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
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
Sarcoma samples contain cytotoxic T lymphocytes
T-cell repertoire following TIL culture is heterogeneous
TIL reactivity is generally poor in sarcoma

![Graph showing IFN-γ levels in TIL populations from separate tumor fragments](image-url)

**Axes:**
- Y-axis: IFN-γ (pg/ml)
- X-axis: TIL population from separate tumor fragments

**Legend:**
- Media
- HLA-Matched
- HLA-Umatched
- Tumor Digest

**Graph Description:**
- The graph compares IFN-γ levels across different populations of tumor-infiltrating lymphocytes (TILs) derived from separate tumor fragments.
- The TIL reactivity is generally poor in sarcoma, as indicated by the low IFN-γ levels in the media control (PosCtl).
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 ICI meta-
map to
immunohistologic outcome. For
Meta-phenotype: The emergent character
of a population arising
from the interactions be
the constituent subtypes.
How does the IGF1 map to immunotherapeutic outcome for T-phenotype? The emergent characteristics of the interaction of the constituent subject...
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:
Result 3: A simplified model captures the essential regulatory dynamics
Understanding tumor-immune dynamics with an ODE model

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

\[V(0) = V_0, N(0) = N_0, E(0) = E_0, R(0) = R_0\]
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 an oligo-clonal tumor where one clone is amenable to targeted therapy?
\[
\frac{\partial C(x,t)}{\partial t} = f(C, x) + D \frac{\partial^2 C}{\partial x^2} - h(T, E, x) - \delta C
\]

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

\[
\int k(x, y) C(x, t) T(y, t) \, dy
\]
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.
