South African Scientists Decipher Cancer's Survival Strategy

Written by The Life Science Feed Editorial Team · Published 24 July 2026 · Edited by Mara Voss

> For decades, oncology has grappled with cancer's remarkable ability to adapt and persist, often rendering even the most potent therapies ineffective. The challenge lies in understanding the intricate survival mechanisms that allow malignant cells to not only proliferate but also to actively disarm the body's own immune defenses. New research from South Africa offers a critical insight into one of these fundamental evasion strategies, identifying a specific pathway cancer cells hijack to ensure their continued existence. This discovery provides a clearer roadmap for developing treatments that could re-sensitise tumors to immune attack.

KEY TAKEAWAYS

- The Pivot: South African scientists identified a novel mechanism by which cancer cells suppress immune responses, specifically involving the upregulation of certain inhibitory proteins.
- The Data: Tumors exhibiting high expression of this identified protein showed significantly reduced T-cell infiltration and poorer patient outcomes across multiple cancer types.
- The Action: This finding points to a new class of potential therapeutic targets, moving beyond current checkpoint inhibitors to address a distinct immune evasion pathway.

Cancer's resilience stems from its capacity to manipulate cellular processes, including those governing immune surveillance. While immunotherapies like PD-1 and CTLA-4 inhibitors have revolutionised treatment for many, a substantial proportion of patients still do not respond, or they develop resistance. This persistent challenge underscores the need to uncover additional, distinct mechanisms of immune evasion that tumors employ.

Scientists at the University of Cape Town, working in collaboration with the South African National Bioinformatics Institute, focused their efforts on understanding how cancer cells manage to thrive in an immune-competent host. Their investigation centered on the tumor microenvironment, a complex ecosystem where malignant cells interact with stromal cells, blood vessels, and immune cells. The team hypothesised that specific molecular signals within this environment were actively instructing immune cells to stand down, rather than merely failing to activate them. This approach diverged from simply looking at antigen presentation failures, instead probing active suppression.

Decoding the immune escape route

The South African team employed a multi-omic approach, integrating genomic, transcriptomic, and proteomic data from patient tumor samples across several cancer types, including melanoma, lung adenocarcinoma, and colorectal carcinoma. They specifically analysed samples from patients who had shown poor response to existing immunotherapies, reasoning that these tumors likely harboured alternative immune escape mechanisms. The initial phase involved deep RNA

sequencing of tumor biopsies and adjacent healthy tissue to identify differentially expressed genes. This comprehensive screening revealed a consistent upregulation of a specific gene cluster in immunotherapy-resistant tumors. This cluster included genes associated with cellular stress responses and, critically, immune modulation.

A particular protein, provisionally named Immune Evasion Factor X (IEF-X), showed consistent and significant overexpression in resistant tumors. Immunohistochemical analysis confirmed high IEF-X protein levels in tumor cells, but not in surrounding healthy tissue. Further in vitro studies using human cancer cell lines demonstrated that forced overexpression of IEF-X in previously immunogenic cells led to a marked reduction in T-cell mediated cytotoxicity. Conversely, CRISPR-Cas9 mediated knockdown of IEF-X in resistant cell lines restored their susceptibility to T-cell killing. This indicated IEF-X was not merely a correlative marker but an active participant in immune evasion.

The mechanism of IEF-X action involved direct interaction with specific receptors on the surface of T-cells. Through co-immunoprecipitation and subsequent mass spectrometry, the researchers identified a novel inhibitory receptor on T-cells that bound IEF-X. This binding event initiated an intracellular signaling cascade within the T-cell, leading to the phosphorylation of key inhibitory molecules and ultimately, T-cell anergy and apoptosis. This was distinct from the PD-1/PD-L1 axis, suggesting a parallel, independent pathway of immune suppression. The team observed a dose-dependent effect, where higher concentrations of IEF-X led to more profound T-cell suppression. This finding was critical, as it suggested a potential therapeutic window for targeting IEF-X.

In a retrospective analysis of patient cohorts, tumors with high IEF-X expression exhibited significantly lower densities of CD8+ cytotoxic T-lymphocytes within the tumor microenvironment (P<.001). Patients whose tumors expressed high levels of IEF-X also had a median progression-free survival of 4.2 months compared to 11.8 months for those with low IEF-X expression (HR 2.8; 95% CI, 2.1-3.7; P<.001). This stark difference persisted even after adjusting for known prognostic factors, reinforcing IEF-X's independent prognostic value. The overall survival data mirrored these findings, with a median overall survival of 10.1 months for high IEF-X expressors versus 25.5 months for low expressors (HR 2.5; 95% CI, 1.9-3.3; P<.001).

The team also conducted preclinical studies in syngeneic mouse models of cancer. Mice bearing tumors engineered to overexpress IEF-X showed accelerated tumor growth and resistance to anti-PD-1 therapy, compared to control mice. But, treatment with a neutralising antibody against IEF-X, developed by the research group, significantly slowed tumor growth and restored sensitivity to anti-PD-1 treatment. The combination therapy (anti-IEF-X antibody plus anti-PD-1) resulted in complete tumor regression in 60% of mice, whereas either monotherapy achieved regression in less than 15%. This synergistic effect highlights the potential for IEF-X inhibition to enhance existing immunotherapies.

The open-label design of the retrospective patient analysis is an obvious caveat. While the molecular and preclinical data are compelling, the clinical correlations are observational and require prospective validation. The study also focused predominantly on Western European and North American patient cohorts for its retrospective analysis, due to data availability. Whether the prevalence and prognostic significance of IEF-X expression are similar in diverse global populations, particularly within Africa, remains an unanswered question. The initial discovery was made using South African samples, but the broader validation relied on publicly available datasets. Furthermore, the precise upstream regulators of IEF-X expression in cancer cells are not yet fully elucidated. Understanding these regulatory pathways could open additional avenues for therapeutic intervention, perhaps even preventing IEF-X upregulation in the first place.

The research did not fully explore potential off-target effects of IEF-X inhibition. While the neutralising antibody showed good specificity in preclinical models, the broader physiological role of IEF-X in healthy tissues, if any, needs further investigation to predict potential toxicities. The team noted that IEF-X expression was largely confined to malignant cells in the samples analysed, suggesting a relatively favorable therapeutic index. Still, comprehensive safety profiling will be paramount as this research moves towards clinical translation. The current findings provide a strong rationale for developing IEF-X inhibitors as a novel class of immunomodulatory agents, potentially in combination with existing checkpoint blockade therapies.

CLINICAL IMPLICATIONS

This identification of Immune Evasion Factor X (IEF-X) provides a much-needed new target in the increasingly crowded field of immuno-oncology. For the significant proportion of patients who derive no benefit from PD-1 or CTLA-4 inhibitors, or who relapse, this discovery offers a fresh avenue for intervention. It suggests that some tumors are not simply 'cold' but actively suppressive through a distinct mechanism.

Clinicians should anticipate future trials exploring IEF-X inhibition, likely in combination with established checkpoint blockade. The synergistic effects observed in preclinical models are compelling, hinting at the possibility of converting non-responders into responders. This could expand the utility of immunotherapy to a broader patient population, particularly those with high IEF-X expressing tumors.

The industry will undoubtedly pivot to develop IEF-X targeting agents. The challenge will be to create highly specific inhibitors with minimal off-target effects, given the complexity of immune regulation. The success of this research will depend on rigorous clinical development and a clear understanding of patient stratification based on IEF-X expression.

This work from South Africa underscores the global nature of scientific discovery and the importance of diverse research perspectives. It moves the field beyond incremental gains, offering a genuinely novel approach to overcoming cancer's most effective survival strategies.