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# CD84 as a Prognostic Biomarker and Therapeutic Target in Breast Cancer: Interconnections With PDL1, CD74, and Immune Tolerance Mechanisms

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## Abstract

*Background/Aim:* Cluster of differentiation 84 (CD84), a member of the signalling lymphocytic activating molecule (SLAM) family, has emerged as a potential prognostic biomarker and therapeutic target in breast cancer. This study explored CD84 expression and its correlation with clinicopathological features in a well-characterised cohort.

*Materials and Methods:* Using quantitative real-time PCR, mRNA expression levels of CD84 and related molecules, including PDL1, CD74, and other immune tolerance markers, were analysed.

*Results:* The findings reveal that elevated CD84 expression predicts poor overall survival, independent of conventional prognostic factors such as the Nottingham Prognostic Index (NPI). Notably, a combined signature of CD84, CD48, VAV1, and CTNNB1 demonstrated stronger prognostic power than individual markers. CD84 exhibited significant correlations with immunosuppressive molecules, including PDL1 and CD74, underscoring its role in fostering immune tolerance within the tumour microenvironment.

*Conclusion:* CD84 may mediate an immunosuppressive phenotype, facilitating immune evasion in breast cancer. This highlights its potential as a therapeutic target, particularly in triple-negative breast cancer, to overcome immune resistance and enhance treatment efficacy.

**Keywords:** CD84, CD74, VAV1, CTNNB1, CD48, PD-L1, breast cancer, immune tolerance, checkpoint inhibitors, TNBC, immunotherapy.

## Introduction

Cluster of differentiation 84, also known as signalling lymphocytic activating molecule 5 (CD84/SLAMF5) has been known to be an immune cell marker and a member of the signalling lymphocytic activating molecule (SLAM) family of cell-surface immunoreceptors (1). Its role in immunity and autoimmune conditions has been studied

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extensively (2). CD84, along with other members of the SLAM family, plays a role in multiple myeloma (3) and other blood cancers (4).

More recently, evidence suggests a role for CD84 in breast cancer. Specifically, it has been proposed as a therapeutic target for breaking immune tolerance in triple-negative breast cancer (TNBC) (5). This adds to earlier evidence of the role of related molecules in breast cancer tolerance to chemotherapy (6).

In this study, we examine the correlations between CD84 and clinicopathological characteristics in breast cancer within a well-documented cohort, as well as the roles of other known members of CD84-related pathways.

## Materials and Methods

*Samples.* Following ethical approval from the Bro Taf Health Authority (ethics approval numbers 01/4303 and 01/4046) and after obtaining informed consent, tissue samples were collected. Immediately after surgical removal, a sample was taken from the tumour itself, and a second sample was collected from adjacent non-cancerous tissue within 2 cm of the tumour. This adjacent tissue served as a control for comparison with the cancerous tissue and did not interfere with the assessment of tumour margins. A total of 124 breast cancer tissues and 30 normal background tissues were collected and stored at −80˚C in liquid nitrogen until analysis. This patient group has been included in several previous and ongoing studies (7-10).

Patient treatment followed local multidisciplinary guidelines. Patients that had undergone breast-conserving surgery also received radiotherapy. Tamoxifen was given for hormone-sensitive disease, while adjuvant chemotherapy was used for hormone-insensitive, high-grade, and node-positive cancers. Clinicopathological data (Table I) were collected from patient charts and stored in an encrypted database (11, 12).

Tissue processing, RNA extraction and cDNA synthesis. RNA extraction and reverse transcription kits were purchased from AbGene Ltd. (Epsom, Surrey, UK). A custom-made hot-start Master Mix for quantitative polymerase chain reaction (qPCR) was also obtained from AbGene Ltd. A literature review was conducted to identify molecules known to interact with CD84. The molecules included in the panel studied in this cohort are listed in Table II (13-15).

Approximately 10 mg of cancerous tissue was homogenised. A larger amount of matched normal material from adjacent tissue (20-50 mg) was used because its higher fat content, which made it difficult to obtain sufficient RNA for analysis. RNA concentration was determined using a UV spectrophotometer (Wolf Laboratories, York, UK) to ensure adequate RNA for analysis. Reverse transcription was performed using a reverse transcription kit (AbGene) with an anchored oligo(dT) primer, using 1 μg of total RNA in a 96-well plate to produce complementary DNA (cDNA). The quality of cDNA was verified using β-actin primers (11, 12). Primers are listed in Table III.

*Quantitative analysis.* The levels of transcripts within the cDNA library were quantified using real-time qPCR based on Amplifluor technology. The PCR primers were designed utilising Beacon Designer software (Premier Biosoft International Ltd., Palo Alto, CA, USA), incorporating an additional sequence (5'-ACTGAACCTGACCGTACA-3') complementary to the universal Z probe (Intergen Inc., Oxford, UK). The primers were synthesised by Invitrogen Ltd. (Paisley, UK).

The reaction was conducted under the following parameters: an initial denaturation at 94˚C for 12 min, followed by 50 cycles of denaturation at 94˚C for 15 s, annealing at 55˚C for 40 s, and extension at 72˚C for 20 s. The abundance of each transcript was determined through comparison with a standard amplified concurrently within the samples. Expression levels of the target molecules were normalised against cytokeratin 19 (CK19). Each PCR run incorporated a negative and positive control, employing a known cDNA sequence (podoplanin) (11, 12).

*Statistical analysis.* The relationships between CD84 and other molecules on the selected panel were examined

Table I. *Clinicopathological data.*

| Parameter | Number of samples |
|---|---|
| Tissue type | |
| Background, normal | 30 |
| Tumour | 124 |
| Tumour grade | |
| 1 | 24 |
| 2 | 42 |
| 3 | 58 |
| Nottingham Prognostic Index | |
| Grade 1 | 68 |
| Grade 2 | 38 |
| Grade 3 | 16 |
| Unknown | 2 |
| TNM stage | |
| 1 | 70 |
| 2 | 40 |
| 3 | 7 |
| 4 | 4 |
| Unknown | 3 |
| Histology | |
| Ductal | 94 |
| Lobular | 14 |
| Other | 16 |
| Patient outcome | |
| Alive and well | 85 |
| Metastatic disease | 7 |
| Death from breast cancer | 15 |
| All poor outcomes (Metastatic disease & disease-related mortality) | 27 |

Table II. *Panel of molecules included in the study.*

| Gene symbol | Alternative names | Molecule encoded |
|---|---|---|
| PD1 | PDCD1 | Programmed cell death 1 |
| PDL1 | CD274 | PD1 ligand 1 |
| CD48 | | Cluster of differentiation 48 |
| CD74 | | Cluster of differentiation 74 |
| VAV1 | | Vav guanine nucleotide exchange factor 1 |
| CTNNB1 | | Catenin beta interacting protein 1 |

Table III. *Primers used in the study.*

| Primer | Sequence |
|---|---|
| CD48F12 | tggaagatcaagctgcaa |
| CD48ZR12 | actgaacctgaccgtacaacagttgtcatccatgtct |
| CD74F1 | cgcgaccttatctccaac |
| CD74ZR1 | actgaacctgaccgtacagagcagagtcaccaggat |
| CD74F2 | caccccgctgctgatg |
| CD74ZR2 | actgaacctgaccgtacagcatcacatggtcctctg |
| CD84F1 | ctgatccctacaccacca |
| CD84ZR1 | actgaacctgaccgtacatcacagatgccattaaactct |
| β-actinF1 | cgctcggtgaggatcttca |
| β-actinR1 | atgatatcgccgcgctcgtc |

using the SPSS (version 29) statistical software package (SPSS Inc., Chicago, IL, USA). Spearman's correlation test was employed to study these correlations. Survival analysis was performed using the Kaplan–Meier method. The optimal cut-off point for each molecule was determined by Receiver Operating Characteristic (ROC) analysis. All samples within the cohort were included in the analysis. However, the exclusion of some specimens was necessitated by depletion of sample cDNA or pipetting errors affecting PCR. Correlations yielding p-values of less than 0.05 were considered statistically significant.

## Results

*CD84 and overall survival (OS).* The cohort, studied with regards to the relation of OS and mRNA expression, was divided into high and low transcription groups by the optimal cutoff point from the ROC analysis. High mRNA expression of CD84 was associated with a significantly worse OS in this cohort (Figure 1 and Figure 2).

Furthermore, a combined signature of CD84 with CD48, VAV1 and CTNNB1 (CD84/CD48/VAV1/CTNNB1) has shown to be a stronger negative predictor of OS and recurrence free survival (RFS) in breast cancer. Cox regression analysis found this to be more predictive than the Nottingham Predictive Index (NPI) ($p$=0.0008 *vs.* 0.032). This effect on OS persisted when the cohort was stratified by whether they were TNBC or not, by oestrogen receptor status (ER+/ER–), and Her2 status (Her2+/Her2–). However, this effect was significant in progesterone receptor negative (PR–) cases, but not in PR+ cases.

*Correlations of CD84 with related markers.* The mRNA expression of CD84 was correlated with 37 candidate molecules that may interact with CD84 using Spearman

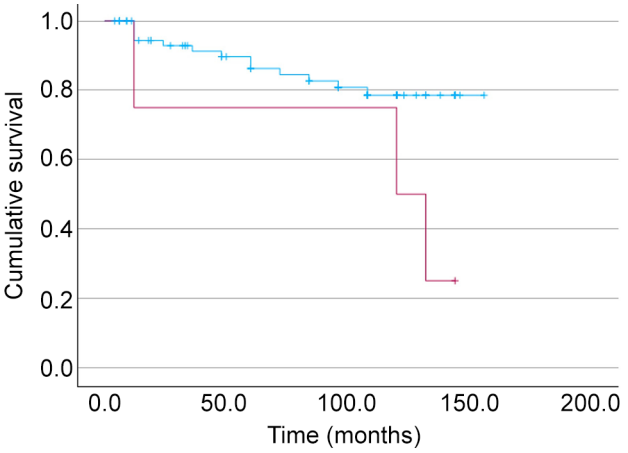


Figure 1. *Association between CD84 expression and overall survival in breast cancer. Kaplan–Meier survival curve comparing overall survival (OS) between patients with high versus low CD84 mRNA expression levels. High CD84 expression is associated with significantly lower overall survival (p=0.034).*

correlation test. Those with significant correlations are shown in Table IV.

## Discussion

This is the first study to demonstrate that high CD84 expression is a powerful predictor of poor prognosis in breast cancer, with its signature surpassing conventional prognostic parameters. This aligns with emerging evidence that CD84 mediates immune tolerance within the tumour microenvironment (5). Moreover, CD84 shows significant correlations with other immunological tolerance markers, such as PDL1 and CD74, underscoring its central role in promoting an immunosuppressive phenotype in breast cancer.

CD74 is a well-established signalling molecule in both immunity and transcription. It is a component of the major histocompatibility complex II (MHC class II) antigen presentation pathway (16) and an intracellular activator of transcription (17).

CD74 has been identified to be a factor in oncogenesis with its role varying across tumour subtypes and primarily involving the immune microenvironment. In certain aggressive tumours, CD74 is suggested to support immune

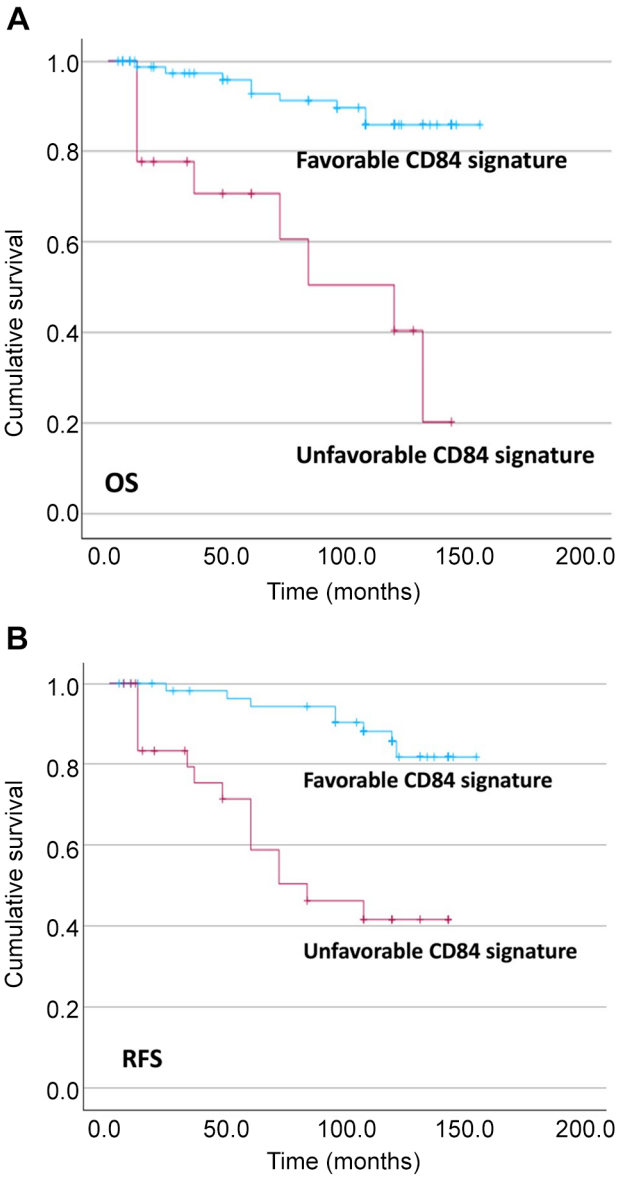


Figure 2. *Prognostic value of the CD84/CD48/VAV1/CTNNB1 combined signature in breast cancer. A) Kaplan–Meier survival analysis showing overall survival (OS) in patients with high vs. low expression of the combined CD84/CD48/VAV1/CTNNB1 signature (p=0.000025). B) Kaplan–Meier survival analysis showing recurrence-free survival (RFS) in patients with high vs. low expression of the same combined signature (p=0.000077).*

evasion mechanisms (18). However, in certain scenarios (*e.g.,* basal-like cancers with high MHCII expression), it may promote a more robust immune response, improving

Table IV. *Correlations of CD74 mRNA expression with candidate molecules.*

| Candidate molecule | Correlation coefficient (R) *vs.* CD84 | *p*-Value |
|---|---|---|
| VAV1 | 0.229 | 0.029* |
| CTNNB1 | 0.536 | <0.001** |
| ALCAM | 0.484 | <0.001** |
| CD48 | 0.366 | 0.009** |
| CD84 | 0.479 | <0.001** |
| PD1 | 0.469 | <0.001** |
| PDL1 | 0.268 | 0.011** |
| PTPN11 | 0.516 | <0.001** |
| WASP | 0.361 | <0.001** |
| nWASP | –0.023 | 0.836 |
| WAVE1 | 0.139 | 0.198 |
| WAVE2 | 0.372 | <0.001** |
| WAVE3 | –0.014 | 0.899 |
| HAVCR1 | 0.022 | 0.838 |
| HAVCR2 | 0.651 | <0.001** |
| IL7R | 0.163 | 0.128 |
| IL10 | 0.232 | 0.027* |
| PLA2 | –0.003 | 0.979 |
| PLA21b | –0.171 | 0.115 |
| PLA2b | –0.07 | 0.52 |
| PLA2gama | 0.084 | 0.436 |
| PLA2x | –0.384 | <0.001** |
| RHO6 | –0.182 | 0.087 |
| RHO7 | –0.122 | 0.269 |
| RHO8 | 0.059 | 0.62 |
| RHOA | –0.272 | 0.009** |
| RHOB | –0.309 | 0.004** |
| RHOC | –0.015 | 0.886 |
| RHOG | –0.337 | 0.001** |
| RHO-GDI | –0.192 | 0.072 |
| RHO-GDI-G | –0.159 | 0.148 |
| DOK1 | 0.233 | 0.153 |
| DOK2 | 0.242 | 0.138 |
| DOK3 | 0.332 | 0.002** |
| DOK4 | 0.2 | 0.105 |
| DOK6 | 0.266 | 0.028* |
| DOK7 | 0.380 | <0.001** |

*Correlation is significant at the 0.05 level (2-tailed). **Correlation is significant at the 0.01 level (2-tailed).

patient outcomes (19). Thus, CD74 acts as a "double-edged sword" in breast cancer, with highly context-dependent effects. It has been identified as a potential therapeutic target, particularly in TNBC (15, 20).

Similarly, PDL1 is a protein expressed on the surface of various cells, including some immune cells and tumour cells. It plays a key role in suppressing the immune system by binding to the PD1 receptor on T-cells, effectively "turning off" the immune response. This mechanism helps maintain immune tolerance and prevent autoimmunity under normal conditions.

In cancer, PDL1 is often overexpressed by tumour cells and mediates immune detection, allowing unchecked growth (21). As a result, PDL1 has become a key target in immunotherapy, with drugs such as pembrolizumab and atezolizumab blocking the interaction between PDL1 and PD1 to reactivate the immune system against cancer cells (22).

PDL1 expression levels are frequently assessed to guide immunotherapy, particularly in cancers such as non-small cell lung cancer, TNBC, and melanoma (23, 24). Pembrolizumab is an anti-PD1 antibody, which is evaluated for use in the treatment of melanoma and lymphoma (25).

Recent studies have highlighted significant associations between CD84 and markers such as CD48, VAV1, and CTNNB1. CD48, like CD84, participates in immune cell signalling, particularly in T-cell and natural killer cell activity, suggesting potential cooperative roles in modulating immune responses (26). VAV1, a guanine nucleotide exchange factor, is a downstream mediator of SLAM family receptor signalling, potentially linking CD84 to cytoskeletal reorganisation and cell migration (27, 28). CTNNB1, encoding β-catenin, is a key component of the Wnt signalling pathway, which has been shown to intersect with CD84-mediated pathways in maintaining cellular adhesion and regulating transcriptional programs (29). Together, these markers form a synergistic signature that underscores their combined relevance in immunological and oncological contexts, as evidenced by our study's findings.

The strength of our study lies in its use of robust RT-PCR methodology to analyse mRNA expression levels of CD84 and related immune tolerance markers in human breast cancer samples with a 10-year clinical follow-up. To our knowledge, this is the first study to correlate CD84 expression with clinical outcomes in human breast cancer. Additionally, we identified a powerful prognostic signature that should be included in future validation studies.

*Study limitations.* Specifically, we measured only mRNA transcript levels and did not quantify protein expression. This is particularly relevant, as CD84 is a potential therapeutic target for monoclonal antibody development.

## Conclusion

CD84 may mediate an immunosuppressive phenotype, facilitating immune evasion in breast cancer. This highlights its potential as a therapeutic target, particularly in triple-negative breast cancer, to overcome immune resistance and enhance treatment efficacy. We believe CD84 would be a good subject for future proteomic, *in vivo* and clinical research, and may open the possibility of the development of new therapeutic strategies and prognostic tools.

## Conflicts of Interest

Kefah Mokbel has received honoraria for offering academic and clinical advice to Merit Medical and QMedical and Sebbin corporations. The other Authors declare no conflict of interest in relation to this study. Merit Medical had no role in the design of the study, collection and interpretation of data or the decision to proceed with the publication.

## Authors' Contributions

KM and WGJ formulated the idea. WGJ supervised the study and curated the cohort tissue library. AXL, CCW, HHG, TAM conducted the procedures. KM and WGJ performed the analyses. Wazir U drafted the manuscript and conducted the literature reviews. WGJ and Mokbel L proof-read the final draft.

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## Artificial Intelligence (AI) Disclosure

During the preparation of this manuscript, a large language model (Google Gemini, Alphabet Inc., Mountain View CA, USA) was used solely for language editing and stylistic improvements in select paragraphs. No sections involving the generation, analysis, or interpretation of research data were produced by generative AI. All scientific content was created and verified by the authors. Furthermore, no figures or visual data were generated or modified using generative AI or machine learning–based image enhancement tools.

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