Commentary

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It Takes Two to Click: Host Immune Profiles Are Critical Determinants of Effective Immunotherapy Responses

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Immunotherapies such as adoptive cell therapy (ACT) and immune checkpoint inhibition (ICI) have revolutionised the treatment of many solid and haematological malignancies [1,2]. In particular, immune checkpoint inhibitors (e.g., anti-PD-1 and anti-CTLA-4) represent a promising approach for markedly improving 5-year survival rates in patients with metastatic cancers, and have therefore been incorporated into clinical practice for a range of malignancies [3]. Despite the remarkable success of these immunotherapies, only a subset of patients exhibits a durable response [4,5]. These heterogeneous clinical outcomes not only highlight the importance of predictive biomarkers for the early identification of responders and non-responders, but also underscore the need for a deeper understanding of individual patient responses. Although predictive biomarkers hold great promise for identifying optimised and effective treatments for all patients, most currently known biomarkers are tumour-intrinsic, focusing solely on tumour characteristics [6,7]. Nevertheless, immunotherapy response depends on a dynamic interplay between the tumour and the host [8], and host-related factors can significantly influence therapeutic outcomes [9]. Indeed, beyond the specific immunotherapeutic strategies employed, the systemic immune response plays a critical role in determining immunotherapy efficacy [10] (Fig. 1).

An integrated role of host immune-intrinsic features in predicting responses to immunotherapies has been repeatedly supported by emerging evidence. For example, in melanoma patients treated with immune checkpoint inhibitors, tumour regression or progression can be characterised by two distinct $CD8^+$ T-cell states. Transcription factor TCF7-positive, memory-like $CD8^+$ T cells correlate with favourable clinical responses, whereas non-responsiveness is associated with TCF7-negative, exhausted $CD8^+$ T cells [11]. In a Phase II clinical trial involving independent cohorts of patients with either metastatic or refractory thymic epithelial tumours (TET) or metastatic non–small cell lung cancer (NSCLC), a greater fold increase in $Ki\text{-}67^+$ cells within tumour antigen–specific $PD\text{-}1^+$ $CD8^+$ T cells in peripheral blood following anti–PD-1 therapy predicted durable responses and prolonged survival [12]. Consistent with an earlier report linking the proliferative response of tumour-infiltrating $CD8^+$ T cells to positive clinical outcomes in melanoma patients receiving anti–PD-1 therapy [13], these findings suggest that durable responses to anti–PD-1 treatment depend on the *in vivo* reinvigoration of tumour antigen–specific T cells in the host. Furthermore, an earlier study in melanoma revealed that a higher ratio of T-cell reinvigoration to tumour burden—rather than reinvigoration alone—was a stronger predictor of favourable clinical response. Interestingly, pre-existing elevated levels of $Ki\text{-}67^+$ $PD\text{-}1^+$ $CD8^+$ T cells prior to treatment were in fact indicative of poor prognosis [14]. In an autologous T-cell therapy based on *ex vivo*–expanded tumour-infiltrating lymphocytes (TILs), a memory-progenitor, stem-like phenotype ($CD39^-CD69^-$) was shown to drive TIL persistence and complete tumour regression [15]. Although the total number of infused TILs did not differ among patients, responders exhibited a four-fold higher proportion of $CD39^-CD69^-$ $CD8^+$ T cells, while non-responders displayed a predominance of terminally differentiated $CD39^+CD69^+$ phenotypes [15]. Similarly, in NSCLC patients, an increased frequency of $CX3CR1^+$ circulating $CD8^+$ T cells following anti–PD-1 therapy correlated with improved clinical response and survival [16]. A post-therapy elevation of peripheral $CX3CR1^+$ $CD8^+$ T cells was also observed in renal carcinoma and melanoma patients who responded to anti–PD-1 therapy compared with non-responders [17,18].

Long-term anti-tumour immunity and improved survival suggest continual reinvigoration and recovery of exhausted T cells within the tumour microenvironment. A systemic approach is therefore required to sustain both the replenishment and functional engagement of activated T cells in proximity to tumours. Accordingly, in addition to targeted therapy, systemic host immunity is essential for tumour control or eradication [19,20]. Evidence from both experimental studies and external datasets indicates that the sustained anti-cancer immune activity observed in responsive patients is driven by parallel intratumoural and peripheral clonotypic expansions of effector T cells, with intratumoural populations being replenished by fresh, non-

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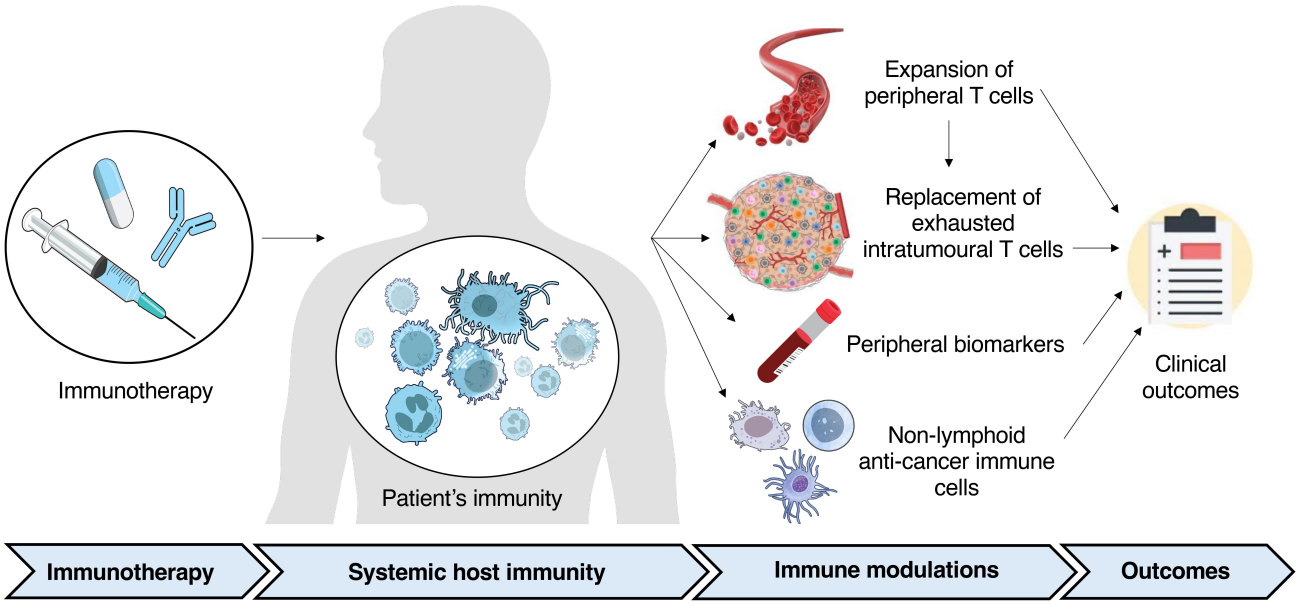

Fig. 1. Clinical outcomes of immunotherapy are driven by systemic host immunity. Following immunotherapy, several host immunity–driven immune modulations—such as peripheral expansion of anti-cancer T-cell clones, replacement of exhausted intratumoural T cells, and activation of non-lymphoid immune cells (including neutrophils, monocytes, and macrophages), along with associated biomarkers—are evident in responsive patients. The overall clinical outcome (whether a positive or negative response) is therefore dictated by the extent of these host-mediated immune modulations. Consequently, the clinical response to immunotherapy varies according to the individual patient's systemic immunity. The figure was completed using the Microsoft PowerPoint software (version 16.89.1).

exhausted clonotypes originating outside the tumour [21]. Interestingly, substantial inter-patient variability was observed in the degree of peripheral clonal expansion and subsequent infiltration of effector T cells, which appeared to correlate with differing clinical responses to checkpoint blockade [21]. Overall, infiltration of newly derived $CD8^+$ T-cell clones from the circulation into tumours—termed *clonal replacement*—has been consistently associated with favourable immunotherapy responses across several studies [22–24]. Given the integral role of peripheral T-cell clones in anti-cancer immunity, further characterisation of these matched circulating clones is critical for understanding the coordination and extent of anti-tumour T-cell responses in patients. Despite the inherent challenge posed by their extremely low frequency in peripheral blood, these T-cell clones have been further investigated. Using single-cell RNA sequencing (scRNA-seq) to track and compare TCR-shared peripheral and intratumoural T-cell clones in melanoma patients, researchers identified upregulation of multiple effector-like genes in tumour-matched circulating T cells, indicating elevated activation compared with both non-matching peripheral T cells and matched intratumoural clones [25]. In contrast, tumour-resident matching clones exhibited upregulation of exhaustion-associated genes, reflecting a more dysfunctional phenotype [25]. In a separate cohort of metastatic cancer patients who had not received immune checkpoint therapy, peripheral anti-tumour T-cell clones displayed a distinct transcriptional signature characterised by higher expression of stemness markers and lower expression of dysfunction markers compared with their tumour counterparts [26], suggesting a self-renewal capacity and long-term persistence of peripheral clones. Transcriptomic profiling also revealed features of a tissue-resident memory phenotype, implying prior antigen encounter and relevance to tumour sites [26].

Host immunity shapes immunotherapy responses not only through T cells but also via other immune cell populations. For instance, studies in both mouse models and patients with various cancers have identified peripheral $Ly6E^{hi}$ neutrophils as predictive biomarkers of immunotherapy response [27]. Induced by tumour-intrinsic activation of the STING (stimulator of interferon genes) signalling pathway, $Ly6E^{hi}$ neutrophils exhibit the ability to enhance cytotoxic $CD8^+$ T-cell activity through IL-12b secretion, thereby directly sensitising tumours to anti–PD-1 therapy. Moreover, gene expression analyses of $Ly6E^{hi}$ neutrophils revealed upregulation of pro-inflammatory factors and downregulation of immunosuppressive mediators, consistent with an anti-cancer phenotype [27]. In another study, transcriptomic profiling of triple-negative breast cancer (TNBC) patients treated with paclitaxel or its combination with anti–PD-L1 therapy identified $CXCL13^+$ T cells as predictive biomarkers of response, which were closely associated with proinflammatory macrophages [28]. Simi-

larly, in a Phase I clinical study of osteosarcoma and neuroblastoma patients receiving GD2-targeted CAR-T cells, *in vivo* CAR-T expansion—an essential determinant of CAR-T efficacy—was found to depend not only on T-cell subsets but also on the myeloid phenotype [29]. Patients exhibiting robust CAR-T expansion ("good expanders") showed increased frequencies of naïve T cells and $CXCR3^{+}$ monocytes, whereas "poor expanders" displayed enrichment of $CXCR3^{-}$ monocytes and exhausted T cells [29]. Consistent with previous reports highlighting the indispensable role of myeloid cells in anti-cancer immunity [30–33], these findings underscore the importance of myeloid cell subsets in modulating immunotherapy responses by influencing *in vivo* T-cell expansion.

These observations underscore the need for a deeper understanding of systemic immunity, particularly its role in modulating anti-tumour immune responses and determining immunotherapy outcomes (Fig. 1). Further investigations are essential not only to identify predictive biomarkers that can guide early clinical decisions regarding immunotherapy, but also to develop therapeutic strategies aimed at converting non-responders into responders. Moreover, a comprehensive, system-wide immune profiling approach—rather than a tumour-restricted, intrinsic one—may reveal critical subsets of anti-cancer immune cells that could be harnessed to enhance immunotherapeutic efficacy.

Author Contributions

AUA single-handedly performed all literature search, conceived the draft outlines, drafted the manuscript, revised the manuscript and prepared Fig. 1. AUA also single-handedly contributed to all editorial changes as a part of the revision process. AUA read and approved the final manuscript. AUA agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

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Conflict of Interest

The author is an employee of Aeterna Health Services Pty Ltd. The judgments in data interpretation and writing were not influenced by this relationship.

References

[1] Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nature Reviews Cancer. 2012; 12: 252–264. https://doi.org/10.1038/nrc3239.

[2] Rosenberg SA, Restifo NP. Adoptive cell transfer as personalized immunotherapy for human cancer. Science (New York, N.Y.). 2015; 348: 62–68. https://doi.org/10.1126/science.aaa4967.

[3] Robert C. A decade of immune-checkpoint inhibitors in cancer therapy. Nature Communications. 2020; 11: 3801. https://doi.org/10.1038/s41467-020-17670-y.

[4] D'Avanzo C, Blaeschke F, Lysandrou M, Ingelfinger F, Zeiser R. Advances in cell therapy: progress and challenges in hematological and solid tumors. Trends in Pharmacological Sciences. 2024; 45: 1119–1134. https://doi.org/10.1016/j.tips.2024.10.016.

[5] Valero C, Lee M, Hoen D, Zehir A, Berger MF, Seshan VE, *et al*. Response Rates to Anti-PD-1 Immunotherapy in Microsatellite-Stable Solid Tumors With 10 or More Mutations per Megabase. JAMA Oncology. 2021; 7: 739–743. https://doi.org/10.1001/jamaoncol.2020.7684.

[6] Alix-Panabières C, Pantel K. Advances in liquid biopsy: From exploration to practical application. Cancer Cell. 2025; 43: 161–165. https://doi.org/10.1016/j.ccell.2024.11.009.

[7] Kilgour E, Rothwell DG, Brady G, Dive C. Liquid Biopsy-Based Biomarkers of Treatment Response and Resistance. Cancer Cell. 2020; 37: 485–495. https://doi.org/10.1016/j.ccell.2020.03.012.

[8] Rieth J, Subramanian S. Mechanisms of Intrinsic Tumor Resistance to Immunotherapy. International Journal of Molecular Sciences. 2018; 19: 1340. https://doi.org/10.3390/ijms19051340.

[9] Stadler JC, Keller L, Mess C, Bauer AT, Koett J, Geidel G, *et al*. Prognostic value of von Willebrand factor levels in patients with metastatic melanoma treated by immune checkpoint inhibitors. Journal for Immunotherapy of Cancer. 2023; 11: e006456. https://doi.org/10.1136/jitc-2022-006456.

[10] Chen Q, Zhao B, Tan Z, Hedberg G, Wang J, Gonzalez L, *et al*. Systems-level immunomonitoring in children with solid tumors to enable precision medicine. Cell. 2025; 188: 1425–1440.e11. https://doi.org/10.1016/j.cell.2024.12.014.

[11] Sade-Feldman M, Yizhak K, Bjorgaard SL, Ray JP, de Boer CG, Jenkins RW, *et al*. Defining T Cell States Associated with Response to Checkpoint Immunotherapy in Melanoma. Cell. 2018; 175: 998–1013.e20. https://doi.org/10.1016/j.cell.2018.10.038.

[12] Kim KH, Cho J, Ku BM, Koh J, Sun JM, Lee SH, *et al*. The First-week Proliferative Response of Peripheral Blood $PD\text{-}1^{+}CD8^{+}$ T Cells Predicts the Response to Anti-PD-1 Therapy in Solid Tumors. Clinical Cancer Research. 2019; 25: 2144–2154. https://doi.org/10.1158/1078-0432.CCR-18-1449.

[13] Tumeh PC, Harview CL, Yearley JH, Shintaku IP, Taylor EJM, Robert L, *et al*. PD-1 blockade induces responses by inhibiting adaptive immune resistance. Nature. 2014; 515: 568–571. https://doi.org/10.1038/nature13954.

[14] Huang AC, Postow MA, Orlowski RJ, Mick R, Bengsch B, Manne S, *et al*. T-cell invigoration to tumour burden ratio associated with anti-PD-1 response. Nature. 2017; 545: 60–65. https://doi.org/10.1038/nature22079.

[15] Krishna S, Lowery FJ, Copeland AR, Bahadiroglu E, Mukherjee R, Jia L, *et al*. Stem-like CD8 T cells mediate response of adoptive cell immunotherapy against human cancer. Science (New York, N.Y.). 2020; 370: 1328–1334. https://doi.org/10.1126/science.abb9847.

[16] Yamauchi T, Hoki T, Oba T, Jain V, Chen H, Attwood K, *et al*. T-cell CX3CR1 expression as a dynamic blood-based biomarker of response to immune checkpoint inhibitors. Nature Communications. 2021; 12: 1402. https://doi.org/10.1038/

s41467-021-21619-0.

[17] Wallin JJ, Bendell JC, Funke R, Sznol M, Korski K, Jones S, *et al*. Atezolizumab in combination with bevacizumab enhances antigen-specific T-cell migration in metastatic renal cell carcinoma. Nature Communications. 2016; 7: 12624. https://doi.org/10.1038/ncomms12624.

[18] Yan Y, Cao S, Liu X, Harrington SM, Bindeman WE, Adjei AA, *et al*. CX3CR1 identifies PD-1 therapy-responsive CD8+ T cells that withstand chemotherapy during cancer chemoimmunotherapy. JCI Insight. 2018; 3: e97828. https://doi.org/10.1172/jci.insight.97828.

[19] Hiam-Galvez KJ, Allen BM, Spitzer MH. Systemic immunity in cancer. Nature Reviews Cancer. 2021; 21: 345–359. https://doi.org/10.1038/s41568-021-00347-z.

[20] Spitzer MH, Carmi Y, Reticker-Flynn NE, Kwek SS, Madhireddy D, Martins MM, *et al*. Systemic Immunity Is Required for Effective Cancer Immunotherapy. Cell. 2017; 168: 487–502.e15. https://doi.org/10.1016/j.cell.2016.12.022.

[21] Wu TD, Madireddi S, de Almeida PE, Banchereau R, Chen YJJ, Chitre AS, *et al*. Peripheral T cell expansion predicts tumour infiltration and clinical response. Nature. 2020; 579: 274–278. https://doi.org/10.1038/s41586-020-2056-8.

[22] Cloughesy TF, Mochizuki AY, Orpilla JR, Hugo W, Lee AH, Davidson TB, *et al*. Neoadjuvant anti-PD-1 immunotherapy promotes a survival benefit with intratumoral and systemic immune responses in recurrent glioblastoma. Nature Medicine. 2019; 25: 477–486. https://doi.org/10.1038/s41591-018-0337-7.

[23] Valpione S, Galvani E, Tweedy J, Mundra PA, Banyard A, Middlehurst P, *et al*. Immune-awakening revealed by peripheral T cell dynamics after one cycle of immunotherapy. Nature Cancer. 2020; 1: 210–221. https://doi.org/10.1038/s43018-019-0022-x.

[24] Yost KE, Satpathy AT, Wells DK, Qi Y, Wang C, Kageyama R, *et al*. Clonal replacement of tumor-specific T cells following PD-1 blockade. Nature Medicine. 2019; 25: 1251–1259. https://doi.org/10.1038/s41591-019-0522-3.

[25] Pauken KE, Shahid O, Lagattuta KA, Mahuron KM, Luber JM, Lowe MM, *et al*. Single-cell analyses identify circulating anti-tumor CD8 T cells and markers for their enrichment. The Journal of Experimental Medicine. 2021; 218: e20200920. https://doi.org/10.1084/jem.20200920.

[26] Yossef R, Krishna S, Sindiri S, Lowery FJ, Copeland AR, Gartner JJ, *et al*. Phenotypic signatures of circulating neoantigen-reactive $CD8^+$ T cells in patients with metastatic cancers. Cancer Cell. 2023; 41: 2154–2165.e5. https://doi.org/10.1016/j.ccell.2023.11.005.

[27] Benguigui M, Cooper TJ, Kalkar P, Schif-Zuck S, Halaban R, Bacchiocchi A, *et al*. Interferon-stimulated neutrophils as a predictor of immunotherapy response. Cancer Cell. 2024; 42: 253–265.e12. https://doi.org/10.1016/j.ccell.2023.12.005.

[28] Zhang Y, Chen H, Mo H, Hu X, Gao R, Zhao Y, *et al*. Single-cell analyses reveal key immune cell subsets associated with response to PD-L1 blockade in triple-negative breast cancer. Cancer Cell. 2021; 39: 1578–1593.e8. https://doi.org/10.1016/j.ccell.2021.09.010.

[29] Kaczanowska S, Murty T, Alimadadi A, Contreras CF, Duault C, Subrahmanyam PB, *et al*. Immune determinants of CAR-T cell expansion in solid tumor patients receiving GD2 CAR-T cell therapy. Cancer Cell. 2024; 42: 35–51.e8. https://doi.org/10.1016/j.ccell.2023.11.011.

[30] Alicea-Torres K, Sanseviero E, Gui J, Chen J, Veglia F, Yu Q, *et al*. Immune suppressive activity of myeloid-derived suppressor cells in cancer requires inactivation of the type I interferon pathway. Nature Communications. 2021; 12: 1717. https://doi.org/10.1038/s41467-021-22033-2.

[31] Loeuillard E, Yang J, Buckarma E, Wang J, Liu Y, Conboy C, *et al*. Targeting tumor-associated macrophages and granulocytic myeloid-derived suppressor cells augments PD-1 blockade in cholangiocarcinoma. The Journal of Clinical Investigation. 2020; 130: 5380–5396. https://doi.org/10.1172/JCI137110.

[32] Mulder K, Patel AA, Kong WT, Piot C, Halitzki E, Dunsmore G, *et al*. Cross-tissue single-cell landscape of human monocytes and macrophages in health and disease. Immunity. 2021; 54: 1883–1900.e5. https://doi.org/10.1016/j.immuni.2021.07.007.

[33] Veglia F, Hashimoto A, Dweep H, Sanseviero E, De Leo A, Tcyganov E, *et al*. Analysis of classical neutrophils and polymorphonuclear myeloid-derived suppressor cells in cancer patients and tumor-bearing mice. The Journal of Experimental Medicine. 2021; 218: e20201803. https://doi.org/10.1084/jem.20201803.