A et al. Int J Cancer 2001; 92: 856**

**TABLE I - NY-ESO-1 EXPRESSION IN NORMAL TISSUES:** IMMUNOHISTOCHEMICAL STAINING WITH MAB ES121 IN NORMAL TISSUES

<table>
<thead>
<tr>
<th>Tissue</th>
<th>ES121 immunoreactivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salivary gland</td>
<td>—</td>
</tr>
<tr>
<td>Pancreas</td>
<td>—</td>
</tr>
<tr>
<td>Liver</td>
<td>—</td>
</tr>
<tr>
<td>Esophagus</td>
<td>—</td>
</tr>
<tr>
<td>Stomach</td>
<td>—</td>
</tr>
<tr>
<td>Adipose tissue</td>
<td>—</td>
</tr>
<tr>
<td>Small bowel</td>
<td>—</td>
</tr>
<tr>
<td>Large bowel</td>
<td>—</td>
</tr>
<tr>
<td>Thyroid</td>
<td>—</td>
</tr>
<tr>
<td>Adrenal</td>
<td>—</td>
</tr>
<tr>
<td>Lung</td>
<td>—</td>
</tr>
<tr>
<td>Spleen</td>
<td>—</td>
</tr>
<tr>
<td>Lymph node</td>
<td>—</td>
</tr>
<tr>
<td>Kidney</td>
<td>—</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>—</td>
</tr>
<tr>
<td>Prostate</td>
<td>—</td>
</tr>
<tr>
<td>Breast</td>
<td>—</td>
</tr>
<tr>
<td>Ovary (adult)</td>
<td>—</td>
</tr>
<tr>
<td>Vagina</td>
<td>—</td>
</tr>
<tr>
<td>Placenta</td>
<td>—</td>
</tr>
<tr>
<td>Cervix</td>
<td>—</td>
</tr>
<tr>
<td>Testis</td>
<td>++++ germ cells</td>
</tr>
<tr>
<td>Skin</td>
<td>—</td>
</tr>
</tbody>
</table>

**TABLE III - NY-ESO-1 EXPRESSION IN HUMAN CANCERS WITH NY-ESO-1 MAB ES121**

<table>
<thead>
<tr>
<th>Histological type</th>
<th>Total tested</th>
<th>ES121 positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastatic melanoma</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>Breast carcinoma</td>
<td>14</td>
<td>2</td>
</tr>
<tr>
<td>Urinary bladder carcinoma</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>Synovial sarcoma</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Carcinomas of the head and neck</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Colonic carcinoma</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Leiomyosarcoma</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Liposarcoma</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Renal cell carcinoma</td>
<td>10</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diagnosis/histological type (total)</th>
<th>RT-PCR pos/total</th>
<th>IHC pos/total</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACC (33)</td>
<td>6/33</td>
<td>6/33</td>
</tr>
<tr>
<td>LCC (9)</td>
<td>2/9</td>
<td>4/9</td>
</tr>
<tr>
<td>SQCC (9)</td>
<td>4/9</td>
<td>2/9</td>
</tr>
<tr>
<td>Carcinosarcoma (1)</td>
<td>1/1</td>
<td>1/1</td>
</tr>
<tr>
<td>Total</td>
<td>13/52 (25%)</td>
<td>13/52 (25%)</td>
</tr>
</tbody>
</table>

**Melanoma**

![Melanoma image](image)
Cancer-germ cell antigen expression: synovial sarcoma

Immunohistochemical analysis

<table>
<thead>
<tr>
<th></th>
<th>NY-ESO-1</th>
<th>MAGE-A1</th>
<th>CT7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive tumors</td>
<td>80% (20/25)</td>
<td>16% (4/25)</td>
<td>8% (2/25)</td>
</tr>
<tr>
<td>Homogeneous</td>
<td>56% (14/25)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>expression</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Jungbluth A et al. Int J Cancer 2001; 94: 252
Part II of a vaccine - adjuvant

• Many adjuvants impact Toll-like receptors (TLR)
  – Toll can serve a primitive immune system function in Drosophila, e.g.

• TLR agonists trigger stimulation of the innate immune system and link innate and adaptive immunity in a concerted fashion

• Natural adjuvants include viruses through induction of IFNg and other cytokines and chemokines
  – Viral agents as immunotherapeutics (HSV – melanoma)
Cellular immunotherapeutics
(much more to follow)
Anti-NY-ESO-1 T cell therapy

1. Cyclophosphamide
2. T cells
3. (IL2)

Pheresis for T cells

Anti-NY-ESO-1 TCR transduction

Grow ex vivo 3-6 months

Robbins PF et al. J Clin Oncol. 2011; 29:917
Responding patient: single infusion
Synovial sarcoma CAR T cell protocol: NY-ESO-1 specific

- Clinicaltrials.gov # NCT01343043
- NCI, MSKCC, CHOP
- Ages 4-55
- HLA-A*02:01 patients only; tumor must be NY-ESO-1 (+) by IHC
- No prior therapy for 3 weeks
- Evaluation for T cell #: days 0-14, 21, 28, 42, 60, months 3, 4, 5, 6, 9, 12; q6mo x 3 yrs
Immune checkpoint inhibitors

• Perhaps best evidence of immunoselection, immuno-editing
• Tumors escape recognition via negative co-stimulation of T cells
• Release *pre-existing* (but otherwise repressed) immune response for anticancer effect
  – Role of mutational burden? NSCLC, melanoma
    • Counter example: RCC
    • What about sarcomas?
• As we are learning in other diseases, can combine these agents with other agents
Pembrolizumab phase I: n=3 sarcoma pts

More at ASCO 2016...

- IgG4 (non opsonizing) mAb
- n=6 synovial sarcoma ipilimumab study without a responder (advanced disease)
- SARC28 pembrolizumab study; ALLIANCE nivolumab + ipilimumab accrued

Patnaik A et al.  CCR 2015 Oct 7;  PMID: 26446947
Maki RG et al. Sarcoma. 2013:168145. PMID: 23554566
How many co-stimulators?

Microenvironment: IDO

Indoleamine 2,3-dioxygenase

• IDO is the 1st step in tryptophan catabolism (to kynurenine)
• Depleting tryptophan is permissive for cancer growth and is immunosuppressive
  – Akin to L-asparaginase in acute lymphoblastic leukemia
• IDO induction decreases tryptophan → decreased transcription factors GLK1 and GCN2 → mTORC1 decreased
• lmatinib inhibits IDO; can it help T cells attack GIST?
• Single agent inhibitor studies underway
• IDO inhibitors can / will be combined with other therapeutics

Balachandran VP et al. Nat Med 2011; 17: 1094
↑ IDO turns off tumor immunity

↑ T<sub>reg</sub>

↑ IDO

↑ IDO

fewer CTL

Net ↑ MDSC

Prendergast GC et al. C I I 2014; 63:721
CD47

• Different way to promote ADCC
• “Don’t eat me” signal to APCs
  – Also found on RBCs
• Anti-CD47 – present antigen to immune system more effectively?
  – Hemolysis seen in some studies
• Also eminently combinable with other immunotherapeutic approaches

McCracken MN et al CCR 2015; 21: 3597
Conclusions

• Plethora of options for immunotherapy studies
• Complication: Over 50 sarcoma subtypes / biologies
  – In which diagnoses is immunotherapy germane?
    • Translocation sarcomas: CAR-T vs specific antigen?
    • Aneuploid sarcomas: immune checkpoint agents?
    • ANY: TLR agonist, viral agents, IDO inhibitors, anti-CD47
  – Hard to test in any environment other than people
    • PBMC are not representative of what happens in the tumor
    • Feasible but very expensive to get repeat tissue biopsies
• Will we be talking about a mechanism this year, or looking at a few exceptional responders?