ORIGINAL ARTICLE DOI: 10.20515/otd.1840107

Osmangazi Journal of Med, 2026;48(3):533-538

Osmangazi Journal of Medicine

e-ISSN: 2587-1579

In Silico Identification of Tacrolimus As A Candidate Anticancer Agent Targeting PBRM1-Associated Pathways

PBRM1 ile İlişkili Yolakları Hedefleyen Aday Bir Antikanser Ajan Olarak Takrolimusun İn Silico Tanımlanması

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Received :11.12.2025

Accepted : 11.03. 2026

Abstract: Cancer continues to be a significant global health burden, and the search for new therapeutic strategies remains an important priority. Computational drug repurposing offers an efficient approach to exploring drug effects across multiple cancer cell line models by identifying novel applications of existing molecules through the integration of molecular and pharmacological data. In this study, we applied an in silico drug-repositioning approach to identify compounds with potential as cancer therapeutics. Using Gene2Drug, a pathway-based screening tool, we focused on agents interacting with the PBRM1 (polybromo-1) gene. Drug Set Enrichment Analysis (DSEA) was used to assist in in silico screening. The anti-tumor activities of candidate drugs were extracted from DepMap via a PRISM viability assay on various cancer cell lines. A total of 655 compounds were evaluated using the Drug Sensitivity AUC (from the CTD2 resource) tool. Among the compounds analyzed, tacrolimus—a calcineurin inhibitor approved for atopic dermatitis and organ transplant rejection—showed a statistically significant association with drug sensitivity (P = 8.29E-9). This finding underscores tacrolimus as a promising candidate for subsequent investigation. While further research is needed, these findings suggest tacrolimus is a potential in silico-identified candidate that could serve as a therapeutic option for various cancer cell line models.

Keywords: PBRM1, targeted treatment, drug repurposing, tacrolimus, in silico screening

Özet: Kanser, küresel ölçekte önemli bir sağlık sorunu olmaya devam etmektedir ve yeni tedavi stratejilerinin geliştirilmesi hâlâ öncelikli bir araştırma alanıdır. Hesaplamalı ilaç yeniden konumlandırma (computational drug repurposing), mevcut moleküllerin yeni kullanım alanlarını belirlemek için moleküler ve farmakolojik verilerin entegrasyonu yoluyla, birden fazla kanser hücre hattı modeli üzerinde ilaç etkilerinin araştırılmasını sağlayan verimli bir yaklaşımdır. Bu çalışmada, potansiyel kanser tedavi ajanlarını keşfetmek amacıyla in silico bir ilaç yeniden konumlandırma yaklaşımı uygulanmıştır. Gen temelli, yolak odaklı bir tarama aracı olan Gene2Drug kullanılarak, PBRM1 (polybromo-1) geni ile etkileşime giren bileşiklere odaklanılmıştır. Drug Set Enrichment Analysis (DSEA) yöntemi, bu in silico taramayı desteklemek amacıyla kullanılmıştır. Aday ilaçların antitümör aktiviteleri, DepMap veri tabanından elde edilen PRISM canlılık testleri aracılığıyla çeşitli kanser hücre hatlarında değerlendirilmiştir. Toplam 655 bileşik, CTD2 kaynağından elde edilen Drug Sensitivity AUC aracı kullanılarak analiz edilmiştir. Analiz edilen bileşikler arasında, atopik dermatit ve organ nakli reddi tedavisinde onaylanmış bir kalsinörin inhibitörü olan takrolimusun, kanser hücre hatlarında ilaç duyarlılığı ile istatistiksel olarak anlamlı bir ilişki gösterdiği belirlenmiştir ($P = 8.29\times10^{-9}$). Elde edilen sonuçlar, takrolimusun ileri çalışmalar açısından dikkate alınabilecek bir aday olabileceğini düşündürmektedir. Ek çalışmalara ihtiyaç duyulmakla birlikte, elde edilen sonuçlar takrolimusun farklı kanser hücre hattı modellerinde terapötik bir seçenek olarak değerlendirilebilecek potansiyel bir in silico aday olduğunu düşündürmektedir.

Anahtar Kelimeler: PBRM1, hedefe yönelik tedavi, ilaç yeniden konumlandırma, takrolimus, in silico tarama

Ethics Committee Approval: Ethics approval was not required for this study because it uses publicly available in-silico datasets and does not involve human or animal subjects.

Informed Consent: Not applicable.

Authorship Contributions: A.T. and R.K. collaborated on the study design, data analysis, and manuscript preparation. A.T. and R.K. verified the validity of the raw data. Both authors checked the data and confirmed the final publication.

Copyright Transfer Form: Copyright Transfer Form was signed by all authors.

Peer-review: Internally peer-reviewed.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

How to cite/ Atıf için: Tuncal A, Kalkan R. In Silico Identification of Tacrolimus As A Candidate Anticancer Agent Targeting PBRM1-Associated Pathways, Osmangazi Journal of Medicine, 2026;48(3):533-538

1. Introduction

The genetic complexity of cancer shows that identifying essential regulatory genes may provide novel treatment opportunities. The polybromo-1 (*PBRM1*, also known as BAF180) gene is a key component of the PBAF chromatin remodelling complex, which plays crucial roles in transcription regulation and the preservation of vital cellular functions such as differentiation, proliferation, and DNA repair, by recognising histone modifications and facilitating chromatin remodelling [1,2]. Approximately 80% of *PBRM1* somatic mutations may result in protein dysfunction [3].

PBRM1 is the second most commonly mutated gene in clear cell renal cell carcinoma (ccRCC) and is recognized as a driver mutation in this cancer form, following *VHL* [4]. Varela and colleagues reported that 41% of ccRCC tumors harbor inactivating mutations in the SWI/SNF chromatin remodeling complex gene known as *PBRM1* [5]. Loss of *PBRM1*, a SWI/SNF chromatin remodeler, has been linked to more advanced ccRCC tumors and poorer patient outcomes, acting as a critical step in the progression of *VHL*-loss-driven cancers by amplifying HIF1 and STAT3 signaling and converging on mTOR activation [6]. Furthermore, reduced expression of *PBRM1* has been associated with unfavorable prognosis and advanced clinicopathological characteristics in ccRCC [7].

PBRM1 mutations have also been reported in several malignancies, including lung adenocarcinoma [8], cholangiocarcinoma [9], metastasizing pleomorphic adenomas [10], esophageal squamous cell carcinoma [11], and breast cancer [12]. Recent studies suggest that *PBRM1* alterations may also affect the immune environment and influence therapeutic responses, in addition to driving tumor growth, particularly in cancers such as ccRCC and lung adenocarcinoma [8,13,14]. Given that mutation status has been connected to immunological signaling and tumor mutational burden [15], *PBRM1* may be a potential therapeutic target as well as a predictive biomarker across diverse cancer types. Furthermore, *PBRM1* status has been associated with differential responses to immune checkpoint inhibitors, highlighting its potential importance for targeting in personalized cancer therapy [13].

Drug repositioning, or finding new uses for existing medications, has gained attention in cancer research because it can reduce costs, minimize risk, and speed up clinical translation [16,17]. By utilizing compounds with known safety profiles [18], researchers can test hypotheses more efficiently. Moreover, repurposing methodologies allow the integration of molecular, pharmacological, and pathway-level data to suggest potential therapeutic effects across various cancer models [19].

Here, we employed the Gene2Drug platform—an in silico computational method that integrates gene expression profiles with drug-induced transcriptional responses—to identify compounds that may target *PBRM1*-related pathways. This approach enables the systematic evaluation of both FDA-approved and investigational compounds, providing a rational framework for subsequent experimental validation [16,20]. Among the compounds identified, tacrolimus (CAS No. 104987-11-3) emerged as a promising candidate due to its predicted interactions with *PBRM1*-associated pathways and its potential anti-proliferative effects in cancer cell lines. To our knowledge, this is the first study to explore the potential relationship between tacrolimus and *PBRM1* using in silico drug repositioning approaches. While these findings are encouraging, further experimental validation and mechanistic studies are warranted to elucidate the biological basis of this association.

2. Materials and Methods

2.1. Data source

We employed in silico screening tools to identify targeted therapeutic compounds for *PBRM1*. The Gene2Drug platform was used to obtain candidate compounds associated with *PBRM1*-related pathways [20]. The Gene2Drug output included compound lists from several gene-set categories, including Biological Process, Molecular Function, Cellular Component, Chemical and Genetic Perturbations, and Transcription Factor Targets. After removing duplicate compounds across these categories, a total of 655 compounds remained for further analysis.

Compounds showing negative enrichment scores were identified as potential candidates [20]. The selected candidates were further evaluated using the DepMap Public 23Q2 dataset (Broad Institute) to assess the relationship between *PBRM1* expression and drug sensitivity in cancer cell lines [22,23]. Cancer cell sensitivity to potential treatments was assessed using the DRUG Sensitivity (PRISM Repurposing Primary) dataset together with PBRM1 expression data.

Candidate compounds were subsequently filtered according to enrichment scores and statistical

significance thresholds, and compounds with statistically significant results were selected for further analysis.

2.2. Gene-to-Drug Interaction Analysis

The Gene2Drug website tool was used for the identification of the compounds that targeted *PBRM1* [20]. Compounds with negative enrichment scores were first identified and subsequently prioritized based on their involvement in multiple pathways [20].

The Drug Sensitivity AUC (CTD2) values of different drugs obtained from Gene2Drug were analyzed against *PBRM1* Expression Public 23Q2 in all cancer cell lines in the DepMap website tool [22,23]. The P value produced by DepMap determines the sensitivities of cancer cell lines to the compounds. The compounds implicated were those with a P < 1E-5, which are listed in Table 1. To minimize false-positive results, compounds with a significance threshold of P < 1E-9 were selected for further evaluation.

Table 1. Association between gene expression (DepMap Public 23Q2) and drug sensitivity AUC (CTD2)

Compound	***Pearson***	***Spearman***	***Slope***	***Intercept***	***p-value (linregress)***
tacrolimus	-0.213	-0.190	-2.61E-1	1.53E+1	8.29E-9
camptothecin	-0.284	-0.251	-8.90E-1	1.45E+1	2.73E-13
doxorubicin	-0.315	-0.315	-8.82E-1	1.14E+1	2.73E-19
prochlorperazine	-0.148	-0.165	-1.48E-1	1.40E+1	5.04E-5

Abbreviations: AUC: Area Under the Curve; CTD2: Cancer Target Discovery and Development; linregress: linear regression analysis.

3. Results

Gene-to-drug analysis and the sensitivity of cancer cells to candidate drugs

The lists of potential *PBRM1*-targeted compounds were produced by Gene2Drug (Supplementary file). Table 1 indicates that the implicated compounds had P values less than 1E-5.

Cancer cell lines' sensitivity to potential medications was assessed using the DepMap website tool together with the DRUG Sensitivity (PRISM Repurposing Primary) module, and *PBRM1* expression [22, 23]. A total of 655 drugs from Gene2Drug were analyzed against *PBRM1* Expression Public 23Q2 in all cancer cell lines in the DepMap website tool. A total of four compounds were significantly more sensitive in cancer cell lines (P < 1E-5). Here, we selected the implicated compounds with P < 1E-9, indicating a stronger statistical association with drug sensitivity.

4. Discussion

Although there have been improvements in oncology, there remains an urgent need for new therapeutic approaches for numerous tumor types. In this study, our in silico analysis identified tacrolimus (DrugBank Accession Number: DB00864) as a promising candidate agent that interacts with *PBRM1*-related pathways, supported by cell line drug-sensitivity profiles. This raises the possibility that an established immunosuppressant might be repurposed for cancer therapy [24].

According to BindingDB [25], tacrolimus primarily binds to FKBP1A (also known as FKBP12), a member of the FKBP family that includes intracellular receptors for immunosuppressive drugs. The tacrolimus–FKBP12 complex inhibits calcineurin, a serine/threonine phosphatase, thereby preventing NFAT translocation into the nucleus and IL-2 transcription, thereby suppressing T-cell activation [26]. Beyond immunosuppression, the literature has shown that the calcineurin/NFAT axis may play a role in tumor angiogenesis and that tacrolimus may have indirect effects on this pathway [27]. Additionally, tacrolimus is clinically used topically to treat severe atopic dermatitis, refractory uveitis following bone marrow transplantation, and vitiligo [28,29]. These data suggest that the long-term immunosuppressive effects of tacrolimus carry limited risks.

Evidence linking tacrolimus to anticancer activity is mixed, but several experimental studies support its inhibitory effects on oral carcinogenesis. Tacrolimus has been reported to reduce epithelial proliferation, induce G1/S cell cycle arrest, and downregulate key cell cycle regulators such as cyclin D1, cyclin E1,

and c-Myc in oral squamous cell carcinoma models, acting in a manner apparently independent of systemic immunosuppression [30]. Additionally, Choi and colleagues demonstrated that tacrolimus induces apoptosis in leukemia Jurkat cells through inactivation of the ROS-dependent PI3K/Akt signaling pathway, providing further experimental support for its potential anticancer effects [31]. Importantly, other preclinical and clinical observations raise concern that tacrolimus exposure can promote tumor progression or recurrence in certain contexts (notably hepatocellular carcinoma models and post-transplant HCC recurrence analyses), suggesting dose-, context-, and tissue-dependent effects [32]. Overall, these data indicate that tacrolimus effects on cancer biology are complex and likely context-specific.

Analysis of the DepMap dataset showed a statistically significant negative correlation for tacrolimus (Pearson r = -0.213, p = 8.29×10^{-9}), consistent with our computational findings. This correlation suggests that tacrolimus-associated activity may be related to cell drug sensitivity. Furthermore, scatter plot analysis using the DepMap Public 23Q2 dataset visualized the relationship between *PBRM1* expression and tacrolimus sensitivity at the cell line level. While the overall correlation was weak, it was observed that high *PBRM1* expression in some cell lines may be associated with higher sensitivity (lower AUC); these hypothesis-generating findings suggest that the effect of tacrolimus is likely context-dependent within different tumor settings.

Our in silico findings suggest that tacrolimus may interact with *PBRM1*-related networks, therefore suggesting two non-exclusive hypotheses. First, tacrolimus influences tumor-intrinsic signaling (for example, via FKBP12-linked modulation of mTOR/BMP or other pathways) that intersects with chromatin remodeling and *PBRM1*-dependent transcriptional programs. Second, tacrolimus alters the tumor microenvironment and immune signaling in ways that could modulate outcomes in *PBRM1*-altered tumors [13]. Given that *PBRM1* loss can create a non-immunogenic tumor environment resistant to immune checkpoint blockade [14], tacrolimus-mediated modulation of immune signaling may have context-dependent implications for *PBRM1*-deficient tumors. Prior work showing FKBP12 ligands impact BMP and other signalling cascades supports potential non-calcineurin-mediated effects relevant to chromatin or transcriptional regulation. Indeed, FK506-mediated FKBP12 displacement has been shown to activate ALK2/BMP-SMAD signaling and promote apoptosis in multiple myeloma cells [33], and to rescue endothelial dysfunction via BMPR2-dependent BMP activation in pulmonary hypertension models [34]. These studies highlight the broader capacity of FKBP12 ligands to modulate BMP pathways independent of calcineurin, providing a mechanistic rationale for our proposed hypotheses in *PBRM1*-altered tumors. While none of these works directly test *PBRM1* mutation/loss contexts, their demonstration of BMP / FKBP12-mediated signal modulation suggests that such effects may also occur in *PBRM1*-altered cancers.

There are several challenges in the translational development process. First, our findings are computational and hypothesis-generating; therefore, experimental validation (protein-binding assays, cellular perturbation with tacrolimus, and assays in *PBRM1* wild-type vs. mutant models) of tacrolimus binding to *PBRM1*-associated proteins is necessary. Second, the literature contains conflicting results regarding the tumour-suppressive and tumour-promoting roles of tacrolimus, underscoring the importance of context-dependent evaluation regarding dose, timing, and tumour type. Third, immunosuppressive side effects may limit its use alone; however, combination strategies at lower doses or with targeted drugs may allow potential beneficial effects to be separated from systemic immunosuppression.

Taken together, our in silico analyses identify tacrolimus as a candidate modulator of *PBRM1*-related biology and support the need for further mechanistic and translational studies. Given the drug's clinical availability, confirming a reproducible, tumor-specific anticancer effect could accelerate translational paths. Our findings suggest that tacrolimus could hold promise for *PBRM1*-associated tumors, but extensive preclinical validation is required to distinguish context-specific risks.

5. Conclusion

Tacrolimus may be a candidate for drug repurposing in cancer therapy due to its association with *PBRM1*-related pathways. The results of this study suggest that tacrolimus could have possible anticancer relevance based on the in silico analyses performed. Previous experimental studies demonstrating activation of apoptotic pathways in Jurkat cells also support a possible biological role for this compound. However, the present findings are based on computational analysis, and further experimental studies are needed to confirm these results. Additional in vitro and in vivo investigations

will be important to better understand the potential role of tacrolimus in cancer therapy.

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