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Preferentially Expressed Antigen in Melanoma (PRAME) as a diagnostic and predictive marker in melanocytic tumors: An updated narrative review

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Summary. Melanocytic neoplasms range from benign nevi to malignant melanomas, and accurate differentiation between these lesions is crucial for effective treatment. Among the various immuno-histochemical markers available, PRAME (Preferentially Expressed Antigen in Melanoma) has emerged as a significant diagnostic tool in the evaluation of melanocytic lesions due to its high sensitivity and specificity, particularly in distinguishing malignant melanomas from benign nevi. PRAME is strongly expressed in malignant melanomas, including cutaneous, uveal, and mucosal variants, while its expression is minimal or absent in benign and dysplastic nevi. Its utility extends to identifying metastases, especially in difficult-to-diagnose cases such as metastatic melanoma, where it aids in differentiating melanoma from other malignancies. Additionally, the presence of PRAME is associated with poor prognosis, as higher expression levels correlate with increased metastatic risk. Despite its effectiveness, the use of PRAME in immunohistochemistry is not without limitations. It is not exclusive to melanoma, as its expression can be seen in some non-melanocytic tumors, which may reduce its specificity in certain cases. Nevertheless, PRAME remains a valuable tool in the diagnostic and prognostic evaluation of melanocytic lesions, particularly when histological features are unclear or ambiguous. Further research is needed to refine its role in different melanoma subtypes and to explore its potential as a target for immunotherapy.

Key words: Melanoma, Immunohistochemistry, Benign Nevi

Introduction

Melanocytic neoplasms are classified according to the latest WHO classification of melanocytic skin tumors, 5th edition (Moysset et al., 2024). Melanocytic lesions represent a broad category of skin conditions ranging from benign nevi to malignant melanomas, each with different clinical, histological, and prognostic characteristics. Accurate and timely diagnosis is essential to ensure the best possible treatment, especially in melanoma cases, a skin cancer that can progress rapidly into aggressive and metastatic forms. In recent years, immunohistochemistry has gained importance in the diagnosis of melanocytic lesions due to the identification of specific tumor markers. Among these, the PRAME (PReferentially expressed Antigen in MElanoma) marker has stood out for its high sensitivity and specificity in distinguishing between benign and malignant lesions (Bose, 2023). PRAME is a melanoma-associated antigen that was isolated by autologous T cells from a melanoma patient (Lezcano et al., 2018). PRAME is encoded in a 12-kilobase region on chromosome 22, where it functions as a corepressor of nuclear retinoic acid receptor signaling, inhibiting cell differentiation and apoptosis. Additionally, PRAME may regulate the transcription of genes promoting cell

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Abbreviations. PRAME, Preferentially Expressed Antigen in Melanoma; DN, dysplastic nevus; HG-DN, high-grade dysplastic nevi; CM, cutaneous melanoma; LG-DN, low-grade dysplastic nevi; UM, uveal melanoma; PAM, primary acquired melanosis; MM, mucosal melanoma.

proliferation. As a member of the Cancer-Testis Antigen (CTA) family, PRAME is an attractive target for immunotherapy due to its tumor-specific expression and immunogenicity (Al-Khadairi and Decock, 2019). The use of PRAME in immunohistochemistry is emerging as a useful diagnostic tool, particularly in situations where histological features of melanocytic lesions are unclear. In melanoma, PRAME is typically highly expressed, whereas its expression is weak or absent in benign nevi, thereby enhancing the accuracy of differential diagnoses (Bahmad et al., 2023; Rasic et al., 2023). The diagnostic value of PRAME extends across various lesions. It is significantly expressed in uveal melanoma (UM), where its presence is associated with an increased risk of metastasis (Field et al., 2016; Broggi et al., 2023). In acral melanomas, particularly those with histopathological ambiguity, PRAME expression helps improve diagnostic precision (Santandrea et al., 2022). However, its expression in spitzoid and nail apparatus melanocytic lesions is inconsistent, necessitating a comprehensive diagnostic approach for accurate evaluation (Cassalia et al., 2024). The result of semiquantitative staining is typically recorded as the percentage of cells with nuclear staining for PRAME and cytoplasmic staining for HMB-45 on a scale from 0 to 4+, where 0 corresponds to a negative reaction (absence of staining in tumor cells), 1+ indicates a positive reaction in 1-25% of tumor cells, 2+ corresponds to a positive reaction in 26-50% of cells, while 3+ indicates a positive reaction in 51-75% of cells. Tumors assigned a 4+ score show a positive reaction in at least 76% of cells (Rasic et al., 2023). The present review focuses on the primary applications and uses of PRAME in various melanocytic lesions, along with its potential diagnostic and prognostic roles.

Benign nevus

A benign nevus is a proliferation of melanocytes, generally presenting no malignant characteristics. These lesions are typically benign and do not require aggressive treatments, but correct differential diagnosis is essential to rule out more serious conditions such as melanoma. The expression of the PRAME marker in a benign nevus is generally absent or very low, as PRAME is strongly expressed in malignant neoplasms, particularly in melanoma. Although immunohistochemistry for PRAME is usually not necessary to diagnose a benign nevus, in some complex cases where histological diagnosis is uncertain (e.g., in atypical or dysplastic nevi), the PRAME marker can be helpful in confirming the absence of malignancy. In these cases, the lack of PRAME expression helps exclude melanoma. In particular, negativity for PRAME and positivity for p16 are highly valuable in the differential diagnosis between benign nevus and melanoma. A melanocytic lesion that is $PRAME^{+}/p16^{-}$ is more suggestive of melanoma, whereas the majority of benign nevi are typically $PRAME^{-}/p16^{+}$ (Bahmad et al., 2023). Similarly, the combined use of PRAME and HMB45 is of significant diagnostic importance in differentiating between primary melanoma and benign nevus. (Rasic et al., 2023).

Recently, some authors investigated the frequency of positive PRAME expression in benign melanocytic nevi, along with its diagnostic implications (Knittel et al., 2025); they found that, although PRAME is usually linked to melanoma, it can also be expressed in benign nevi, especially those with sun damage or a lentiginous pattern (Knittel et al., 2025). Interestingly, pathologists aware of a PRAME-positive status in a nevus were more likely to label it as severely atypical (Knittel et al., 2025). However, when other pathologists reviewed the same cases without knowing the PRAME results, they often rated them as less concerning (Knittel et al., 2025). This suggests that PRAME immunoreactivity may bias diagnoses, potentially leading to overtreatment. Accordingly, PRAME can be helpful, but it should not be used alone, as the clinical and histological context still remains crucial.

Melanoma

Melanoma is an aggressive form of skin cancer originating from melanocytes, which can share clinical and pathological features with benign or dysplastic lesions, making differential diagnosis often challenging. Unlike benign nevi, melanomas exhibit uncontrolled growth and the ability to metastasize rapidly. Dermatologists use the ABCDE criteria (Asymmetry, Border irregularity, Color change, Diameter greater than 6 mm, and Evolution) to distinguish melanoma from benign nevi (Moore and Gasparini., 2011). However, when the clinical diagnosis is unclear, clinicians perform a biopsy and histological staining to examine the morphological features in detail (Fig. 1). Despite thorough analysis, some cases remain difficult to diagnose. Immunohistochemical (IHC) tests are employed to increase diagnostic accuracy, with common markers including S-100, SOX10, Melan-A, and HMB-45 (Pop et al., 2023). However, none of these markers are exclusive to melanoma, and the final diagnosis relies on a combination of clinical, pathological, and molecular data.

PRAME is strongly expressed in melanomas, even in advanced stages, making it a highly sensitive marker for this type of neoplasm (Fig. 2). Immunohistochemically, PRAME expression in melanocytic cells can be used to confirm a melanoma diagnosis, especially in cases where histological features are not definitive. Moreover, the sensitivity of PRAME in detecting early-stage melanomas or melanoma *in situ* has been well documented, making it a valuable diagnostic tool for dermatologists and pathologists.

In the study by Lezcano et al., a total of 155 primary cutaneous melanomas (CM) were analyzed, including superficial spreading melanomas, lentigo maligna melanomas, acral melanomas, desmoplastic melanomas,

and non-desmoplastic nodular melanomas (Lezcano et al., 2018). Among the 155 primary melanomas tested, 83.2% showed diffuse immunoreactivity for PRAME. Additionally, PRAME IHC expression was notably lower in desmoplastic melanomas, with only 35% of cases demonstrating positivity (Lezcano et al., 2018).

Although PRAME has lower sensitivity than other markers, such as S100 and Melan-A, it is considered more specific for melanoma. Furthermore, PRAME offers advantages in assessing tumor margins and determining Breslow thickness, both critical factors for melanoma staging and clinical management (Pop et al., 2023).

PRAME has also been utilized to differentiate metastatic melanomas from metastatic nodal nevi (Lezcano et al., 2020). A study highlighted that 100% of lymph node metastases from melanoma were PRAME-positive, while none of the nodal nevi were positive (Lezcano et al., 2020). Acral melanomas, which appear on the palms, soles, and nails, have also been studied for PRAME expression, showing 87.1% sensitivity in melanomas and 82.5% specificity in benign nevi (Santandrea et al., 2022). Studies have also indicated that PRAME is useful in diagnosing spitzoid melanomas, though in some cases, it may also be positive in benign lesions, complicating its diagnostic interpretation (Googe et al., 2021).

In addition to its diagnostic utility, PRAME is associated with an unfavorable prognosis in melanoma. Elevated PRAME expression has been linked to a higher risk of metastasis and poorer overall survival in various melanoma types, including Class 1 UM and mucosal melanoma (Field et al., 2016). PRAME is a highly sensitive and specific biomarker for melanoma with significant potential for diagnosis, margin evaluation, and melanoma staging. Its expression is correlated with an unfavorable prognosis and could have therapeutic implications in the future, however, further research is needed to clarify its role in different melanoma subtypes and other malignancies.

A recent study by some colleagues introduced a digital image-analysis tool designed to quantify PRAME and Ki67 expression in challenging melanocytic lesions (Brogård et al., 2025). This approach aimed to enhance diagnostic accuracy by providing objective, reproducible assessments, potentially reducing variability in

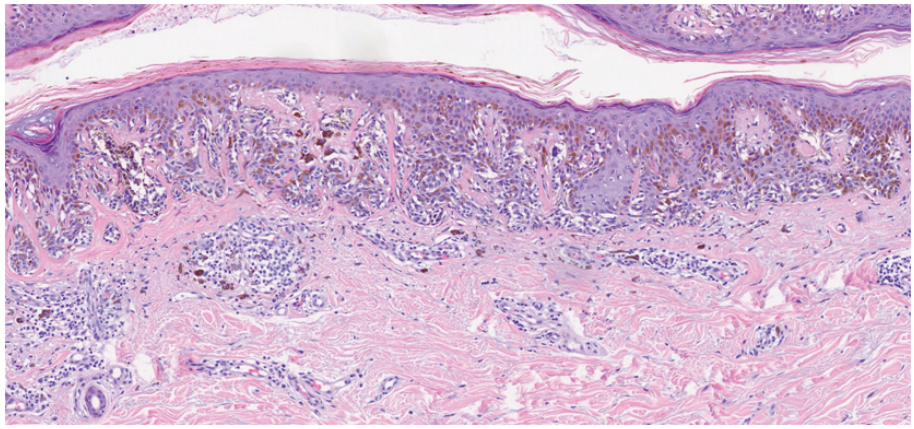

Fig. 1. H&E staining of a superficial spreading dorsal melanoma in the radial growth phase. From our archive. x 200.

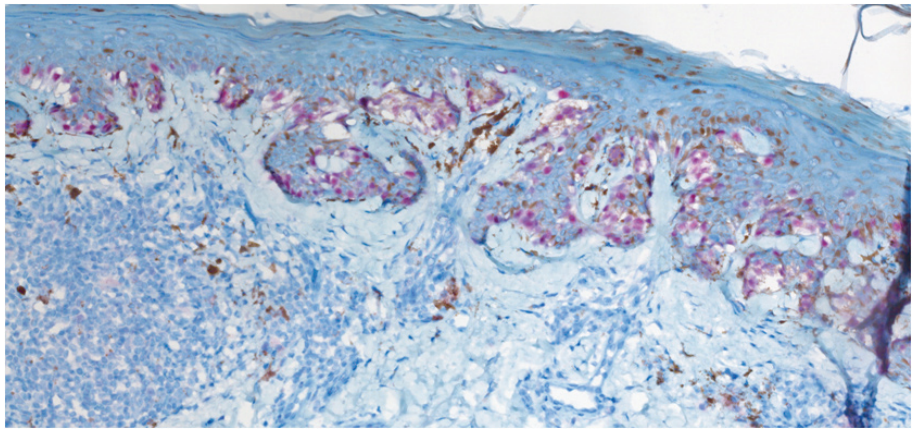

Fig. 2. Immunohistochemical staining showing positive PRAME expression in a superficial spreading dorsal melanoma in the radial growth phase. From our archive. x 200.

traditional evaluations (Brogård et al., 2025). The digital quantification demonstrated high specificity and sensitivity in distinguishing melanomas from benign nevi, suggesting its utility as a valuable tool in dermatopathology (Brogård et al., 2025).

Dysplastic nevus

An atypical nevus, also known as a dysplastic nevus (DN), is a melanocytic lesion that presents histological features intermediate between benign nevi and melanoma. These lesions can have an irregular appearance with uneven borders and color variations, sometimes making it difficult to differentiate from melanoma. In these cases, PRAME expression can be useful. Although PRAME is not expressed as strongly as in melanomas, its presence in an atypical nevus may raise a suspicion of neoplastic transformation, suggesting the need for closer monitoring or an excisional biopsy. In practice, a negative PRAME result can reassure that the lesion is benign, while a positive result may require further investigation to exclude melanoma.

The study by Innocenti et al. confirms PRAME as a valuable marker in distinguishing between high-grade dysplastic nevi (HG-DN) and CMs (Innocenti et al., 2024). Moreover, this study was the first to observe a trend of increasing PRAME expression from low-grade dysplastic nevi (LG-DN) to HG-DN (Innocenti et al., 2024). However, the unpredictable behavior of PRAME expression in the context of melanocytic dysplasia significantly limits its current clinical utility.

Further research focusing on PRAME biology is needed to better define the strengths and limitations of PRAME testing in routine diagnostic practice (Innocenti et al., 2024).

Uveal melanoma

UM is a rare neoplasm that originates in the uvea, the middle layer of the eye, and is the most common form of intraocular melanoma (Salzano et al., 2025). Unlike cutaneous melanoma, UM is more difficult to diagnose in its early stages as it does not present the typical clinical characteristics of skin lesions (Longhitano et al., 2022). PRAME has shown significant expression in the tumor cells of UM, making it a useful marker for diagnosing this form of melanoma, particularly when the histological diagnosis is uncertain. Immunohistochemistry for PRAME can be used to confirm the presence of UM in ocular biopsies, especially in cases where histopathological examination is complex or when the lesions present atypical features. The sensitivity of PRAME in detecting UM is high, making it a valuable diagnostic tool, even in the management of ocular metastases from CMs.

PRAME has been identified as an independent prognostic biomarker in UM, capable of detecting an increased risk of metastasis in patients with Class 1 tumors or those exhibiting chromosome 3 disomy (Field et al., 2016). The integration of PRAME expression analysis has the potential to further refine the prognostic accuracy of existing clinical assays and enhance the application of precision medicine in UM management (Field et al., 2016). Specifically, in Class 1 tumors, incorporating PRAME status into the currently available 12-gene expression classifier may significantly improve risk stratification (Field et al., 2016).

This approach allows for the categorization of patients into Class 1/PRAME-negative (low metastatic risk), Class 1/PRAME-positive (intermediate metastatic risk), and Class 2 (high metastatic risk) groups, thereby facilitating more tailored metastatic surveillance protocols and optimizing patient selection for clinical trials investigating targeted adjuvant therapies (Field et al., 2016). Recently, our research group analyzed 85 UM cases and found a significant correlation between PRAME IHC expression and increased metastatic risk, as well as reduced metastasis-free survival, suggesting that the inclusion of PRAME in the diagnostic panel for UM may help predict metastasis and guide patient prognosis (Broggi et al., 2023).

Conjunctival melanoma

A 2021 study by LeBlanc et al. examined PRAME expression in conjunctival melanomas and melanocytic proliferations (LeBlanc et al., 2021). Conjunctival melanomas and primary acquired melanosis (PAM) with high-grade atypia show strong and diffuse PRAME expression, while PAM without atypia and nevi are generally negative for PRAME. Some nevi exhibited faint cytoplasmic PRAME expression in type-A melanocytes and melanophages but without evident nuclear staining, suggesting that cytoplasmic PRAME expression should not be interpreted as a sign of malignancy in heavily pigmented melanocytic lesions. PRAME could be helpful in distinguishing melanoma *in situ* and its probable precursors from low-grade intraepithelial lesions, including PAM without atypia, melanocytic hyperplasia, and recurrent nevus phenomenon. However, larger studies are needed to further substantiate these promising findings (LeBlanc et al., 2021).

Mucosal melanoma

Mucosal melanoma (MM) is a rare form of melanoma that originates from mucosal surfaces, such as those in the oral cavity, respiratory tract, or genital and anal regions. MM is particularly difficult to diagnose, as its clinical manifestations can resemble other benign mucosal lesions or non-melanocytic neoplasms. PRAME is also expressed in these melanomas, and its detection through immunohistochemistry can be crucial for differential diagnosis. In particular, PRAME can help distinguish MM from other mucosal neoplasms that may appear similar, such as squamous cell carcinomas. The presence of PRAME in mucosal tumor lesions suggests a

malignant melanocytic nature, while its absence helps exclude melanoma, improving diagnostic accuracy and allowing for timely and targeted treatment (Scheurleer et al., 2023).

MM arises from melanocytes within the mucosal lining, with the nasal cavity and paranasal sinuses being the primary sites of occurrence in the head and neck region. An unexplained increase in the incidence of sinonasal MM has been observed. These tumors exhibit distinct genetic characteristics compared with CM, including a lower mutational burden related to UV radiation but a higher frequency of structural chromosomal variants. Common mutations in genes such as *BRAF* and *KIT* are rare in sinonasal MM, while mutations in *NRAS* are found in approximately 42% of cases. Treatment options for MM remain limited, and response rates to immunotherapy are lower than those observed in CM. One potential therapeutic target is the PRAME antigen, which is expressed in MM. PRAME expression was found in all cases examined by some authors, suggesting that it could serve as a future therapeutic target (Scheurleer et al., 2023). However, further studies are required to develop effective treatments (Scheurleer et al., 2023).

Metastatic melanoma

Metastatic melanoma is an advanced form of melanoma in which the tumor cells spread to other organs. In these cases, PRAME expression remains elevated, even in metastases, making the marker useful for identifying melanoma in extra-cutaneous lesions (Gradecki et al., 2021). Immunohistochemistry for PRAME in metastases can, therefore, assist clinicians in the differential diagnosis, particularly when melanoma metastases are observed in organs such as lymph nodes or the liver, where primary tumor cells might not be easily identified as melanomas (Gradecki et al., 2021). PRAME IHC is a valuable tool for differentiating metastatic melanoma from benign melanocytic lesions, particularly in lymph nodes (Lezcano et al., 2020). However, caution is required as the absence of PRAME expression does not completely exclude metastatic melanoma. Moreover, the presence of PRAME in other tumor types (e.g., squamous cell carcinoma, breast carcinoma, and renal cell carcinoma) may limit its specificity in melanoma diagnosis. In conclusion, PRAME represents a promising marker for metastatic melanoma diagnosis, but its expression is not exclusive to melanoma and can vary between cases. Its potential as a target for immunotherapy is significant, and ongoing clinical studies suggest that PRAME-targeted therapies could benefit a large proportion of melanoma patients. Nevertheless, further research is needed to refine its clinical application (Gradecki et al., 2021).

Discussion

The integration of immunohistochemistry for PRAME has significantly enhanced the diagnostic accuracy of melanocytic neoplasms, especially in complex cases such as cutaneous, uveal, and mucosal melanomas (Cassalia et al., 2024). PRAME, an antigen associated with melanoma, is predominantly expressed in malignant melanocytic tumors, and its expression has been strongly linked to poor prognosis in various melanoma subtypes (Blount et al., 2024). Its high sensitivity in advanced and metastatic melanomas, including uveal and mucosal melanomas, makes it a valuable diagnostic tool for distinguishing these neoplasms from benign lesions (Bose, 2023). One particularly relevant aspect of the diagnostic use of PRAME is its role in improving diagnostic precision in melanocytic lesions with ambiguous histopathological features, such as dysplastic nevi (Innocenti et al., 2024). The presence of PRAME in these lesions raises the suspicion of possible neoplastic transformation, prompting clinicians to consider the need for further investigation or excisional biopsy. Conversely, negative PRAME expression should provide reassurance that the lesion is benign (Innocenti et al., 2024). This ability to help differentiate between benign and malignant lesions improves clinical management, reducing unnecessary procedures and ensuring that malignant cases are appropriately addressed. Despite its advantages, PRAME is not entirely specific to melanoma and may be expressed in other neoplasms, such as squamous cell carcinoma, breast carcinoma, and renal carcinoma (Li et al., 2020). This limits its exclusivity in melanoma diagnosis, particularly in metastatic tumors. However, PRAME remains one of the most sensitive and specific markers for melanoma, providing significant prognostic value, especially when evaluating tumor margin status and Breslow thickness (Pop et al., 2023). Furthermore, PRAME has the potential to serve as a therapeutic target, particularly in cases of metastatic melanoma, where therapies targeting PRAME expression could offer new treatment opportunities.

The future prospects for PRAME in the realm of melanoma diagnosis, prognosis, and therapy are promising. Larger studies that explore its expression in various melanoma stages and subtypes could lead to more refined diagnostic algorithms that incorporate PRAME as a standard biomarker. In addition, there is growing interest in using PRAME as a therapeutic target (Aljabali et al., 2024). Given its selective expression in malignant melanocytic tumors, PRAME-based therapies could offer a more targeted approach with fewer side effects compared with traditional chemotherapies (Aljabali et al., 2024). The development of PRAME-targeted immunotherapies, including vaccines or adoptive T-cell therapies, holds significant potential. Such treatments could provide patients with a more personalized and effective option, particularly in the case of advanced or metastatic melanoma, where current therapies often have limited success (Aljabali et al., 2024). Ongoing clinical trials investigating these therapies could revolutionize the treatment landscape, making PRAME a cornerstone of

melanoma immunotherapy.

Another promising area is the integration of PRAME with other biomarkers to create comprehensive diagnostic panels. By combining PRAME with other key molecular markers, such as BRAF, NRAS, or KIT mutations, we could improve the sensitivity and specificity of melanoma diagnosis. This combination approach would also enable more personalized treatment strategies tailored to the individual's tumor profile, which could enhance treatment outcomes. The development of multiplex assays that assess multiple markers, including PRAME, would be a step toward more comprehensive and precise diagnostic workups.

Despite its promising potential, the clinical use of PRAME still faces several limitations. One of the primary challenges is its lack of absolute specificity. Although PRAME is highly sensitive in melanoma, its expression is not exclusive to melanocytic neoplasms. As mentioned earlier, PRAME can also be expressed in other malignancies, such as squamous cell carcinoma and some carcinomas. This reduces its ability to definitively differentiate melanoma from other cancer types, particularly in metastatic tumors where the primary site of origin may not be easily identified. Therefore, while PRAME is an important diagnostic tool, it should ideally be used in combination with other specific markers to increase diagnostic accuracy. Furthermore, the variation in PRAME expression across different melanoma subtypes and stages is still not fully understood. For instance, some melanoma subtypes, such as acral or mucosal melanomas, may not exhibit consistent PRAME expression, limiting its utility in these cases. The sensitivity of PRAME may also decrease in certain clinical contexts, particularly in early-stage melanomas or where the tumor burden is low. This variability in expression patterns suggests that PRAME should be considered as part of a broader diagnostic and prognostic framework rather than as a standalone marker.

Another challenge is the limited availability of standardized testing methods for PRAME expression. While immunohistochemistry is widely used, differences in laboratory techniques and antibody reagents could lead to variability in results, making it difficult to establish universal diagnostic criteria. The need for the standardization of testing procedures and the development of widely accepted guidelines for PRAME testing is critical for ensuring its reproducibility and reliability in clinical practice. Additionally, while PRAME holds promise as a therapeutic target, significant challenges remain in developing effective PRAME-based therapies. Research into the development of PRAME-targeted vaccines or immunotherapies is still in its early stages, and much more work is needed to determine their safety, efficacy, and long-term outcomes. These therapies also face hurdles in terms of immune response variability between patients and the potential for resistance, which could limit their broad applicability.

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