HARNESSING THE LYMPHOCYTE META-PHENOTYPE TO OPTIMIZE ADOPTIVE CELL THERAPY

#TeamBlue #MoffittIMO
Sarcoma is a heterogeneous group of cancers arising from connective tissue. We can cure localized disease with surgery and radiation. We can NOT cure metastatic disease by any means.
Formally: Standard therapy in metastatic soft tissue sarcoma is minimally effective and highly toxic.

The best targeted agent was compared to placebo as recently as 2012 and only won by 3 months in OS.
Adoptive Cell Therapy with Tumor Infiltrating Lymphocytes

Rosenberg & Restifo, Science, 2015
TIL therapy works in melanoma

Of initial 36 consecutive patients treated on trial at MCC:
- 95% success rate for growth (>2e7) by patient
- 34% success rate for growth by fragment
- ~50% response rate in those treated

Pilon-Thomas et al, J Immunother, 2012
Sarcoma samples contain cytotoxic T lymphocytes
T-cell repertoire following TIL culture is heterogeneous
TIL reactivity is generally poor in sarcoma
Result 1: IFN gamma reactivity assay does not correlate with outcome
**Result 2:** Sarcoma TIL are more heterogeneous than melanoma TIL

Colored dots: melanoma patients treated on trial
Grey dots: TIL derived from fragments of resected sarcomas
In contrast to melanoma, sarcoma TILs are diverse.
How does the I17 map to immunotherapeutic outcomes. For **Meta-phenotype**: The emergent characteristics of a population resulting from the interactions between the constituent subtypes.
How does the T cell map to immunotherapeutic outcome of the phenotype? Emergent changes to the interaction of the constituent sub-
Team Blue Question:

How does the TIL meta-phenotype map to sarcoma immunotherapeutic outcome for sarcoma?

Meta-phenotype: The emergent characteristics of a population arising from the interactions between the constituent subtypes.
Modeling tumor-immune interactions is complex… too complex!
A Boolean network approach to reduce regulatory complexity

\[ M = \begin{pmatrix} 0 & -1 & -1 & 0 & -1 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 1 & 1 & 1 & 0 & 1 \\ 1 & 1 & 1 & 1 & 0 \end{pmatrix} \]

Update:
\[ N_j(t + 1) = \chi > 0 \left( \sum_i M_{i,j} N_i(t) \right) \]

Response to stimulation:

Return to homeostasis:
Analysis of network perturbations

Internal perturbations:

External regulation:

Stable states

# transient states

Up-regulated stable state

Down-regulated stable state

Up-regulated stable state

Down-regulated stable state
Result 3: A simplified model captures the essential regulatory dynamics

[Diagram of regulatory dynamics involving CD4, CD8, NK, DN, NKT, and IKR cells]
Understanding tumor-immune dynamics with an ODE model

\[ \dot{V}(t) = r_V V - \left( f_N(N) + f_E(E) \right) V \]
\[ \dot{N}(t) = \sigma_N - \delta_N N + h_N(V) N \]
\[ \dot{E}(t) = \sigma_E + g_N(N) E + g_V(V) E - g_L(R) E \]
\[ \dot{R}(t) = \sigma_R - \delta_L R + l_N(V) R \]

Initial conditions:

\[ V(0) = V_0, N(0) = N_0, E(0) = E_0, R(0) = R_0 \]

Number of variables: 16

Number of parameters: 4
Recapitulating homeostasis, successful immune surveillance and tumor immune evasion
modulating immune response 1: checkpoint inhibitors
Result 4: Shifting the balance of innate and adaptive immune interactions can change tumor fate.
Incorporating tumor/immune co-evolution: effects of heterogeneity on therapeutic response

\[
\frac{\partial C(x, t)}{\partial t} = f(C, x) + D \frac{\partial^2 C}{\partial x^2} - h(T, C, x) - \delta C
\]

\[
\frac{\partial T(x, t)}{\partial t} = g(C, T) - \delta_T T
\]
Treatment with all possible TIL clones
Disease free interval can be measured *in silico*
Treatment with near-clonal TIL (CAR T-cells?)
**Result 5:** Highly heterogeneous tumors are resistant to treatment with specific T-cell populations
What if we have a oligo-clonal tumor where one clone is amenable to targeted therapy?
\[
\frac{\partial C(x,t)}{\partial t} = f(C,x) + D \frac{\partial^2 C}{\partial x^2} - h(T,C,x) - \delta C
\]

\[
\int r(y) M(y,x) C(y,t) \, dy
\]

\[
\int k(x,y) C(x,t) T(y,t) \, dy
\]
Result 1: Standard IFN gamma reactivity assay does not correlate with outcome

Result 2: Sarcoma TIL are more heterogeneous than melanoma TIL

Result 3: A simplified model captures the essential regulatory dynamics

Result 4: Shifting the balance of innate and adaptive immune interactions can change tumor fate

Result 5: Highly heterogeneous tumors are resistant to treatment with specific T-cell populations

Specific aim 1: Identify phenotypic signatures of ex vivo sarcoma-derived TIL that predict ACT efficacy

Specific aim 2: Construct mathematical models to characterize the optimum patient-specific TIL meta-phenotype in metastatic sarcoma
Importance: Our approach will improve ACT for sarcoma, and is generalizable. Originality: We are the world’s leading group applying ACT to sarcoma. A hierarchy of mathematical models tackles the complexity of tumor-immune dynamics. Feasibility: We are augmenting an on-going Moffitt clinical protocol in human subjects with sarcoma.