Tumor-Immune Intelligence (TII) Report - Melanoma

> **RESEARCH USE ONLY (RUO).** Educational/research analysis of public single-cell reference data. **Not for diagnostic use and not a treatment recommendation for any individual.** Archetypes and composites are research constructs positioned against a pan-cancer reference, not clinical predictions.

Dataset. Melanoma | tumour-type key: *melanoma* | 8,000 tumour-condition cells (4,317 immune = 54%, 3,683 malignant = 46%), 8,000 matched-normal cells. **Reference.** Pan-cancer solid-tumour atlas, leave-one-out (ccRCC, CRC, GBM, LUAD, TNBC). All z-scores are relative to that reference.

1. Archetype & composites

Archetype call: `hot / inflamed`

Composite	z (vs pan-cancer)	reading
Immunotherapy-Response	+0.26	mid-range effector/inflamed program
Immune-Resistance	-0.25	mid-range suppressor/barrier load
Effector-suppressor balance	**+0.52**	the hot/cold index
Stromal barrier (exclusion)	-1.60	reduced

2. Immune contexture (program z-scores, hot to cold)

Programs scored in the immune compartment (barrier programs over all tumour cells), z-scored vs the leave-one-out atlas reference and bounded to +/-3 SD.

Program	z	
cytolytic_activity	+3.00	elevated
tcell_terminal_exhaustion	+3.00	elevated
icr	+2.02	elevated
nk_inhibitory_brake	+1.82	elevated
tcell_inflamed_gep	+0.88	elevated
tls_signature	+0.84	elevated
tcell_stemness	+0.50	elevated
mdsc_granulocytic	-0.53	reduced
mdsc_monocytic	-0.72	reduced
ifn_gamma_signature	-0.88	reduced
tam_protumor_m2	-0.88	reduced
chemokine_trafficking	-0.99	reduced
immune_exclusion_stroma	-1.24	reduced
antigen_presentation_apm	-1.49	reduced
metabolic_immunosuppression	-1.95	reduced
cdc1_recruitment	-3.00	reduced

3. Exhaustion & reinvigoration potential

- **Reinvigoration potential (stemness - terminal exhaustion): -2.50** -> terminally-exhausted skew - lower reinvigoration potential.
- Terminal-exhaustion program: +3.00 (elevated); stem/progenitor (TCF7/IL7R): +0.50.

4. Antigen-presentation integrity & genomic-escape flags

- **APM integrity (z): -1.49** (reduced). Low APM echoes HLA/B2M/JAK escape.
- **PD-L1 (CD274) RNA proxy:** moderate (5.0% of tumour cells positive, mean 0.038). *RNA proxy only - not a validated IHC CPS/TPS score.*
- **Tumour-specific escape candidates (vs immune internal control):** NLRC5 (reduced vs immune: 29.1% malignant vs 69.6% immune).
- *Not assessable in this dataset (zero counts in all cells - a capture artefact, not loss): B2M, HLA-A, HLA-B, HLA-C, TAP1, TAP2, TAPBP.* Classical MHC-I (HLA-A/B/C, B2M) loss therefore cannot be evaluated from this matrix.

5. TLS, metabolic suppression & dominant suppressor

- **TLS status (z): +0.84** (elevated).
- **Metabolic suppression (z): -1.95** (reduced).
- **Dominant suppressor axis: terminal exhaustion** (z +3.00).

6. Candidate CAR/TCR/vaccine targets (expression in malignant cells)

Antigen	class	modality	mean	%pos	vs normal	relevant
PMEL (gp100)*	differentiation	TCR/vaccine	3.605	87.6	tumour>normal	yes
MLANA (MART-1)*	differentiation	TCR/vaccine	2.642	94.1	tumour>normal	yes
PRAME (PRAME)*	cancer-testis	TCR/vaccine	2.004	89.5	tumour>normal	yes
MAGEA3 (MAGE-A3)	cancer-testis	TCR/vaccine	0.464	47.1	tumour>normal	
CD276 (B7-H3)	surface	CAR/mAb	0.333	63.2	tumour>normal	
CD22 (CD22)	surface	CAR/ADC	0.128	53.2	tumour>normal	
BIRC5 (survivin)	over-expressed self	vaccine/TCR	0.109	58.0	similar in normal	
ERBB2 (HER2)	surface	CAR/mAb/ADC	0.096	39.2	similar in normal	
MAGEA4 (MAGE-A4)	cancer-testis	TCR/vaccine	0.165	13.7	tumour>normal	
IL13RA2 (IL13RA2)	surface	CAR	0.116	10.7	tumour>normal	

** listed for this tumour type in the disease matrix. Expression-based discovery only; CAR/TCR development requires surface-vs-intracellular, HLA-restriction, on-target/off-tumour and clonality checks not done here.*

7. Research interpretation - rational counter-axis (educational)

Given the **hot / inflamed** archetype and a dominant **terminal exhaustion** axis, the textbook-supported, *mechanistically rational* research direction is: **if progenitor pool present, checkpoint reinvigoration; if terminal, consider ACT/vaccine ignition**. This is educational mechanism-matching, not a treatment recommendation.

Inflamed/effector-rich contexture - the archetype associated with checkpoint-blockade benefit.

8. Validated readouts requiring orthogonal data

- **TMB** (>=10 mut/Mb) and **MSI-H/dMMR** are DNA readouts - not derivable from scRNA expression. The engine would integrate them as response modifiers if WES/panel data were supplied.
- **PD-L1 IHC (CPS/TPS)** is a protein assay; only the CD274 RNA proxy is shown above.

9. Concordance / novelty flags & limitations

- **Disease-matrix expectation** for *melanoma*: archetype "hot", biomarker ['TMB', 'CD8 TIL']. **Concordance:** this dataset scored `hot / inflamed` - concordant.
- Single dataset, single cohort: relative positioning only; no biological replication or outcome labels.

- Cross-dataset absolute scores are offset-prone; mitigated by atlas-referenced z-scoring.
- scRNA dropout can mimic gene 'loss'; APM/escape flags are hypotheses, not calls.

Generated by tii_report.py (Phase 2). Panels: status_panels.json group J; composites + readouts: io_reference.json; reference: Phase-1 pan-cancer atlas. Textbook paraphrased (CIT), not redistributed.