Customizing cancer immunotherapies to match the intrinsic tumor microenvironment

Brad Nelson, PhD
British Columbia Cancer Agency
Precision Medicine Retreat, August 9 2017
The cancer genome is an altered version of self

Spectral karyotype analysis
No two cancers are alike

Chromosomes from 6 different breast cancers
Immune recognition of cancer:
Tumor-infiltrating lymphocytes (TIL)

Multi-colour IHC of high-grade serous ovarian cancer (HGSC)

CD8+ killer T cells
CD4+ T cells
CD20+ B cells
Tumor cells
TIL are strongly associated with survival in human cancer

Dense CD8+ TIL

Sparse CD8+ TIL

BCCA/VGH cohort
high-grade serous (HGSC)
optimally de-bulked
n = 200
p = 0.0008

Clarke, B. et al. 2009
Milne, K. et al. 2009
HGSC shows extensive intratumoral heterogeneity

A McPherson...S Shah, Nature Genetics 2016
HGSC shows extensive intratumoral heterogeneity

How does the immune system contend with ITH?
HGSC shows extensive intratumoral heterogeneity

How does the immune system contend with ITH?

• the players
• the strategy

A McPherson...S Shah, Nature Genetics 2016
The strongest TIL responses involve both T cells and B cells

Three cases of HGSC:

- Few TIL
- Weak TIL
  - CD4+ T cells
  - CD8+ T cells
  - CD20+ B cells
- Robust TIL
  - CD4+ T cells
  - CD8+ T cells
  - CD20+ B cells
  - T cells and B cells
T cells and B cells show a combined effect on survival

*Kaplan-Meier based on TIL patterns in HGSC (n=167, optimally de-bulked)*

- No TIL (n=20)
- CD8 TIL alone (n=17)
- CD8 + CD4 TIL (n=58)
- CD8 + CD4 + CD20 TIL (n=72)

Log-rank P<0.0001

*Julie Nielsen et al, Clin Can Res 2012*
Strong TIL responses involve Tertiary Lymphoid Structures (TLS)
Optimal TIL responses involve both cytolytic and antibody-based mechanisms.
HGSC shows extensive intratumoral heterogeneity

How does the immune system contend with ITH?

- the players
- the strategy

A McPherson...S Shah, Nature Genetics 2016
Do TIL recognize truncal or branch 
features of the tumor phylogeny?
Do TIL recognize truncal or branch features of the tumor phylogeny?
Extensive spatial profiling of 120 tumors from 21 HGSC patients

Allen Zhang, Sohrab Shah, in preparation
T-cell clones appear to track with tumor clones across space

Patient 1

\[ P = 0.0106, \rho = 0.65 \]

Patient 2

\[ P = 0.0167, \rho = 0.943 \]

Patient 3

\[ P = 0.175, \rho = 0.657 \]

Patient 4

\[ P = 0.113, \rho = 0.539 \]

Patient 9

\[ P = 0.000467, \rho = 0.915 \]

Patient 10

\[ P = 0.919, \rho = 0.0857 \]

Allen Zhang, Sohrab Shah, in preparation
TIL may recognize branch features of the tumor phylogeny.
Different tumor types harbour different immune “communities” (and strategies?)

- RNA-seq data from 21 cancer types in TCGA (7,893 cases)
- xCell used to estimate abundance of 38 immune cell types
- TIL “communities” are projected in 2D using tSNE

Phineas Hamilton, unpublished
How can we best enhance anti-tumor immunity?

Three cases of HGSC:

- Few TIL
- Weak TIL
  - CD4+ T cells
  - CD8+ T cells
  - CD20+ B cells
- Robust TIL
  - T cells
  - T cells and B cells
The PD-1 pathway has emerged as a major control point in anti-tumor immunity.
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PD-L1 is expressed in TIL-rich tumor regions

PD-L1 is expressed in TIL-rich tumor regions

Checkpoint blockade releases the brakes on anti-tumor immunity

**PD-L1/PD-1 binding inhibits T cell killing of tumor cell**

- PD-L1
- Antigen
- T cell receptor
- T cell

**Blocking PD-L1 or PD-1 allows T cell killing of tumor cell**

- PD-L1
- Anti-PD-L1
- Anti-PD-1
- PD-1
- T cell death
- T cell
anti-CTLA-4 (eg, Ipilimumab)

- Metastatic melanoma – FDA approval

anti-PD-1 (eg, Nivolumab, Pembrolizumab, others):

- Metastatic melanoma – 38% Objective Responses (Hamid, NEJM 2013), 53% Objective Responses with Ipilimumab (Wolchok, NEJM 2013) and FDA approval
- Non-small cell lung cancer – 18% Objective Responses and FDA approval
- Kidney cancer – 27% Objective Responses (Topalian, NEJM 2012); 52% ORR nivolumab + sunitinib (Amin, JCO abstract, 2014), FDA approval
- Bladder cancer – 52% Objective Responses (Powles, Nature 2014), FDA approval
- Hodgkin’s Lymphoma – 87% Objective Responses (Ansell, NEJM 2015), FDA approval
- Colorectal cancer (MSI) – 40% Objective Responses (Le, NEJM 2015), FDA Breakthrough Status 2015
- Any adult or pediatric metastatic solid tumor with mismatch repair deficiency (dMMR), FDA approval
- Replacing frontline chemotherapy for melanoma and lung cancer (so far)
**Cost**

- approx. $100k/treatment cycle
- combinations may be required for some cancers (e.g. Ipi + Nivo for melanoma)
- long-term use may be required for some cancers

**Efficacy**

- many cancers (e.g. ovarian, breast) have low response rates (10-20% range)
- responses are often transient (e.g. lung)
Stimulatory and inhibitory pathways in T cells

Antigen-presenting cell or tumor cell

T cell
How can we best enhance anti-tumor immunity?

Three cases of HGSC:

Few TIL

Weak TIL

Robust TIL

T cells

T cells and B cells

CD4+ T cells

CD8+ T cells

CD20+ B cells
Cold tumors exhibit profound lymphocyte infiltration barriers

- CD8+ killer T cells
- CD4+ T cells
- CD20+ B cells
Adoptive T cell therapy (ACT)

1. Identification/Engineering of Tumor-Reactive T Cells
2. Expansion of T Cells
3. Infusion of T Cells with Immune Modulation

Tumor or Blood Sample

Identify/engineer tumor-reactive T cells

Expand T cells

Infuse T cells with immune modulation
Clinical grade T cell production unit

BCCA’s Deeley Research Centre, Victoria
Clinical grade T cell production unit

BCCA’s Deeley Research Centre, Victoria
Keys to successful T cell therapy

Antigens
Access
Activity
Targeting driver mutations in lymphoma

1. Collect tumour samples
   BCCA and affiliated hospitals

2. Identify mutations
   Michael Smith Genome Sciences Centre

3. Assess immunogenicity of mutations
   BCCA’s Deeley Research Centre

4. Vaccinate patients and assess clinical outcomes
   BCCA Clinical Trials Unit

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Patient’s tumor biopsy at relapse

Sequence panel of 50 genes to identify driver mutations

Identify and expand mutation-specific CD4 and/or CD8 T cells

Infusion with immune modulation

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Team:
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Joe Connors, MD
Raewyn Broady, MD
John Webb, PhD
Ryan Morin, PhD
Brad Nelson, PhD

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MYD88
EZH2
MEF2B
CREBBP
EP300
CARD11
MLL2
PIM1
FOXO1
IRF4
CD79B
etc.

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Chimeric Antigen Receptors (CARs)

**CD19 CAR-T cells:**

- 90% Complete Responses (67% sustained) in pediatric and adult leukemia (*Davila, Sci Trans Med 2013; Maude, NEJM 2014*)
- FDA Breakthrough Designation pediatric and adult leukemia in 2014
- 80% Objective Responses in lymphoma (*Kochenderfer, JCO 2014*)
Canadian CAR-T Cell Network

- Vector development (Holt, Yung)
- T cell production (Webb, Nelson)
- Clinical trial site (Broady)

- Clinical-grade virus production (Bell)
- Socioeconomic (Ferguson)
- Clinical trial site (Atkins, Kekre)
Mutual Antibody T Cell Engagers (MATEs)

With Marty Boulanger (UVic):

- Targeting element (e.g. single-chain variable fragments, scFvs)
- Spacer
- Dimerization domain A (e.g. Jun leucine zipper)
- Non-covalent interactions
- Dimerization domain B (e.g. Fos leucine zipper)
- Spacer
- Transmembrane domain (e.g. CD8 alpha)
- Costimulatory domain (e.g. 4-1BB or CD28)
- Activation domain (e.g. CD3 zeta)
Engineering logic gates to enable T cells to recognize “constellations” of antigens

Adapted from Davies and Maher, Trans Can Res 2016
Keys to successful T cell therapy

Antigens
- driver mutations
- cell surface antigens (CARs, MATEs)

Access

Activity
Cold tumors exhibit profound lymphocyte infiltration barriers

- CD8+ killer T cells
- CD4+ T cells
- CD20+ B cells
Circumventing infiltration barriers using Cbl-b deficient CD8+ T cells

Adoptive T cell therapy of mammary tumors using CD8+ OT-I T cells

Taimei Yang et al, CII 2009
Antigens
- driver mutations
- cell surface antigens (CARs, MATEs)

Access
- enhanced T cell receptor signaling (cbl-b -/-)

Activity
Clinician-controlled cytokine signaling using exclusive cytokine:receptor pairs

With Marty Boulanger (UVic), Surjit Dixit (Zymeworks):

Mutant cytokine:receptor complex
Keys to successful T cell therapy

Antigens
- driver mutations
- cell surface antigens (CARs, MATEs)

Access
- enhanced T cell receptor signaling (cbl-b -/-)

Activity
- clinician-controlled cytokine receptors
The cancer genome is an altered version of self
Re-wiring T cells to recognized altered self

Engineered T cell

Cancer
Special thanks to our patients