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Comprehensive Review: IRIS Model's Role in Uncovering Ligand-Receptor Downregulation and ICB Therapy Resistance

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***Abstract*—** *Immune checkpoint blockade (ICB) therapy has shown promise in treating melanoma, yet resistance remains a critical obstacle, with many tumors evolving mechanisms to evade immune detection. This review explores the development and application of the Immunotherapy Resistance cell-cell Interaction Scanner (IRIS), a machine learning model designed to predict and analyze ICB resistance by identifying ligand-receptor interactions in the tumor microenvironment (TME). Specifically, IRIS uncovers Resistance Downregulated Interactions (RDIs)—cell-specific ligand-receptor pathways that are downregulated in resistant tumors, particularly those involving chemokine signals critical for CD8+ T cell infiltration, such as the CXCL9-CXCR3 interaction. The IRIS model analyzes bulk transcriptomic data, identifies relevant interactions using the CODEFACS and LIRICS algorithms, and generates a Resistance Downregulated Score (RDS) to predict patient response. IRIS outperforms traditional biomarkers, offering a more dynamic and cell-type-specific approach to assessing TME interactions and ICB resistance mechanisms. Understanding RDIs enables stratification of patients likely to benefit from ICB and informs potential combination therapies to re-engage immune infiltration in resistant tumors. This review highlights IRIS's role in advancing personalized medicine by addressing tumor heterogeneity and providing insights into ICB resistance mechanisms, ultimately contributing to more effective cancer immunotherapy strategies.*

***Keywords*—** *Immune checkpoint blockade (ICB), Melanoma, Ligand-receptor interactions, Tumor microenvironment (TME), Resistance to immunotherapy, CD8+ T cell, Machine learning in cancer therapy, IRIS model (Immunotherapy Resistance cell-cell Interaction Scanner), Resistance Downregulated Interactions (RDIs), Predictive biomarkers, Chemokine signaling,, Cancer immunotherapy, Tumor immune evasion, Personalized medicine, Prognostic biomarkers, Resistance mechanisms, Tumor heterogeneity, Cell-cell interactions, Computational immunology.*

I. INTRODUCTION

A. Background of Immune Checkpoint Blockade (ICB) Therapy:

Immune checkpoint blockade (ICB) therapy is a type of cancer treatment that uses antibodies to block proteins on immune cells, known as immune checkpoints, which prevent the immune system from attacking cancer cells. (15) (31) Tumour cells can exploit this mechanism to evade immune detection. ICB therapy works by blocking these checkpoints, which allows the immune system to recognise and destroy cancer cells. (31) The first immune checkpoint to be identified was CTLA-4, a protein on T cells that competes with the costimulatory molecule CD28 for the same ligands, CD80 and CD86. (31) CTLA-4 has a higher binding affinity than CD28, so it can suppress the activation of T cells by binding to CD80 and CD86 on antigen-presenting cells. (31) Blocking CTLA-4 with antibodies, such as ipilimumab, can improve T cell priming and counteract Treg suppression, which can lead to tumour regression. (31) PD-1 is another immune checkpoint that is expressed on activated, antigen-experienced tumour-infiltrating lymphocytes (TILs). PD-1 is overexpressed by exhausted CD8+ T cells (TEX), which progressively lose their effector functions upon chronic antigen stimulation during cancer. (31) Blockade of PD-1 or its ligand PD-L1 can reinvigorate these cells, resulting in their expansion and enhanced anti-tumour activity. (31) Antibodies blocking PD-1 or PD-L1 include pembrolizumab and nivolumab. (31)

ICB therapy has been particularly successful in treating melanoma, a type of skin cancer. (31) ICB was pioneered by Jim Allison and colleagues, who showed that blocking CTLA-4 in mice could cause tumour regression. (31) This discovery paved the way for the development of human CTLA-4 blocking antibodies. (31) Ipilimumab was the first therapy shown to extend survival in patients with metastatic melanoma, leading to its approval in 2011. (31) PD-1 was later recognised as another crucial T cell immune checkpoint, and clinical trials with PD-1 blocking antibodies in refractory solid tumours yielded promising results. (31) Phase 3 studies in melanoma confirmed that PD-1 inhibitors like pembrolizumab and nivolumab could prolong survival compared to ipilimumab or chemotherapy. (01) (31) These agents were approved for metastatic melanoma treatment in 2014. (31)

The clinical success of ICB in melanoma underscores the therapeutic potential of reinvigorating the immune system to effectively target this disease. (31) However, even with combination ICB, a significant proportion of patients do not experience long-lasting benefits, necessitating further research into predictive biomarkers of response and new targets for combination therapies to overcome immune resistance. (31)

CD8+ T cells are essential for anti-tumour immunity, as they are responsible for directly killing cancer cells. (03) (24) Tumour-infiltrating lymphocytes (TILs) are enriched for

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melanoma-associated antigen specificity, indicating the priming, expansion, and recruitment of anti-melanoma T cells to the tumour. (31) However, the effectiveness of cancer immunotherapy in solid tumours is contingent upon the adequate distribution of effector T cells into malignant lesions. (24) Immune-cold tumours, characterised by a scarcity of effector T cells, employ diverse mechanisms to exclude T cells, including the lack of tumour antigens, defects in antigen presentation, absence of T cell activation, and a deficiency in trafficking signals towards the tumour core. (24)

Resistance to ICB therapy is a major challenge. (15) (26) While ICB therapies have shown significant promise in treating various cancers, a large proportion of patients do not respond, or develop resistance to these therapies. (07) (13) (15) (17) (20) (21) (23) (29) This resistance can be intrinsic, meaning that the tumour is resistant to ICB from the outset, or acquired, meaning that the tumour develops resistance over time. (08) (15)

Understanding the mechanisms of resistance is critical for improving the effectiveness of ICB therapy and developing new therapies to overcome resistance. (07) (08) (19) (24) (26) (31) Research suggests that a resistance program is expressed by malignant cells that promote T cell exclusion and immune evasion. (15) This program, present before immunotherapy, characterises cold niches within the tumour and predicts clinical responses to anti-PD-1 therapy in melanoma patients. (15) Further investigation is needed to fully understand the complex interplay of factors within the tumour microenvironment that contribute to ICB resistance. (24) This involves studying the various cell populations, signalling pathways, and molecular interactions that can either suppress or enhance the immune response against cancer. (11) (18) (28) (31)

By elucidating the mechanisms of immune evasion and developing novel therapeutic strategies that target these pathways, it may be possible to improve response rates to immunotherapy and achieve better outcomes for patients with melanoma and other cancers. (07) (08) (19) (26) (29) (31)

B. Role of Tumor Microenvironment (TME) in Resistance:

The effectiveness of cancer immunotherapy, particularly Immune Checkpoint Blockade (ICB), depends on the adequate presence of effector T cells within the tumour lesions. (24) However, non-responsive or 'cold' tumours can evade ICB through mechanisms that exclude T cells from the tumour microenvironment (TME). (24) (34) Tumours actively modulate the TME to hinder T cell infiltration, leading to resistance to ICB treatment. (34)

The TME encompasses various components such as immune cells, stromal cells, blood vessels, and the extracellular matrix. These elements interact dynamically with cancer cells, influencing tumour growth, invasion, and metastasis. (22) The presence and functionality of different immune cells within the TME can significantly impact the response to therapies. (04) For instance, a higher density of T cells, particularly CD8+ cytotoxic T cells and CD45RO+ memory T cells is generally associated with a positive prognosis in various cancers, including melanoma and head and neck, breast, bladder, urothelial, ovarian, colorectal, renal, prostatic, and lung cancer. (04) However, other immune cells, such as regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), and M2 macrophages, can suppress anti-tumour immune responses, hindering ICB efficacy. (08) (21) (23) (25)

Understanding the diverse roles of immune cells within the TME is crucial for developing effective immunotherapies. (04) The TME can impact ICB effectiveness through several mechanisms:

- T cell Exclusion: Cold tumors often lack sufficient chemokine signals to attract T cells to the tumour core. Factors like vascular endothelial growth factor (VEGF) can suppress chemokine production and hinder T cell infiltration. (24)
- T cell Dysfunction: Suppressive factors within the TME can impair T cell function. (10) For instance, regulatory T cells (Tregs) can limit T cell activity through direct contact and inhibitory cytokines. (21) (23) Myeloid-derived suppressor cells (MDSCs) also contribute to immune evasion and tumour growth, hindering ICB response. (08)
- Immune Checkpoint Molecules: Immune checkpoint molecules like PD-1 and CTLA-4 are often upregulated in the TME, suppressing T cell activity and contributing to ICB resistance. (08)
- Cytokine and Chemokine Milieu: The balance of cytokines and chemokines in the TME can impact immune cell recruitment and activity. Some chemokines recruit immunosuppressive cells like Tregs and MDSCs, while others attract effector T cells. (19)

Therefore, targeting these TME-mediated resistance mechanisms through combination therapies may be necessary to improve ICB efficacy. (26)

Importance of Ligand-Receptor Interactions in TME for Immune Responses:

Ligand-receptor interactions play a crucial role in regulating immune cell activity within the TME and influence response to ICB. (06) (16) (34)

- Cells communicate through these interactions, where a ligand from one cell binds to a receptor on another cell, triggering downstream signalling pathways that modulate cellular behaviour. (16)
- The specificity and strength of these interactions can influence the recruitment, activation, and function of various immune cells within the TME. (16) (26)
- Dysregulation of ligand-receptor interactions can contribute to immune suppression and ICB resistance. (26)

For example:

- Chemokine-mediated T cell recruitment: Chemokines are a type of cytokine that guide the migration of immune cells. (29) Chemokine receptors on T cells interact with specific chemokine ligands expressed by cells within the TME, directing their movement towards the tumour site. (27) The CXCL9 and CXCL10 chemokines, which bind to the CXCR3 receptor on activated CD8+ T cells, are essential for effective T cell recruitment and response to ICB therapy. (30) Tumours can develop resistance to ICB by

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downregulating or inactivating these chemokine signals, preventing T cell infiltration and creating a 'cold' TME. (26) (30) (34)

- Immune checkpoint interactions: Immune checkpoint molecules, such as PD-1 and CTLA-4, act as inhibitory receptors on T cells. Their ligands, PD-L1 and B7 family members, are often upregulated in the TME, suppressing T cell activation and contributing to ICB resistance. (08) Blocking these interactions with ICB therapy can reinvigorate T cell responses. (26) However, tumours can develop resistance by downregulating MHC expression or upregulating alternative inhibitory checkpoints. (19)

Characterising the ligand-receptor interactions within the TME is crucial for understanding ICB response and identifying potential therapeutic targets. (34) Using computational tools like IRIS (Immunotherapy Resistance cell-cell Interaction Scanner), researchers can identify ICB resistance-associated ligand-receptor interactions from bulk transcriptomic data. (34) This approach can reveal specific ligand-receptor pairs whose downregulation is linked to ICB resistance. (34)

Furthermore, investigations of ligand-receptor interactions in the TME can:

- Predict ICB Response: The activity of specific ligand-receptor pairs in pre-treatment samples can help predict response to ICB therapy. (26) For instance, the activity of RDIs (Resistance Deactivated Interactions) in pre-treatment samples is associated with a higher likelihood of response. (34)
- Uncover Resistance Mechanisms: Analysing changes in ligand-receptor interactions can reveal how tumours evade immune attack. (26) For example, downregulation of chemokine signalling pathways that recruit CD8+ T cells to the tumour is a significant mechanism of ICB resistance. (26) (34)
- Identify Therapeutic Targets: Ligand-receptor pairs involved in ICB resistance may serve as potential therapeutic targets. (26) Strategies to enhance stimulatory chemokine expression or block inhibitory interactions could improve anti-tumour responses. (26) (34)

II. Current Challenges in ICB Therapy

A. *Primary and Acquired Resistance:*

Primary resistance refers to a clinical scenario where a cancer does not respond to an immunotherapy strategy. *(08)* The mechanistic basis of the lack of response to immunotherapy may include adaptive immune resistance, which occurs when the immune system recognizes a cancer, but the cancer protects itself through adaptation. *(08)* Acquired resistance describes a situation where a patient initially responds to immunotherapy but later experiences disease progression. *(08)* This can occur due to the selection of resistant clones already present before treatment or because of true acquired resistance that develops during immunotherapy. *(08)*

Mechanisms of Primary and Adaptive Resistance

Both tumor-cell-intrinsic and tumor-cell-extrinsic factors contribute to these resistance mechanisms. *(08)*

Tumor-Cell-Intrinsic Factors:

- Absence of antigenic proteins: This can occur due to low mutational burden, a lack of viral antigens, or the absence of cancer-testis antigens. *(08)* Without sufficient tumor-specific antigens, the immune system may not effectively recognize and target cancer cells. *(08)*
- Absence of antigen presentation: Tumor cells can evade immune recognition by downregulating or losing the expression of molecules involved in antigen presentation, such as major histocompatibility complex (MHC) class I molecules. Deletions or silencing of genes involved in antigen processing and presentation, like TAP and B2M, can lead to reduced MHC I expression and impaired T cell recognition. *(08)*
- Genetic T cell exclusion: Certain genetic alterations within tumor cells can promote T cell exclusion from the tumor microenvironment (TME). *(08)* For example, activation of the MAPK oncogenic signaling pathway or stabilization of β-catenin can create a TME that hinders T cell infiltration. *(08) (15)* additionally, a mesenchymal transcriptome signature in tumor cells is associated with T cell exclusion and resistance to ICB. *(15)*
- Oncogenic PD-L1 expression: Some tumors constitutively express high levels of PD-L1, an immune checkpoint molecule that suppresses T cell activation. *(08)* This oncogenic PD-L1 expression can contribute to primary resistance to anti-PD-1 therapy. *(08)*
- Insensitivity to T cells: Tumor cells can develop insensitivity to T cell-mediated killing, even if T cells infiltrate the TME. *(08)* Mutations in interferon-gamma (IFN-γ) signaling pathways, a critical cytokine for T cell activation and anti-tumor immunity, can render tumor cells less susceptible to T cell attack. *(08)*

Tumor-Cell-Extrinsic Factors:

- Immunosuppressive cells: The TME often harbors immunosuppressive cells such as regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), and M2 macrophages. *(08)* These cells can suppress the activity of anti-tumor T cells, limiting the effectiveness of immunotherapy. *(08)*
- Physical barriers: The extracellular matrix and other structural components of the TME can form physical barriers that prevent T cells from reaching tumor cells. *(08)*

Mechanisms of Acquired Resistance

Acquired resistance can develop through various mechanisms, often involving alterations within tumor cells or changes in the TME:

- Loss of target antigen: Tumor cells can lose expression of the target antigen recognized by the immune system. *(08)* This can occur through genetic mutations or epigenetic modifications, leading to immune escape and resistance to therapies targeting that specific antigen. *(08)*
- Loss of HLA expression: Tumors can downregulate or completely lose expression of HLA molecules, particularly MHC class I, which are essential for presenting tumor antigens to CD8+ T cells. *(08)* This loss

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of antigen presentation can lead to immune evasion and resistance to T cell-mediated killing. *(08)*

- Altered interferon signaling: Tumor cells can acquire mutations or epigenetic changes that disrupt IFN-γ signaling pathways. *(08)* This disruption can dampen the anti-tumor immune response, impairing T cell activation and effector functions. *(08)*
- Loss of T cell functionality: T cells within the TME can become exhausted or dysfunctional due to chronic antigen stimulation and exposure to immunosuppressive factors. *(08)* Exhausted T cells exhibit reduced cytokine production, impaired cytotoxic activity, and increased expression of inhibitory receptors, leading to diminished anti-tumor immunity. *(14)*

B. Limitations of Existing Biomarkers:

Transcriptomic biomarkers are becoming increasingly important in cancer research, especially in the field of immunotherapy. However, they have limitations, particularly when used to predict a patient's response to immune checkpoint blockade (ICB) therapy. *(17) (26) (34)*

- Bulk transcriptomic analyses overlook the inherent heterogeneity of the tumour microenvironment (TME). *(26) (34)* Different cell types, including immune cells, stromal cells, and tumour cells, contribute to the overall gene expression profile of a tumour sample. Bulk RNA sequencing provides an averaged gene expression signal across all cell types, potentially masking crucial cell-type-specific changes associated with response or resistance to ICB therapy. *(26) (34)*
- Single-cell RNA sequencing can address cell heterogeneity but has limitations. *(26) (34)* Single-cell transcriptomic signatures might not generalise well to the larger bulk ICB cohorts, which are more commonly available. *(26) (34)* Additionally, single-cell studies are more expensive and complex than bulk analyses, limiting their widespread application in clinical settings. *(15)*
- Many existing transcriptomic biomarkers are based on genes that are not directly targetable. *(26) (34)* This limits their translational potential, as they cannot inform the development of new therapies that directly modulate the identified resistance mechanisms. *(26) (34)*
- The predictive power of transcriptomic biomarkers remains suboptimal. *(26) (34)* While some signatures show promising results, there is still room for improvement in accuracy and robustness across different patient populations and cancer types. (15) *(26) (34)* This limitation stems from the complex interplay of multiple factors influencing ICB response and the dynamic nature of the tumour-immune interactions during treatment. *(08) (24)*

III. Machine Learning Models in Cancer Immunotherapy

A. Machine Learning Predicts Immunotherapy Outcomes

Machine learning (ML) is being used to build predictive models that forecast patient outcomes for cancer immunotherapies, especially immune checkpoint blockade (ICB) therapy. While these treatments show promise, they do not benefit all patients, and those who do respond see varying levels of success. *(23) (31)*

- Researchers are exploring how to predict which patients will respond to ICB and how well they might respond. *(21)*
- One approach leverages ML to create models that can identify complex patterns in patient data, such as gene expression profiles, immune cell composition, and clinical characteristics.
- These models can be used to identify biomarkers associated with ICB response and non-response. *(23) (26)*

Here are some examples of ML applications in predicting therapy outcomes:

- IMPRES (Immune Prediction of Response) uses 15 transcriptomic connections between immune checkpoint genes to predict ICB response in melanoma patients. IMPRES has an accuracy of AUC=0.83, surpassing other predictors by identifying almost all responders while minimising false positives. *(13)*
- TIDE (T cell dysfunction and exclusion) predicts ICB response in melanoma patients by analysing gene expression signatures related to T cell dysfunction and immunosuppressive cell infiltration. This method has shown superior accuracy compared to PD-L1 level and mutation load when predicting outcomes for patients treated with anti-PD1 or anti-CTLA4. *(14)*
- IRIS (Immunotherapy Resistance cell-cell Interaction Scanner) was developed to identify ligand-receptor interactions in the tumour microenvironment (TME) that contribute to ICB resistance. This model has been used to analyse multiple melanoma ICB cohorts *(26) (34)*, and researchers have found that specific downregulated interactions, called resistance downregulated interactions (RDI), are strongly associated with ICB response. *(34)* These RDIs frequently involve chemokine signalling pathways. *(34)*
- CODEFACS & LIRICS are tools that work together to analyse bulk tumour expression data and identify cell-type-specific interactions in the TME. *(32)* Using a machine-learning-based genetic algorithm, researchers can identify interactions that predict clinical responses to ICB. *(32)*

These examples highlight the potential of ML in improving cancer immunotherapy outcomes.

- By using ML to identify biomarkers and predict response to therapy, clinicians can better select patients for treatment and develop more effective therapeutic strategies. *(24)*
- These ML-based models can also shed light on the mechanisms of ICB resistance, which could lead to the development of novel treatments that overcome these challenges. *(24) (26)*

B. Development of IRIS model

The Immunotherapy Resistance cell-cell Interaction Scanner (IRIS) is a machine learning model designed to identify cell-type-specific ligand-receptor interactions in the

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tumour microenvironment (TME) that are associated with resistance to immune checkpoint blockade (ICB) therapy. *(26) (34)* IRIS was developed to address the limitations of existing transcriptomic-based biomarkers for predicting ICB response, which often fail to account for cell type heterogeneity within the TME. *(34)*

- IRIS utilises bulk RNA sequencing data from patients treated with ICB therapy.
- The data is first DE convolved using CODEFACS to estimate the expression profiles of ten different cell types within the TME. *(26) (34)*
  - These cell types include B cells, CD8+ T cells, CD4+ T cells, cancer-associated fibroblasts, endothelial cells, macrophages, malignant cells, natural killer cells, plasmacytoid dendritic cells, and skin dendritic cells. *(34)*
- Next, LIRICS is used to infer the activity of cell-type-specific ligand-receptor interactions in each patient based on the DE convolved expression profiles. *(26) (34)*
- IRIS then uses a two-step supervised machine learning approach to identify interactions that are associated with ICB resistance. *(26) (34)*

Step 1: Differential Activation Analysis

- The first step of IRIS identifies interactions that are differentially activated between pre-treatment and post-treatment non-responder patients. *(26) (34)*
- A Fisher's exact test is used to identify interactions that are significantly activated in either the post-treatment non-responder or the pre-treatment groups. *(34)*
- These interactions are then classified as either resistant activated interactions (RAI) or resistant deactivated interactions (RDI) based on their differential activity. *(26) (34)*

Step 2: Hill Climbing Aggregative Feature Selection

- The second step of IRIS uses a hill-climbing aggregative feature selection algorithm to choose the optimal set of RDIs or RAIs for classifying responders and non-responders in pre-treatment samples. *(26) (34)*
- This process involves iteratively adding or removing interactions from the model and evaluating the model's performance at each step. *(26) (34)*
- The final output of IRIS is a set of RDIs and RAIs that are hypothesised to be involved in ICB resistance. *(26) (34)*
- These interactions can then be used to predict ICB therapy response in new patients. *(26) (34)*

C. Why Machine Learning is Essential

Machine learning is essential to uncovering complex interaction networks in the TME because the TME is a complex and dynamic ecosystem composed of multiple cell types that interact with each other through a variety of signalling pathways. *(16) (26) (29)*

- These interactions can have a profound impact on tumour growth and response to therapy. *(16) (26) (34)*
- Traditional methods for studying the TME, such as immunohistochemistry, are limited in their ability to capture the complexity of these interactions. *(26) (34)*
- Machine learning algorithms can be used to analyse large, high-dimensional datasets and identify patterns that would be difficult or impossible to detect using traditional methods. (26)
- This allows researchers to gain a deeper understanding of the complex interactions that occur within the TME and identify potential therapeutic targets. *(26) (34)*

For example, IRIS has been used to identify RDIs that are strongly associated with ICB response in melanoma. *(34)* Many of these RDIs involve chemokine signalling pathways, which are important for regulating the trafficking of immune cells to the tumour site. *(34)*

By identifying these interactions, IRIS can help researchers to understand the mechanisms of ICB resistance and develop new strategies to overcome these challenges. *(26) (34)* For example, one potential strategy would be to develop drugs that target the RDIs that are downregulated in resistant tumours. *(34)* This could help to restore the trafficking of immune cells to the TME and enhance the efficacy of ICB therapy. *(34)*

IV. Key Findings from the Study

A. Ligand-Receptor Interactions and ICB Resistance

Ligand-receptor interactions form the basis of communication between cells in the tumour microenvironment (TME). *(34)* This communication is essential for coordinating immune responses against cancer.

- When a ligand, which is a molecule produced by one cell, binds to its specific receptor on another cell, a series of signals are initiated within the recipient cell.
- These signals can lead to various outcomes, including changes in gene expression, cell proliferation, and cell migration.

Key roles of ligand-receptor interactions in immune cell communication include:

- Immune cell recruitment: Immune cells rely on chemokines, a type of ligand, to guide their movement to specific locations in the body. (50) For example, chemokines CXCL9 and CXCL10 are produced by cells in the TME and attract CD8+ T cells, which are crucial for killing cancer cells, by binding to the CXCR3 receptor on the T cells. *(34)*
- Immune cell activation: The activation of T cells, the orchestrators of adaptive immunity, requires two signals. *(31)*
  - The first signal comes from the T cell receptor (TCR) engaging with an antigen presented by MHC molecules on antigen-presenting cells (APCs).
  - The second signal comes from co-stimulatory molecules. An example is the interaction between CD28 on T cells and CD80/CD86 on APCs, providing a necessary co-stimulatory signal for T cell activation. *(31)*
- Immune suppression: Immune checkpoint molecules, like CTLA-4 and PD-1, are critical regulators of T cell activity, preventing excessive immune responses that could damage healthy tissues. *(31) (33)*
  - CTLA-4 competes with CD28 on T cells for binding to CD80/CD86 on APCs. Its higher affinity for these

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ligands results in the suppression of T cell activation. *(31)*
- PD-1 on T cells, upon interaction with its ligand PD-L1 on tumour cells or other cells in the TME, dampens T cell function. *(31) (33)*

Specific Findings of the Study: RDIs and RUIs in Resistant Tumours

The study employed a machine learning model called IRIS (Immunotherapy Resistance cell-cell Interaction Scanner) to analyse data from five large melanoma ICB cohorts. *(34)* The model identified specific ligand-receptor interactions that are associated with ICB resistance. These interactions are classified as:

- Resistant Downregulated Interactions (RDIs): These interactions are downregulated in tumours that have developed resistance to ICB therapy. *(34)* Many RDIs are involved in chemokine signalling, suggesting that resistant tumours suppress these pathways to reduce the infiltration of lymphocytes, specifically CD8+ T cells, into the TME. *(34)*
  - Examples of RDIs include the interaction between CXCL9 and CXCR3, known to enhance CD8+ T cell responses and the interaction between XCL1, produced by NK cells, and XCR1 on dendritic cells, which is associated with anti-PD-1 response. *(34)* These findings suggest that the loss of these interactions contributes to creating a "cold" TME, characterized by low immune activity and reduced response to immunotherapy. *(34)*
- Resistant Upregulated Interactions (RUIs): These interactions are upregulated in resistant tumours. *(34)* However, the study found that RUIs had a weaker predictive ability for ICB response compared to RDIs. *(34)* Further research is needed to understand the specific roles of RUIs in ICB resistance.

B. Chemokine Signalling and CD8+ T Cell Infiltration

The study uses a model called IRIS to identify ligand-receptor interactions associated with ICB resistance. *(34)* These interactions are classified as resistant downregulated interactions (RDIs) if they are downregulated in tumours that develop resistance to ICB therapy.

Impact of RDIs on CD8+ T Cell Recruitment

Many of the identified RDIs are involved in chemokine signalling, a process crucial for attracting immune cells, including CD8+ T cells, to the tumour site. *(34)* Here's how RDIs involving chemokine signalling can negatively impact CD8+ T cell recruitment:

- Disrupted Chemotaxis: Chemokines act as signposts, guiding immune cells towards areas of inflammation or infection, including the TME. *(34)* Downregulation of RDIs involved in this signalling pathway disrupts this chemotactic gradient, making it difficult for CD8+ T cells to locate and infiltrate the tumour.
- Reduced T Cell Infiltration: As a result of the weakened chemotactic signals, fewer CD8+ T cells are able to penetrate the tumour. This leads to a decrease in the overall number of cytotoxic T cells within the TME, hindering the immune system's ability to mount an effective anti-tumour response. *(34)*
- Transition to a "Cold" TME: The reduced CD8+ T cell infiltration ultimately leads to a shift from a "hot" or immunologically active TME to a "cold" or immunosuppressive TME. *(34)* This "cold" TME is characterized by a lack of immune cell activity, allowing the tumour to grow unchecked and evade immune surveillance.

The Importance of the CXCL9-CXCR3 Interaction

The CXCL9-CXCR3 interaction is a prime example of an RDI that plays a vital role in mediating immune responses against melanoma. *(34)*

- CXCL9 is a chemokine produced by various immune cells, including dendritic cells, in response to inflammatory signals. *(34)*
- CXCR3 is the receptor for CXCL9 and is primarily found on activated T cells, including CD8+ T cells. *(34)*

The importance of the CXCL9-CXCR3 interaction stems from its influence on several key immune processes:

- CD8+ T Cell Trafficking: This interaction is crucial for the recruitment of CD8+ T cells to the tumour site. CXCL9, produced within the TME, attracts CXCR3-expressing CD8+ T cells, facilitating their migration into the tumour and enabling them to target cancer cells. *(34)*
- Enhancing Anti-tumour Immunity: Studies have shown that the presence of the CXCL9-CXCR3 axis is associated with an improved response to PD-1 blockade in melanoma. *(18) (34)* This suggests that the interaction between CXCL9 and CXCR3 not only helps recruit CD8+ T cells but also contributes to their activation and ability to effectively kill tumour cells.
- Predictive Biomarker: Research suggests that CXCR3 ligands in both murine tumours and the plasma of melanoma patients could serve as an indicator of clinical response to anti-PD-1 therapy. *(18)*

C. Predictive Power of RDIs as compared to RUIs

The study highlights the superior predictive power of RDIs compared to RUIs in forecasting patient response to ICB therapy. *(34)* The study used a machine learning model named IRIS, which analyses the activity of ligand-receptor interactions in the tumour microenvironment. *(34)*

RDIs as Superior Predictors of ICB Response

The study demonstrates that RDIs outperform RUIs in predicting patient response to ICB therapy in the following ways:

- Higher Predictive Accuracy: When comparing the performance of RDIs and RUIs in classifying responder versus non-responder patients, RDIs consistently showed higher Area Under the Curve (AUC) values across five melanoma ICB cohorts. *(34)* A higher AUC indicates better discrimination between responders and non-responders, suggesting that RDIs offer a more reliable signal for predicting treatment outcomes.
- Limited Predictive Power of RUIs: In contrast, RUIs, interactions upregulated in resistant tumours, demonstrated weaker predictive power. *(34)* Their AUC

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values were significantly lower, indicating a limited ability to distinguish between patients who would benefit from ICB therapy and those who would not.

Resistance Downregulated Score (RDS) and its Correlation with ICB Therapy Success

The study introduces the concept of the Resistance Downregulated Score (RDS) as a measure of RDI activity within a tumour sample. *(34)*

- Calculating RDS: RDS is calculated as the normalised count of activated RDIs in a patient's pre-treatment tumour sample. *(34)*
- Correlation with ICB Response: A higher RDS indicates a greater likelihood of responding positively to ICB therapy. *(34)*

  This suggests that the more active-state RDIs present in a tumour before treatment, the more likely the patient is to experience a favourable outcome.

RDS as a Robust Biomarker

The study further validates the robustness and clinical significance of RDS:

- Superior to Existing Biomarkers: RDS outperforms or shows comparable performance to several established ICB response predictors, including TIDE, IMPRES, MPS, the cytotoxic signature, and resF. *(34)* This highlights the potential of RDS as a valuable tool for guiding treatment decisions.
- Predictive in the Absence of ICB Therapy: Notably, RDS can also stratify patients based on overall survival and progression-free survival even in the absence of ICB therapy. *(34)* This finding underscores that RDIs reflect fundamental immune response mechanisms that impact patient outcomes beyond the context of ICB treatment.

Validation Using Single-cell Transcriptomics: Analysis of single-cell transcriptomics data confirms the predictive power of RDS in distinguishing between treatment-naïve and post-ICB resistant tumours. *(34)* This finding strengthens the validity of RDS as a reliable biomarker across different data modalities.

V. Applications of the IRIS Model

The IRIS Model, as described in the study offers valuable applications for predicting ICB resistance in melanoma and stratifying patients based on their risk.

A. Predicting ICB Resistance

The IRIS model leverages the identification of RDIs, or interactions that are downregulated in resistant tumours, to predict the likelihood of ICB resistance. By analysing pre-treatment tumour samples, the model can identify patients who exhibit low RDI activity and are therefore at a higher risk of developing resistance to ICB therapy. *(26) (34)* This early identification of potential non-responders can guide treatment decisions, potentially sparing these patients from ineffective therapy and allowing for the exploration of alternative treatment options.

Stratifying Patients Based on RDS Score

The study introduces the concept of the Resistance Downregulated Score (RDS), a quantifiable measure of RDI activity in a tumour sample. The RDS score can be calculated from pre-treatment transcriptomic data, providing a valuable tool for stratifying patients based on their risk of ICB resistance. Here's how the RDS score can be used for patient stratification:

- Identifying High-Risk Patients: Patients with low RDS scores exhibit lower RDI activity and are therefore classified as high-risk. These patients are less likely to respond favourably to ICB therapy and may benefit from alternative treatment approaches or combination therapies that address the underlying resistance mechanisms. *(34)*
- Identifying Low-Risk Patients: Patients with high RDS scores demonstrate robust RDI activity, indicating a higher likelihood of responding to ICB therapy. *(34)* These patients can be confidently treated with ICB, with a greater expectation of a positive outcome.

Benefits of RDS-Based Stratification

Employing the RDS score for patient stratification offers several advantages:

- Improved Treatment Selection: By identifying patients likely to respond to ICB therapy, clinicians can make more informed treatment decisions, optimising treatment outcomes and potentially minimising unnecessary exposure to treatments with limited efficacy. *(26) (34)*
- Early Intervention: Early identification of high-risk patients allows for prompt consideration of alternative treatment strategies or combination therapies, potentially improving their chances of long-term survival. *(07) (08)*
- Personalised Medicine: RDS-based stratification contributes to a more personalised approach to melanoma treatment, tailoring therapies to the individual's unique tumour biology and immune profile. *(19)*

B. Implications for Personalized Medicine

The IRIS model, as detailed in the study holds significant implications for personalized medicine in melanoma treatment. *(34)* It provides a framework for tailoring treatment approaches based on an individual patient's tumour microenvironment and predicted response to immune checkpoint blockade (ICB) therapy.

Guiding Personalized Treatment Approaches

By identifying and quantifying RDIs, IRIS can inform treatment decisions in the following ways:

- Selecting Appropriate Candidates for ICB Therapy: IRIS can predict which patients are most likely to benefit from ICB therapy. Patients with high RDS scores, indicating robust RDI activity, have a greater likelihood of responding positively to ICB and may be prioritized for this treatment modality. *(34)*
- Exploring Alternative Treatment Options: For patients identified as high-risk for ICB resistance (low RDS scores), alternative treatment options can be considered. *(34)* This may include other immunotherapies, targeted

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therapies, chemotherapy, or a combination of these approaches, depending on the specific characteristics of the patient's tumour.

- Tailoring Combination Therapies: IRIS can guide the selection of combination therapies by identifying specific RDIs that are downregulated in the patient's tumour. Targeting these pathways with additional therapies may help overcome ICB resistance. For example, if RDIs involved in T cell recruitment are deactivated, combining ICB with therapies that boost T cell infiltration to the tumour microenvironment could be considered. *(34)*

Benefits of Identifying Patients Who Would or Would Not Benefit from ICB Therapy

Identifying patients who would or would not benefit from ICB therapy through IRIS offers several advantages:

- Maximizing Treatment Efficacy: By selecting patients most likely to respond, IRIS can help maximise the efficacy of ICB therapy, leading to improved tumour control and potentially better long-term survival. *(34)*
- Minimising Unnecessary Treatment and Side Effects: Identifying patients unlikely to benefit from ICB spares them from potentially ineffective treatment and associated side effects. (34) This is particularly important given that ICB therapies can have significant immune-related adverse events.
- Reducing Healthcare Costs: By avoiding ineffective treatments, IRIS can contribute to reducing healthcare costs associated with ICB therapy, allowing resources to be allocated more effectively.
- Facilitating Clinical Trial Design: The insights gained from IRIS can be applied to the design of clinical trials, allowing for more efficient patient selection and potentially accelerating the development of novel ICB-based therapies or combination strategies.

VI. Comparison with Other Biomarker Approaches

A. Comparison of IRIS with Other Biomarker Approaches

The IRIS model, a machine learning method for identifying immune checkpoint blockade (ICB) resistance-relevant ligand-receptor interactions in the tumour microenvironment, offers a novel approach to predicting ICB response in melanoma. *(34)* It distinguishes itself from other existing transcriptomic biomarkers by focusing on the downregulation of specific ligand-receptor interactions, termed RDIs, which are associated with enhanced lymphocyte infiltration in resistant tumours. *(34)* The RDS (Resistance Downregulated Score), derived from IRIS, quantifies RDI activity and demonstrates superior predictive accuracy compared to several established biomarkers. *(34)*

Here's an overview of other existing models and their comparison with IRIS:

- TIDE (Tumour Immune Dysfunction and Exclusion): TIDE infers gene signatures associated with T cell dysfunction and exclusion using bulk transcriptomics data from The Cancer Genome Atlas (TCGA). *(14) (34)* It predicts ICB response by correlating tumour expression profiles with T cell exclusion signatures in tumours with low cytotoxic T lymphocyte (CTL) levels. *(14)* While TIDE has been shown to predict ICB response in melanoma more accurately than PD-L1 levels and tumour mutational burden (TMB), *(14)* the study found that the average AUC of RDS (0.72) was slightly better than that of TIDE (0.70). *(14)* Notably, RDS also demonstrated greater consistency across datasets, with a lower coefficient of variation compared to TIDE. *(34)*
- IMPRES: IMPRES, a predictor of ICB response in melanoma, was developed by learning pairwise relations between 15 immune checkpoint genes associated with spontaneous regression in neuroblastoma using bulk transcriptomics. *(13) (34)* It achieves an overall accuracy of AUC=0.83, outperforming existing predictors by capturing almost all true responders while misclassifying less than half of the non-responders. *(13)* However, the study "A machine learning model reveals expansive downregulation of ligand-receptor interactions that enhance lymphocyte infiltration in melanoma with developed resistance to immune checkpoint blockade" found that RDS outperformed IMPRES (average AUC: 0.62) in predicting ICB response in melanoma. *(34)*
- MPS (Melanocytic Plasticity Signature): This signature was derived from mouse models and bulk transcriptomics of ICB patients, revealing a link between melanocytic plasticity and ICB therapy resistance. *(34)* However, its predictive power is limited, with an average AUC of 0.47, significantly lower than RDS. *(34)*
- Cytotoxic Signature: This signature, correlated with aneuploidy and negatively correlated with immune infiltration, was identified using bulk transcriptomics from melanoma patients. *(34)* While its average AUC (0.72) is comparable to RDS, it lacks the cell-type specificity and focus on ligand-receptor interactions that distinguish IRIS. *(34)*
- resF: This transcriptomic program associated with T cell exclusion and immune evasion was derived from single-cell RNA sequencing of ICB-treated melanoma patients. *(34)* While it offers insights into resistance mechanisms, its average AUC (0.58) is lower than RDS, potentially due to its reliance on single-cell data, which may not be as readily applicable to bulk ICB cohorts. *(34)*
- Tres (T cell resilience model): Tres identifies signatures of T cells resilient to immunosuppressive tumour microenvironments that confer antitumor properties using single-cell transcriptomics. *(34)* Its focus on T cell resilience complements IRIS's emphasis on ligand-receptor interactions; however, direct comparisons of predictive accuracy are not available.

The study highlights that many existing biomarkers, including TIDE, IMPRES, MPS, Cytotoxic Signature, and resF, have limitations, such as overlooking cell type heterogeneity within the tumour microenvironment, relying on single-cell data that may not be generalizable to bulk cohorts, and focusing on genes that are not directly targetable. *(34)* In contrast, IRIS leverages bulk DE convolved transcriptomics to identify cell-type-specific ligand-receptor interactions and

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offers a robust and potentially targetable predictive biomarker in the form of RDS. *(34)*

B. Advantages of Focusing on Cell-Cell Interactions

Advantages of Ligand-Receptor Interactions as Biomarkers

Focusing on cell-cell interactions, specifically ligand-receptor interactions, offers several advantages in understanding therapy resistance over traditional bulk gene expression biomarkers. *(34)* Bulk transcriptomic biomarkers, which analyse gene expression in the entire tumour sample, often overlook the intricate cell type heterogeneity within the tumour microenvironment (TME). *(34)* They provide a generalised picture of gene activity without discerning the specific contributions of different cell types. This lack of granularity can obscure crucial interactions between tumour cells and immune cells that drive resistance to therapies like ICB.

In contrast, examining ligand-receptor interactions provides a more precise lens for understanding therapy resistance for the following reasons:

- Cell-Type Specificity: Ligand-receptor interactions are inherently cell-type specific, meaning that the expression of a particular ligand on one cell type and its corresponding receptor on another cell type signifies a potential communication pathway between those two cell types. *(16)* By identifying these specific interactions, researchers can pinpoint the precise cellular crosstalk that contributes to resistance mechanisms. For instance, the downregulation of chemokine signalling pathways between tumour cells and immune cells, as revealed by the IRIS model, can directly impede the recruitment of cytotoxic T cells into the tumour, hindering the effectiveness of ICB therapy. *(34)*
- Functional Relevance: Ligand-receptor interactions are the fundamental basis of cell signalling and communication within the TME. *(34)* They orchestrate a complex interplay between tumour cells and immune cells, influencing processes like immune cell recruitment, activation, and suppression. Identifying alterations in these interactions, such as the downregulation of RDIs in ICB-resistant tumours *(34)*, provides direct insights into the functional mechanisms driving resistance. This functional understanding goes beyond mere gene expression changes, offering a more mechanistic view of how resistance develops.

Targetable Pathways: Unlike many genes identified through bulk gene expression analyses, ligand-receptor interactions often involve proteins located on the cell surface, making them potentially targetable by therapeutic agents. *(34)* This targetability holds significant therapeutic promise, as it opens avenues for developing novel drugs or combination therapies that directly modulate these interactions to overcome resistance. For example, if specific RDIs are found to be crucial in mediating resistance, targeted therapies could be designed to reactivate these pathways, enhancing the efficacy of ICB therapy..

VII. Clinical and Research Implications

A. Potential for combination therapies

Potential of RDIs to Inform Combination Therapies

RDIs (Resistance Downregulated Interactions) are ligand-receptor interactions that are downregulated in tumours resistant to immune checkpoint blockade (ICB) therapy. *(34)* These interactions play a crucial role in recruiting CD8+ T cells to the tumour site. *(34)* Chemokines, a type of signalling molecule, are particularly relevant to this process. *(34)*

The identification of RDIs, especially those involving chemokine pathways, opens exciting possibilities for developing new combination therapies that target these pathways alongside ICB therapy.

- Reactivating RDI Pathways: Tumours resistant to ICB therapy often exhibit a downregulation of RDIs involved in T cell trafficking. *(34)* This downregulation creates a "cold" TME (tumour microenvironment) characterised by low levels of lymphocyte infiltration. *(29) (34)* One therapeutic strategy could involve reactivating these silenced RDI pathways to restore chemokine signalling and enhance T cell recruitment into the tumour. This could potentially convert a "cold" tumour into a "hot" one, making it more susceptible to ICB therapy. *(29) (34)*
- Enhancing Chemokine Gradients: Another strategy could focus on amplifying the existing chemokine gradients within the tumour. *(01)* By increasing the concentration of chemokines that attract T cells, researchers could enhance the chemotactic signals that guide T cells towards the tumour. This approach could be particularly effective in combination with ICB therapy, as it would create a more favourable environment for T cell infiltration and activation.
- Targeting Multiple Chemokine Pathways: The chemokine system is complex, with multiple chemokines and receptors involved in immune cell trafficking. *(34)* Targeting multiple chemokine pathways simultaneously could potentially have a synergistic effect, leading to a more robust anti-tumour response. This approach could involve combining drugs that target different chemokine receptors or using gene therapy to enhance the production of multiple chemokines within the tumour. *(02)*

Examples of Chemokine-Based Therapies:

The sources cite several examples of how chemokine pathways can be targeted in cancer therapy:

- CXCR3-CXCR3 Ligand Axis: Studies have shown that the CXCR3-CXCR3 ligand biological axis plays a critical role in mediating anti-tumour effects. In a study using a mouse model of renal cell carcinoma, combined therapy with IL-2 (to induce CXCR3 expression on immune cells) and intratumoural CXCL9 (a CXCR3 ligand) led to enhanced anti-tumour immunity and inhibition of tumour-associated angiogenesis. *(01)*
- IP10-EGFRvIIIscFv and CD8+ CTL Therapy: Research on gliomas has shown that combining a recombinant protein of IP10 (CXCL10) fused with a tumour-specific antibody fragment (EGFRvIIIscFv) with CD8+ cytotoxic

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T lymphocytes (CTLs) synergistically inhibited tumour growth. *(06)* This combination therapy promoted CTL infiltration and cytotoxicity while inducing apoptosis in glioma cells. *(06)*

- MIG (CXCL9) Gene Therapy with Cisplatin: Combining MIG (CXCL9) gene therapy with low-dose cisplatin showed improved therapeutic efficacy against murine carcinoma. *(02)*

Clinical and Research Implications:

The emerging understanding of RDIs and their role in ICB resistance has significant implications for both clinical practice and future research:

- Predictive Biomarker: The RDS score, derived from the IRIS model, can serve as a predictive biomarker for ICB response. *(34)* It can potentially identify patients who are more likely to benefit from ICB therapy and those who might require alternative or combination treatment strategies.
- Personalized Treatment Strategies: By identifying specific RDIs that are downregulated in individual tumours, clinicians can potentially tailor treatment plans to reactivate these pathways. This personalized approach could enhance the efficacy of ICB therapy and improve patient outcomes.
- Development of Novel Therapeutics: The identification of RDIs as therapeutic targets opens new avenues for drug development. Researchers can focus on developing agents that specifically reactivate silenced chemokine pathways or enhance chemokine gradients within the tumour.
- Exploring Combination Therapies: RDIs can inform the design of rational combination therapies that target multiple immune evasion mechanisms simultaneously. Combining ICB therapy with agents that boost chemokine signalling or modulate other immune checkpoints could lead to more effective treatment strategies.

B. Challenges in Translating Findings to Clinical Practice

While the Immunotherapy Resistance cell-cell Interaction Scanner (IRIS) shows promise as a tool for understanding and predicting resistance to immune checkpoint blockade (ICB) therapy, several challenges need to be addressed before it can be routinely used in clinical settings. *(34)*

- Validation in Larger and More Diverse Cohorts: The initial development and validation of IRIS primarily focused on melanoma cohorts. *(34)* To establish its clinical utility, it's essential to validate its performance in larger and more diverse patient populations encompassing various cancer types and treatment regimens. *(34)* This will require access to comprehensive clinical data, including treatment response, survival outcomes, and molecular profiling data for different cancers.
- Establishing Clinical Cut-offs: IRIS generates a resistant downregulated score (RDS), which reflects the activity of resistance downregulated interactions (RDIs). *(34)* Determining clinically meaningful cut-off values for RDS to distinguish between responders and non-responders is crucial for its clinical application. This will require careful analysis of RDS scores in relation to clinical outcomes in different patient populations to establish thresholds that accurately predict ICB response.
- Integration into Clinical Workflows: Incorporating IRIS into existing clinical workflows will require developing user-friendly software tools and standardized protocols for data processing, analysis, and interpretation. *(34)* This will necessitate collaboration between computational biologists, clinicians, and software developers to create a streamlined process that seamlessly integrates RDS scores into treatment decision-making.
- Addressing Heterogeneity: Tumours exhibit significant heterogeneity, both within the same tumour and between patients. *(34)* This heterogeneity can influence the activity of RDIs and potentially affect the predictive accuracy of IRIS. Further research is needed to understand how tumour heterogeneity impacts RDS scores and to develop strategies to mitigate the effects of heterogeneity on ICB response prediction.
- Functional Validation of RDIs: While IRIS identifies RDIs associated with ICB resistance, further functional validation is needed to confirm their causal role in mediating resistance. *(34)* This will involve conducting experiments to manipulate RDI activity, for example, using gene editing or pharmacological interventions, and assessing the impact on ICB response in pre-clinical models.
- Considering Chemokine Complexity: The chemokine system, which plays a key role in immune cell trafficking, is highly complex with multiple chemokines and receptors involved. *(34)* The same ligand-receptor pair can mediate both stimulatory and inhibitory effects depending on the target cell type, concentration, and context. *(34)* Addressing this complexity will require a deeper understanding of chemokine biology and the development of more sophisticated models that account for these nuances.

Overcoming these challenges will require a concerted effort from researchers, clinicians, and industry partners. By rigorously validating IRIS in diverse clinical settings, refining its predictive accuracy, and translating the findings into actionable treatment strategies, we can move closer to realizing the potential of personalized immunotherapy guided by cell-cell interaction analysis.

VIII. Limitations of the Study

A. Reliance on Bulk Transcriptomics

Limitations of Using Bulk Transcriptomics: The Need for Single-Cell Analysis

While the study, provides valuable insights into ICB resistance mechanisms, its reliance on bulk transcriptomics presents a limitation in fully understanding the complexities of the tumour microenvironment (TME). *(34)* Bulk transcriptomics measures the average gene expression across all cells in a tissue sample, masking the crucial cell-to-cell

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variations within the TME. *(15) (26) (34)*

To overcome this limitation, single-cell analysis is needed. Single-cell RNA sequencing (scRNA-seq) offers a higher resolution view of the TME by profiling the gene expression of individual cells. *(15) (31)* This technology enables researchers to:

- Identify Cell Subpopulations and their States: The TME comprises a diverse array of cell types, including immune cells, cancer cells, and stromal cells. Each cell type exhibits specific functions and can exist in various states (e.g., activated, exhausted, or senescent). Single-cell analysis can deconvolute this cellular complexity, revealing the presence of rare cell populations and their functional states, which would be obscured in bulk transcriptomic data. *(15) (26) (31) (34)*
- Characterize Cell-Cell Interactions with Precision: Understanding the dynamic interactions between different cell types within the TME is crucial for deciphering the mechanisms of ICB resistance. Single-cell analysis allows researchers to map ligand-receptor interactions with greater precision, providing a detailed picture of the communication networks that govern immune responses and tumour evasion strategies. *(15) (16) (26) (31) (32) (34)*
- Study Spatial Heterogeneity: Tumours are spatially heterogeneous, with different regions exhibiting varying cellular compositions and microenvironmental conditions. Integrating single-cell analysis with spatial transcriptomics techniques can provide a spatial map of gene expression and cellular interactions, offering a more comprehensive understanding of the TME's architecture and its influence on treatment response. *(12)*

B. Model Validation and Generalization

The study, makes significant strides in understanding ICB resistance. However, the study acknowledges the need for further validation of the model, IRIS, in larger and more diverse cohorts to ensure its generalisability and clinical applicability. *(34)*

- Limited Sample Size and Cancer Types: The study's primary analysis relied on five melanoma cohorts, which may not represent the full spectrum of ICB responses across various cancer types. *(34)* Validating IRIS in larger cohorts encompassing a wider range of cancer types, such as head and neck squamous cell carcinoma, gastric cancer, *(09)* and others, is essential. This broader validation can help determine if the identified RDIs and the model's predictive power hold true across diverse tumour microenvironments and immune landscapes.
- Treatment Heterogeneity: The study included patients who received anti-PD1 monotherapy, anti-CTLA4 monotherapy, and combination therapy. While the researchers aimed to identify general ICB resistance mechanisms, the limited sample size within each treatment category prevented them from drawing treatment-specific conclusions. *(34)* Larger cohorts with sufficient representation of different treatment regimens are crucial to uncover potential variations in RDI activity and predictive accuracy based on specific ICB therapies.
- Impact of Tumour Heterogeneity: Tumour heterogeneity, both within and between patients, poses a significant challenge to generalising any predictive model. *(20)* Larger and more diverse cohorts would enable a more robust assessment of how inter- and intra-tumour heterogeneity impacts RDS scores and the model's ability to accurately predict ICB response across diverse patient populations.
- Clinical Trial Design and Patient Selection: The cohorts used in the study were assembled from clinical trials with specific inclusion and exclusion criteria. These criteria may inadvertently introduce biases that limit the model's generalisability to broader patient populations. Validation in real-world clinical settings with less stringent patient selection would provide a more realistic assessment of IRIS's performance and its applicability in routine clinical practice.
- Confirmation with Prospective Studies: The retrospective nature of the study warrants prospective validation to confirm the model's predictive accuracy in a controlled setting. Designing prospective clinical trials that incorporate IRIS analysis at baseline could offer valuable insights into its clinical utility and its ability to guide treatment decisions in real time.

Expanding the validation of IRIS to larger and more diverse patient cohorts is crucial for moving this promising research closer to clinical implementation. Addressing the limitations associated with limited sample size, treatment heterogeneity, and potential biases will strengthen the model's generalisability and ensure its reliable application in guiding personalized immunotherapy decisions for a wider range of cancer patients.

IX. Future Directions

A. Expanding the Use of IRIS in Other Cancers

The IRIS model, developed to identify ligand-receptor interactions associated with resistance to Immune Checkpoint Blockade (ICB) therapy in melanoma, holds potential for application to other cancer types. *(34)* This is because:

- ICB resistance is a common challenge across various cancers: While ICB therapies have transformed cancer treatment, resistance remains a significant issue across different tumour types. *(07) (08) (15) (31)*
- Shared biological mechanisms: The fundamental principles of immune evasion and T cell exclusion often share commonalities across different cancers. *(07) (15)*
- Chemokine signalling and lymphocyte infiltration: The IRIS model highlights the importance of downregulated chemokine signalling in inhibiting lymphocyte infiltration, a crucial aspect of ICB resistance that could be relevant in other cancers. *(34)*

How IRIS could be applied:

- Training on diverse datasets: By training IRIS on transcriptomic datasets from various cancer types with corresponding ICB response data, the model could learn to identify resistance-associated interactions specific to each cancer. *(34)*

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- Identifying targetable interactions: Applying IRIS to other cancers could reveal novel, potentially targetable ligand-receptor interactions that contribute to ICB resistance. *(26) (34)*
- Development of combination therapies: Insights gained from IRIS could facilitate the development of combination therapies that address the specific resistance mechanisms identified in different cancer types. *(26) (34)*

Supporting Evidence from Sources:

- The resistance program identified in melanoma is observed to have varying levels of expression in other tumour types. *(15)*
- Cancers known for being responsive to ICB (kidney, skin, lung) tend to have lower scores on the resistance program, while less responsive cancers (eye, testis) have higher scores. (*15)*
- The study authors of IRIS suggest that the model's approach for identifying resistance-relevant interactions can be applied to other cancer types and scenarios. *(34)*
- The importance of understanding cytokine and chemokine signalling in T cell exclusion is highlighted as a key aspect of overcoming resistance. *(24)*
- Studies focusing on T cell recruitment and chemokine expression in melanoma suggest that manipulating chemokine expression in the tumour microenvironment could hold therapeutic potential. (03)
- The broader context of combination cancer immunotherapies emphasizes the importance of tailoring therapies to specific tumour microenvironments, which the IRIS model could contribute to. (07)

Important Considerations:

- Tumour heterogeneity: Each cancer type exhibits unique biological characteristics and degrees of heterogeneity, which would require careful consideration when adapting the IRIS model. *(15) (25) (31)*
- Data availability: Application of IRIS to other cancers depends on the availability of high-quality, clinically annotated transcriptomic datasets with ICB response data. *(20) (25) (34)*
- Validation: Rigorous validation in independent cohorts and through experimental studies would be essential to confirm the findings and clinical utility of IRIS in other cancer types. *(25) (34)*

B. Incorporating Single-Cell Data

Incorporating single-cell data has the potential to significantly refine the identification of ICB resistance mechanisms revealed by the IRIS model. *(34)*

- Enhanced Cell Type Specificity: Single-cell RNA sequencing (scRNA-seq) allows for the analysis of gene expression at the individual cell level, providing a much more granular view of the tumour microenvironment (TME) compared to bulk RNA sequencing. This would enable IRIS to more precisely pinpoint the specific cell types involved in resistance-associated ligand-receptor interactions. *(15) (34)*
- Uncovering Cellular Heterogeneity: Tumours are composed of diverse cell populations, each with distinct functional states and contributions to resistance. *(15) (31) (34)* Single-cell data can capture this heterogeneity, allowing IRIS to identify interactions that might be masked or diluted in bulk analysis. For instance, it could reveal subpopulations of immune cells or cancer cells driving resistance. *(15) (31) (34)*
- Spatial Context: Integrating single-cell data with spatial transcriptomics could provide insights into the location and organization of cells within the TME, further refining the understanding of how resistance-associated interactions contribute to T cell exclusion. *(12)* This spatial information could be crucial for understanding the dynamics of immune evasion. *(05) (12) (26) (34)*

Potential Benefits:

- Identification of novel therapeutic targets: By pinpointing specific cell types and interactions, single-cell data could guide the development of targeted therapies aimed at disrupting resistance mechanisms. This could include therapies targeting specific chemokines or their receptors. *(03) (34)*
- Development of personalized treatment strategies: Understanding the cellular heterogeneity of resistance could enable the development of personalized treatment approaches tailored to an individual's tumour profile. This could involve selecting the most effective ICB combination or identifying patients who might benefit from alternative treatment strategies. *(08) (18) (31)*

Challenges:

- Technical Complexity: Analysing scRNA-seq data presents technical challenges related to data processing, cell type annotation, and handling sparsity.
- Cost and Scalability: scRNA-seq can be more expensive and time-consuming than bulk RNA sequencing, potentially limiting its application to large patient cohorts.
- Integration with Machine Learning: Integrating scRNA-seq data with the IRIS model would require sophisticated machine learning approaches that can handle the complexity and dimensionality of single-cell data. *(16) (34)*

Examples from Sources:

- The study demonstrating the IRIS model itself applied the model to a single-cell dataset from melanoma, revealing that downregulated interactions were enriched in immune cell types like macrophages and dendritic cells. *(34)*
- A separate study utilized scRNA-seq to identify a resistance program in melanoma associated with T cell exclusion, highlighting the importance of understanding cellular interactions in the TME. *(14)*
- Another study used scRNA-seq to investigate cell-cell communication in mouse tumor models, emphasizing the potential of single-cell data for

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studying ligand-receptor interactions and their association with tumour characteristics. *(16)*

C. Potential for Drug Development

The IRIS model's identification of specific ligand-receptor interactions downregulated in ICB-resistant melanoma presents exciting opportunities for drug development. These downregulated interactions, termed RDIs, often involve chemokine signalling, which is crucial for lymphocyte infiltration into the tumour microenvironment. *(26) (34)* Targeting these RDIs could offer new therapeutic strategies to overcome ICB resistance.

Potential Therapeutic Approaches:

- Enhancing RDI activity: Drugs that directly or indirectly boost the activity of RDIs could promote lymphocyte infiltration and restore immune surveillance in the TME. *(34)* This could involve:
  - Recombinant chemokines: Supplementing the TME with recombinant chemokines corresponding to the downregulated ligands in RDIs could attract lymphocytes and enhance anti-tumour immunity. *(03)* For example, studies suggest that introducing chemokines like CXCL9 or CXCL10 could enhance T cell recruitment. *(18) (30)*
  - Agonists of RDI receptors: Developing agonists that activate the receptors involved in RDIs could mimic the effects of the downregulated ligands and promote lymphocyte trafficking to the tumour site. *(03)*
  - Inhibitors of negative regulators: Targeting negative regulators of RDI pathways could indirectly enhance their activity. *(07)* This could involve inhibiting enzymes that degrade chemokines or blocking signalling pathways that suppress RDI expression.
- Combination therapies: Combining RDI-targeted therapies with existing ICB treatments could synergistically enhance anti-tumour responses. For example, stimulating lymphocyte infiltration via RDI modulation could create a more favourable environment for ICB to exert its effects.

Challenges and Considerations:

- Target specificity and off-target effects: Developing drugs that specifically target the desired RDIs while minimizing off-target effects on other chemokine pathways and immune cells is crucial. *(24)*
- Delivery and penetration: Ensuring efficient drug delivery and penetration into the tumour microenvironment is essential for therapeutic efficacy. *(07)*
- Patient stratification: Identifying patients most likely to benefit from RDI-targeted therapies is important for optimising treatment outcomes. This could involve using the IRIS model or other biomarkers to predict response.
- Understanding the dynamics of the TME: The TME is a complex and dynamic ecosystem, and the effects of manipulating RDIs could vary depending on the specific tumour type and its microenvironment. *(24)* Further research is needed to understand the interplay between RDIs and other immune regulatory mechanisms.

Examples from the Sources:

- One study showed that transfecting tumour cells to express multiple chemokines enhanced tumour control in preclinical models. *(03)*
- Another study suggested that the chemokine receptor CXCR3 and its ligand CXCL9 were critical for a productive CD8+ T cell response in tumour-bearing mice treated with anti-PD-1. *(18)*

X. Conclusion

A. Summary of Key Insights

The Importance of RDIs and the IRIS Model in ICB Resistance

The study highlights the critical role of resistance downregulated interactions (RDIs) in the development of resistance to immune checkpoint blockade (ICB) therapy in melanoma. *(34)* These RDIs are cell-type-specific ligand-receptor interactions that are significantly downregulated in tumours that develop resistance to ICB. The study also introduces the Immunotherapy Resistance cell-cell Interaction Scanner (IRIS) model, a powerful tool for identifying and analysing these crucial interactions. *(34)*

Key insights regarding RDIs and the IRIS model include:

- RDIs as Biomarkers and Therapeutic Targets: RDIs, often involved in chemokine signalling crucial for lymphocyte infiltration, emerge as potential biomarkers for predicting ICB response and as promising targets for new therapeutic strategies to overcome ICB resistance. *(34)*
- Superior Predictive Power: The IRIS model demonstrates superior predictive power compared to existing transcriptomic biomarkers, accurately classifying responders and non-responders and effectively stratifying patients based on survival outcomes. *(34)* This suggests that RDIs reflect fundamental immune response mechanisms impacting clinical outcomes, even in the absence of ICB therapy. *(34)*
- Mechanistic Insights into Resistance: The downregulation of RDIs in resistant tumours disrupts lymphocyte trafficking to the tumour microenvironment (TME), converting a "hot" immune-active TME to a "cold" immune-suppressed state. *(34)* This suppression of immune cell infiltration allows the tumour to evade immune attack and continue growing.
- Potential Therapeutic Strategies: Targeting RDIs could involve enhancing their activity using recombinant chemokines, agonists for RDI receptors, or inhibitors of negative regulators of RDI pathways. *(34)* Combining these strategies with existing ICB treatments could synergistically enhance anti-tumour responses. *(34)*

The IRIS model provides a valuable framework for:

- Understanding ICB resistance: IRIS facilitates a deeper understanding of the complex interplay between ligand-

Ali Mohammad Makbul Tamboli, Julekha Munaf Tade, "Comprehensive Review: IRIS Model's Role in Uncovering Ligand-Receptor Downregulation and ICB Therapy Resistance," *International Research Journal of Pharmacy and Medical Sciences (IRJPMS)*, Volume 8, Issue 2, pp. 100-114, 2025.

receptor interactions, immune cell infiltration, and the development of ICB resistance. *(34)*

- Predicting treatment response: The model's predictive accuracy surpasses current state-of-the-art transcriptomic signatures, potentially paving the way for improved patient stratification and personalized treatment strategies. *(34)*
- Identifying novel drug targets: The RDIs identified by IRIS represent attractive targets for new therapeutic interventions aimed at restoring immune surveillance and overcoming ICB resistance. *(34)*

B. The Future of Personalized Cancer Immunotherapy

The study underscores the potential of machine learning and personalised medicine to overcome resistance to immune checkpoint blockade (ICB) therapy. *(34)* While ICB has revolutionised cancer treatment, a significant portion of patients develop resistance, hindering long-term efficacy. *(08) (31) (34)* The IRIS model, developed in this study, exemplifies how machine learning can identify critical mechanisms driving resistance. *(34)* By analysing complex interactions within the tumour microenvironment (TME), IRIS can predict response to therapy and pinpoint targets for novel interventions. *(34)*

The convergence of machine learning and personalised medicine holds immense promise for the future of cancer immunotherapy:

- Precision Biomarker Discovery: Machine learning algorithms can sift through vast datasets of genomic, transcriptomic, and clinical data to identify biomarkers associated with ICB response. *(20) (23) (34)* These biomarkers can be used to stratify patients, ensuring that only those likely to benefit receive ICB therapy, minimising unnecessary side effects and costs. *(13) (23) (31)* For instance, IRIS identified RDIs as predictive biomarkers that outperform existing signatures based on gene expression, indicating the potential for more precise patient selection. *(34)*
- Unravelling Resistance Mechanisms: As exemplified by the discovery of RDIs and their role in T cell exclusion, machine learning can uncover intricate resistance mechanisms that would be difficult to discern through traditional methods. *(34)* The ability to identify specific ligand-receptor interactions that are downregulated in resistant tumours allows for the development of targeted therapies that restore immune function. *(07) (34)*
- Personalised Treatment Strategies: Machine learning models can integrate diverse data sources to create personalised treatment plans tailored to each patient's unique tumour characteristics and immune profile. *(07) (23) (34)* By identifying targetable pathways specific to resistant tumours, clinicians can tailor ICB combinations or integrate additional immunotherapies that address the underlying resistance mechanisms. *(23) (31) (34)* This could involve using recombinant chemokines, agonists for specific receptors, or inhibitors of negative regulators to enhance RDI activity and promote T cell infiltration. *(07)*
- Predictive Modelling for Combination Therapies: Machine learning can predict the efficacy of different ICB combinations based on a patient's molecular profile. *(07) (23)* Given that the immune landscape is complex, with a multitude of cell types, signalling pathways, and checkpoint molecules, using algorithms to predict the optimal combination strategy can significantly enhance treatment efficacy. *(07) (08) (31)*
- Monitoring Treatment Response: Machine learning algorithms can analyse longitudinal data, including genomic alterations and immune cell dynamics, to monitor treatment response and identify early signs of resistance. *(10) (19) (23)* This allows for timely adjustments to treatment regimens, potentially preventing disease progression and improving outcomes.

The study's focus on RDIs and the development of the IRIS model highlights a paradigm shift in cancer immunotherapy:

- Moving Beyond Single Targets: Traditional approaches have often focused on single immune checkpoints. *(19) (31)* However, the IRIS model demonstrates the importance of understanding the broader network of cell-cell interactions within the TME. *(34)* By targeting multiple RDIs or combining them with other immunomodulatory agents, we can potentially overcome the limitations of targeting single checkpoints. *(07) (19)*

Shifting from Upregulation to Downregulation: While much research has focused on upregulating immune responses, the discovery of RDIs underscores the significance of restoring downregulated pathways critical for immune cell trafficking and activation. *(34)* This shift in perspective expands the landscape of potential therapeutic targets.

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