Hammer Lab @ Mount Sinai

- Backgrounds in math, compsci, ML, compbio
- Focus: cancer immunotherapy
  - Cancer genomics
  - Machine learning for immunology
  - Clinical trial analysis
- github.com/hammerlab
# Flavors of Cancer Immunotherapy

<table>
<thead>
<tr>
<th>Checkpoint blockade</th>
<th>Cellular therapies</th>
<th>Vaccines</th>
</tr>
</thead>
</table>

**Success stories:**
- αCTLA-4 (ipi)
- αPD-1 (pembro, nivo)
- αPD-L1 (atezo)

**Success stories:**
- CD19 CAR T-cells for B-cell malignancies

**Success stories:**
- ???
Therapeutic Cancer Vaccines

- Cancer cells differ significantly from their tissue of origin (mutations, expression, dysregulation)
- Can the immune system detect these differences and selectively kill cancers without harming normal tissue?
- Many cancer vaccine trials, only 1 FDA approval
Complementary w/ Checkpoint Blockade?

- Tumor specific T-cells inhibited?
  - Checkpoint blockade
- Insufficient tumor specific T-cells?
  - Cancer vaccination

Malignant tumors must have feeble antigenic power as well as sufficient resistance to the normal inhibiting influences to provide continued growth in the animal in which they originate, otherwise reactions sufficient to destroy them would occur more frequently.

Ernest Edward Tyzzer
"Tumor Immunity"
The Journal of Cancer Research, 1916
Antigens presented by APCs to T-cells
- Innate activation required "danger signal"
- Protein fragments presented on Class I MHC to cytotoxic (CD8+) T-cells
- Repertoire of CD8+ T-cells undergoes thymic selection to limit self-reactivity
What’s In a Cancer Vaccine?

- Antigen
  - Tumor Lysate
  - Peptides
  - mRNA
  - DNA
  - Viral vector
  - Bacterial vector
- Adjuvant
Shared Tumor Antigens
Shared Tumor Antigens

- Overexpressed and/or tissue-specific
  - Abundant on tumor cells but also present in some normal cells
  - Examples: Her2, Survivin, Telomerase, gp100

- Cancer/Testis Antigens
  - Expressed in testis and placenta
  - Thought to be excluded from tolerance
  - Examples: MAGE-A1, NY-ESO-1
Successful Shared Antigen Vaccine Trial

- Stage III or IV melanoma
- Patients with HLA-A2
- Treated with high dose IL-2
- +/- gp100 (209-217) peptide
  - Specific to melanocytes
  - Adjuvant: montanide

A Phase III Multi-institutional Randomized Study of Immunization with gp100:209-217(210M) Peptide Followed by High Dose IL-2 vs High Dose IL-2 Alone in Patients with Metastatic Melanoma (2009)
A Less Successful Trial...

- MAGRIT: Phase III MAGE-A3 vaccine trial
- ~14k lung cancer patients screened
- ~4k had MAGE-A3 positive samples
- 2,272 patients enrolled
- Randomly assigned (2:1) to receive vaccine or placebo for 27 months
- No difference in Progression Free Survival
### Shared Antigens Mostly Unsuccessful

<table>
<thead>
<tr>
<th>Cancer type</th>
<th>Vaccine</th>
<th>Total patients</th>
<th>Patients responding</th>
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<tbody>
<tr>
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<td>Tyrosinase + GMCSF</td>
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<tr>
<td>Melanoma</td>
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<td>Melanoma</td>
<td>MART-1 + IL-12</td>
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<td>Prostate</td>
<td>Peptides</td>
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<tr>
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<td>Peptides on PBMC + IL-12</td>
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<td>Breast and prostate</td>
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<tr>
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<tr>
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<tr>
<td>Multiple</td>
<td>Avipox-CEA(IGMCSF)</td>
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<tr>
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</tr>
<tr>
<td>Multiple</td>
<td>Vaccinia + avipox-CEA</td>
<td>18</td>
<td>0</td>
</tr>
</tbody>
</table>

*Source: Cancer immunotherapy: moving beyond current vaccines*
Cancer/Testis Antigens Subject to Negative Selection

- Medullary thymic epithelial cells (mTECs) express commonly studied cancer/testis antigens
- Might explain failure of MAGE vaccine trials
Neoantigens
Tumor Specific Neoantigens

- No overlap with normal
  - mutations
  - abnormal splicing
  - abnormal post-translational modifications
- Unlikely to be shared between patients
- Requires personalization
Detecting Mutations That Change Proteins

- **Exome sequencing**
  - SNVs
  - Small indels
  - Exonic splice sites

- **Genome sequencing**
  - Larger indels
  - Gene fusions
  - Intronic splice sites

*Mutated neo-antigens as targets for individualized cancer immunotherapy, Mathias Vohrmer*
Typical Neoantigen Pipeline

- DNA tumor + normal sequencing
  - Somatic variant calling
- Tumor RNA sequencing
  - Prioritize expressed variants
- Predict mutant proteins
- MHC binding prediction
  - NetMHC / NetMHCpan

Computational genomics tools for dissecting tumour–immune cell interactions
Preclinical Evidence

- C57BL/6 mice
- B16.F10 melanoma
- 27mer long peptides
- Poly(I:C) adjuvant
- Single peptide vaccination slows tumor growth

Exploiting the Mutanome for Tumor Vaccination, Castle et al. (2012)
Matt Gubin & Bob Schreiber (2014)

- Taconic 129S6 mice
- MCA-T3 sarcoma cell line
- “mLama4” & “mAlg8” are 8mer neoepitopes
  - Identified with WES + NetMHC
- Long peptide vaccine + Poly(I:C) adjuvant

Checkpoint blockade cancer immunotherapy targets tumour-specific mutant antigens, Gubin et al. (2014)
Mahesh Yadav & Lelia Delamarre (2014)

- C57BL/6 mice
- MC-38 colon cell line
- Vaccine with 3x epitopes
  - + Poly(I:C)
  - + anti-CD40 antibody
- Detected by WES + mass spec

Predicting immunogenic tumour mutations by combining mass spectrometry and exome sequencing, Yadav et al. (2014)
Mathias Vormehr & Ugur Sahin (2016)

- BALB/c mice
- CT26 colon cell line
- mRNA vaccine
- Two groups of 5 epitopes (#2 works)
- Individual epitopes don’t work

Mutated neo-antigens as targets for individualized cancer immunotherapy (Figure 3.18), Vormehr (2016)
Ongoing & Upcoming Neoantigen Vaccine Trials
Neon (NEO-PV-01)

- Synthetic long peptides + Poly-ICLC + anti-PD-1 (nivo)
- In-silico epitope prediction
- Read: *Mass Spectrometry Profiling of HLA-Associated Peptidomes in Mono-allelic Cells Enables More Accurate Epitope Prediction*
- Phase I (NCT02897765) enrolling: 90 patients with {skin, lung, bladder} cancer
Agenus (AutoSynVax)

- Synthetic long peptides + HSP carrier + QS21 adjuvant
- Why heat shock proteins? APCs pick them up via CD91
- In-silico epitope prediction
- Phase I (NCT02992977) enrolling: 20 patients with “advanced cancer”
BioNTech (IVAC MUTANOME)

- Ultrasound guided injection of mRNA into lymph nodes
- Phase I (NCT02035956) ongoing: 15 melanoma patients
- Phase I (NCT02316457) enrolling: 30 TNBC patients
Caperna

- Launched by Moderna
- mRNA vaccine
- 20 variants
- Status: IND (submitted?)
Genocea (GEN-009)

- WES to identify candidate neoantigens
- Screens mutant peptides with patient APCs & T-cells
- No MHC binding predictions
- Only pre-existing T-cell responses
- Status: IND by end of 2017
Advaxis (ADXS-Neo)

- Listeria vector
- 20+ neoepitopes per plasmid
- Translated neoepitopes secreted into APC cytoplasm
- Status: IND accepted

Advaxis slides from AACR 2016
The Near Future

- Targeted delivery
  - RNA lipoplex from BioNTech
- Enhanced retention time in lymph node
  - Particle size matters
  - PEGylated peptides
- Adjuvant + antigen nanodiscs
- Post-translational modifications
- Fine-grained immune modulation
Thanks!