Research Article ISSN: 2836-3647

American Journal of Pathology & Research

B7-H3 as a Target in Emerging Immunotherapy for Penile Cancer (HPV Vaccination in Males)

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Received: 10 Dec 2025; **Accepted:** 22 Jan 2026; **Published:** 31 Jan 2026

Citation: Ghirardi, G, Murguia-Perez, M, Agustin-Godinez, E. B7-H3 as a Target in Emerging Immunotherapy for Penile Cancer (HPV Vaccination in Males). American J Pathol Res. 2026; 5(1): 1-5.

ABSTRACT

Introduction: *Penile cancer is not common in developed countries, although it is common in some Latin American countries. It is related to cervical cancer. Therefore, it is important to promote vaccination in young men. Given the clinical/oncological management, there are new treatment proposals based on immunotherapy (IT), which favor organ preservation. Pathology reports must be increasingly strict regarding classification, IHC markers, and therapeutic strategies.*

Objectives: *To evaluate the perspective on the use of established HPV and IT markers to establish their relevance; to determine the specificity and sensitivity of the markers through IHC focused on the B7 H3 protein.*

Materials and methods: *27 penile cancer samples from patients in Paraguay underwent IHC at Bio SB, CA. USA, with 16 markers.*

Results: *The IHC markers HPV, B7H3, and HSP-27 were highly significant in the relationship between penile cancer and HPV. Based on our results, we recommend further investigation of the B7 homologous protein H3 and its potential as a target in immunotherapy and cancer.*

Conclusion: *Sample management should be performed by pathologists experienced in the pathogenesis, classification, and therapeutics of penile cancer. The function of B7-H3 as an immunoregulator and its practical use, the degree of involvement of agents and/or cofactors, and the local/systemic immune response remain to be elucidated, making it attractive and promising.*

Keywords
HPV, Immunotherapy, Vaccines, Penile cancer.

Introduction
Penile cancer is uncommon in developed countries, although it is relatively frequent in some Latin American countries. It is related to cervical cancer; therefore, promoting vaccination in young males is of particular importance. Given the clinical and oncological management, new treatment approaches based on immunotherapy (IT) have emerged [1]. These approaches support organ preservation. Pathology reports are increasingly expected to adhere strictly to classification and immunohistochemical (IHC)

marker guidelines. Currently, immunotherapy targeting immune checkpoint inhibition with PD-1 and its ligand PD-L1 is being promoted as an important targeted therapy in penile cancer [2]. However, focusing on the B7-H3 protein may open new paradigms [3].

T lymphocytes are powerful immune cells capable of destroying tumors, yet cancers have developed strategies to evade cell death. Tumors are persistent and can progress independently of the presence of tumor-infiltrating lymphocytes (TILs). TILs are considered predominantly "exhausted" due to chronic antigen exposure; however, recent studies have revealed that T cells within tumors exist along a continuum of epigenetic, transcriptional, and metabolic states [4].

A paradox in tumor immunology is that tumor antigen–specific TILs are dysfunctional in situ and yet can mediate the regression of large metastatic tumors following immune checkpoint blockade or adoptive cell transfer [2]. Nevertheless, persistence and progression may be influenced by the patient's immunological status, such as in those with HIV and reduced immune competitiveness [5].

Objectives

Penile cancer is rare and occurs mainly in older adults, particularly those with phimosis, HPV, HIV, smoking habits, or lack of circumcision [6,7]. Standard treatment includes surgical excision, laser ablation, local radiotherapy, and partial or total penectomy. Prognosis and therapeutic approach depend on TNM staging [2]. Given its clinical and oncological management, novel treatment strategies based on immunotherapy—favoring organ preservation—are under development. Pathology reports must increasingly adhere to stricter standards regarding classification, IHC markers, and therapeutic strategies.

This study aims to evaluate the role of the B7-H3 marker (also known as CD276), a member of the B7 family, in HPV-positive (p16) cases and its potential relevance in immunotherapy. It is also essential to address the specificity and sensitivity of markers through immunohistochemistry. Some studies have shown that B7-H3 acts as a costimulatory molecule for T cells, while others suggest that it may function as a coinhibitory molecule for these cells. Although the receptors for B7-H3 have not yet been identified, evidence suggests that, similar to B7-1/CD80 and B7-2/CD86, B7-H3 may have more than one receptor—one stimulating and another inhibiting T-cell activity. B7-H3 expression has been reported in several human tumors and is often correlated with poor prognosis [3-12].

WHO Classification of Penile Cancer:

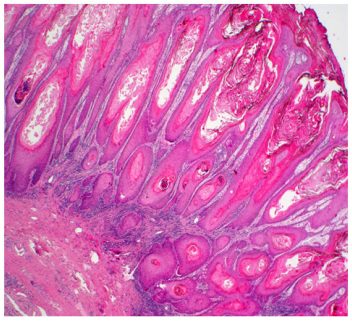
HPV independent squamous cell carcinomas

- Usual-type squamous cell carcinoma.
- Pseudohyperplastic carcinoma.
- Verrucous carcinoma.
- Pure verrucous carcinoma.
- Carcinoma cuniculatum.
- Papillary squamous cell carcinoma, NOS.
- Adenosquamous carcinoma.
- Sarcomatoid squamous cell carcinoma.
- Mixed differentiated carcinoma.

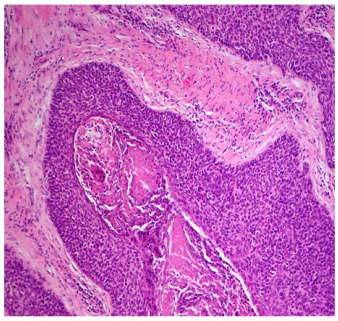
HPV associated squamous cell carcinomas

- Basaloid carcinoma.
- Papillary basaloid carcinoma.
- Warty (condylomatous) carcinoma.
- Warty-basaloid carcinoma.
- Clear cell carcinoma.
- Lymphoepithelioma-like carcinoma.

Picture 1:



Verrucous carcinoma



Basaloid carcinoma

Materials and Methods

A total of **27** penile cancer tissue blocks from patients in Paraguay were evaluated. HPV and immunotherapy markers were assessed to establish their relevance (case study). The aim was to validate the expression of immunotherapy markers in HPV-induced penile carcinomas. Using IHC, a series of tissues diagnosed as penile carcinomas were first analyzed with HPV markers and subsequently with immunotherapy markers to determine their relevance (Tables 1 and 2). (Bio SB, Santa Barbara, CA, USA).

Table 1: Antibodies for HPV detection.

Antibodies	***Clone***
p16	16P04
Ki-67	EP5
MCM2	RBT-MCM2
Topoisomerase IIa	***RBT-Topo2a***
HSP-27	G3.1

Tabla 2: Immunotherapy marker antibodies.

Antibodies	**Clone**
PD-1	NAT-105
PD-L1	RBT-PDL1
LAG-3	EP294
B7H3-CD276	RBT-BTH3
CTLA-4	RBT-CTLA4 (SP355)
OX-40/ CD134	BSB-90
FOXP3	EP340
CD8	C8/144B
CD4	RBT-CD4
GATA3	EP368
T-bet	EP263

Equipment and Reagents

Equipment

- Pipettes and pipette tips: variable ranges.
- Pressure cooker.
- Ink detection system and slide support holder.
- Staining dishes.
- Slide staining racks.
- IHC reagent isolation wells.

IHC Reagents/Auxiliaries

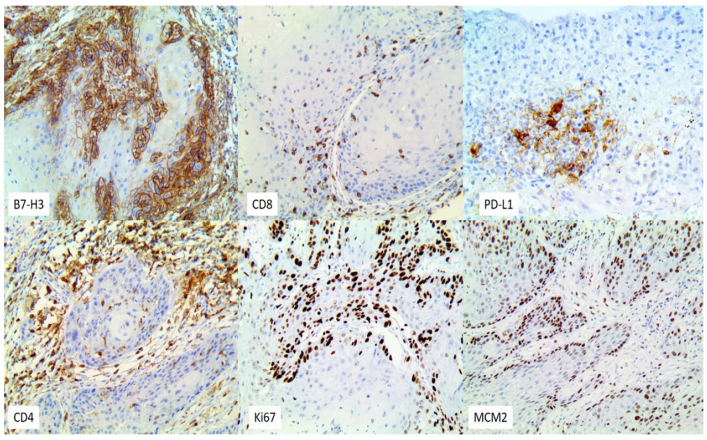
- Xylenes
- 30% -100% EtOH.
- Distilled water.
- ImmunoDNA Washer 20X (wash buffer solution).
- ImmunoDNA Citrate 20X (HIER solution).
- Ab diluent.
- PolyDetector Plus HRP / DAB.
- Antibodies (Tables 1 and 2).

Picture 2: Tinto Stainer Plus (Bio SB).

Results

The study has limitations such as the lack of information regarding the tumor status and the immune status of the cases, as well as missing clinical and epidemiological data. The descriptive study was conducted by analyzing 27 tissue blocks from patients with penile cancer from Paraguay, which posed a challenge for further continuation and in-depth analysis, relying on the authors' own experiences and observations.

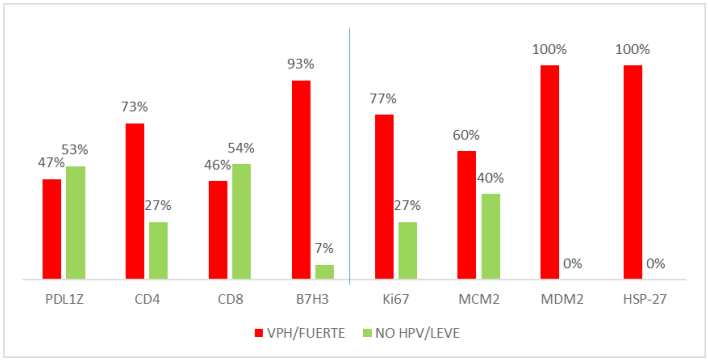
In Table 3 and Picture 1, the most notable findings were: among HPV-positive patients, 93% of those tested for B7-H3 were also positive. In contrast, PD-L1 was positive in only 47%, and CD4 in 73% of the cases (own data source) [7].



Picture 3: HPV Penile Cancer IHCs for B7-H3, PD-L1, CD4, CD8, Ki67 and MCM (16-913 case).

Table 3: Distribution of cases with and without HPV (stained with MDM2 and HSP-27) and their relationship with immunotherapy markers. Values are expressed as percentages (n=27).

	HPV/SEVERE	***NOT HPV/MILD***
PDL1	47%	53%
CD4	73%	27%
CD8	46%	54%
B7-H3	93%	7%
Ki67	77%	27%
MCM2	60%	40%
MDM2	100%	0%
HSP-27	100%	0%

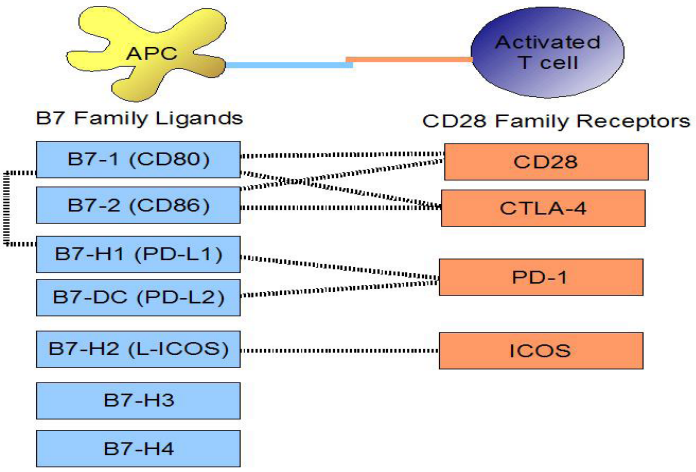


Picture 4: Distribution of cases with and without HPV (stained with MDM2 and HSP-27) and their relationship with immunotherapy markers. Values are expressed as percentages (n=27). Own data source.

Discussion

All evidence suggests that B7-H3 may regulate the activation of neoantigen-specific T cells during cognate interactions between antigen-presenting cells (APCs) and T cells in secondary lymphoid organs. The use of PD-L1 and PD-1 has been highly successful in the treatment of various types of cancer; however, only a fraction of patients achieve significant clinical benefits from this therapy, highlighting the urgent need for more effective and specific alternatives.

In this context, Young-hee Lee et al. have published extensive information on this topic. They reported treating mice with anti-B7-H3, resulting in neutralization of tumor growth across several cancer types. Furthermore, combined blockade of B7-H3 and PD-1 produced a synergistic effect in inhibiting tumor growth [10] (Picture 5).



Picture 5: Schematic representation of costimulatory molecule interactions between antigen-presenting cells (APCs) and T cells, illustrating B7 family ligands and their corresponding CD28 family receptors.
Source: https://es.m.wikipedia.org/wiki/Archivo:B7_family_ligands_and_CD28_family_receptors.JPG.

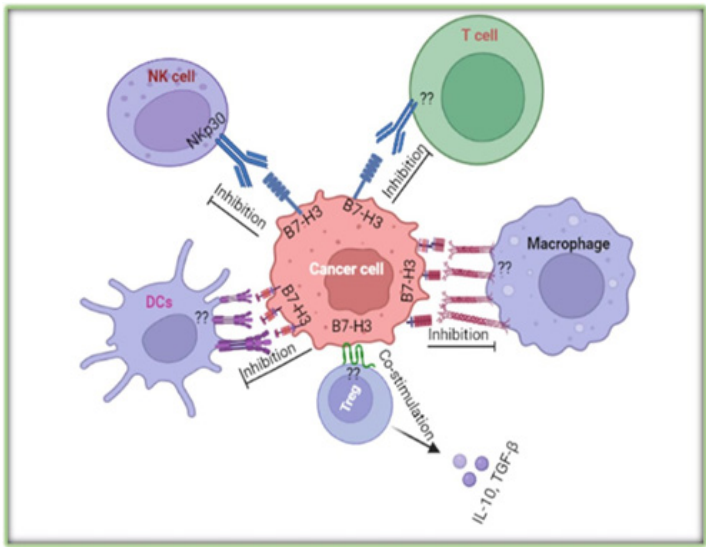
Recent studies have shown an aberrant form of B7-H3 expressed in various cancer types. Nevertheless, the receptor for B7-H3 has not yet been identified. Detecting the B7-H3 receptor would be important for understanding and developing immune responses against cancer.

Picarda et al. report that B7-H3 may play a significant role in the regulation of innate immunity, homeostasis, and inflammation; however, elucidating its precise mechanism of action is complex and requires further study, as its receptor remains unknown.

Regarding the tumor microenvironment and immune evasion, B7-H3 overexpression has been reported in human malignancies, with >60% and up to 93% of tumor tissues showing aberrant expression in a wide range of tumors analyzed by IHC, whereas its expression is limited in normal tissues [3].

B7-H3: An Attractive Immunotherapy Target (Picture 6)

According to Clinical Cancer Research (2021), B7-H3 represents an attractive target for antibody-based immunotherapy. Regarding tumor immune evasion sites from B7-H3 and PD-L1, both are expressed on myeloid cells and tumor cells. Recent findings indicate that the presence of PD-L1 in tumor cells is sufficient to promote tumor invasion in immunogenic tumors and inhibits CD8 cell cytotoxicity. The immunological roles of B7-H3 and PD-L1 are not redundant in antitumor immunity. In terms of antitumor activity, both FDA-approved anti-PD-1 and anti-PD-L1 antibodies have shown efficacy across multiple tumor types [3,8,9].



Picture 6: A diagram of the interaction of B7-H3, a cancer cell expressed immune checkpoint, with immune cells.

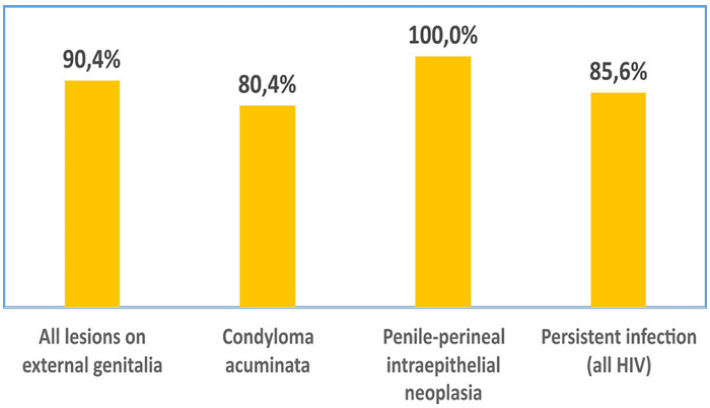
The scientific community is beginning to explore the therapeutic role of B7-H3 through multiple mechanisms, including synergistic combination of targeted therapies with other therapies, potentially serving as a bridge to durable cancer treatment. According to Young-hee Lee et al., [10], B7-H3 immune checkpoint inhibition limits tumor growth by activating cytotoxic lymphocytes, although the interaction between tumors and the immune system remains poorly understood. Favorable responses have been observed with CTLA-4 and PD-1/PD-L1 antibody therapies, though only a small number of patients showed a response to these therapies. These authors also highlight the need to explore additional co-inhibitory molecules, such as B7-H3, a member of the B7 superfamily, which has been shown to inhibit T cell activation and influence autoimmunity [10].

In a 2019 study on small cell lung cancer, the expression and clinical significance of PD-L1, B7-H3, B7-H4, and TILs were analyzed. Limited activity was observed with PD-1/CTLA-4 monotherapy for immune checkpoint blockade, raising concerns about overestimated expectations regarding these markers. The same authors measured three different B7 family members and TILs, finding low levels of PD-L1, B7-H4, and TILs, but prominent B7-H3 presence, similar to that observed in this analysis. This suggests a potential role for B7-H3 in immune evasion and possibly a novel therapeutic opportunity [11].

Additionally, Varki et al., [12] retrospectively analyzed cutaneous squamous cell carcinoma and the expression of PD-L1, B7-H3, and PD-1 in relation to immune suppression in 66 cases. They found PD-L1 expression at 26%, B7-H3 at 85%, and PD-1 in CD8 TILs at 80%. Their conclusion was that results vary based on immune status, with B7-H3 potentially useful in immunocompetent patients and transplant recipients. They also reported high B7-H3 expression in immunocompetent patients and low expression in immunosuppressed HIV-positive patients—findings that differ

from those in this study.

In the context of vaccines and HPV-associated neoplasms, the WHO recommends vaccination not only for women but also for men in national immunization programs. In Europe, the European Centre for Disease Prevention and Control (ECDC), as well as the United States, Australia, and Canada, recommend including males in vaccination programs (Picture 7).



Picture 7: Adapted from: Crosignani P, De Stefani A, Fara GM, Isidori AM, Lenzi A, et al. Towards the eradication of HPV infection through universal specific vaccination. BMC Public Health 2013; 13:642-652.

Conclusions

The handling of samples and histopathological typing should be performed by experienced pathologists in accordance with recent advances in the pathogenesis, classification, and therapeutic strategies for penile cancer. Immunotherapy is an emerging treatment modality that activates or suppresses the immune system and has been associated with reduced side effects.

B7-H3 overexpression not only serves as an early tumor detection marker but also aids in treatment planning, representing a smart option as a cutting-edge technology. Its practical application, the expansion of knowledge regarding its mechanisms, the involvement of certain agents or cofactors, as well as local and systemic immune responses, remain to be fully elucidated. Furthermore, the potential impact of new drugs on disease control or improvement requires further investigation.

It is deemed appropriate to continue contributing knowledge on B7-H3 by conclusively identifying its specific receptors, understanding its role in tumor progression and drug resistance, and considering its potential as a novel immunotherapy target for cancer. Innovation in this field represents a strategic investment.

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