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Invited Perspective

PARP-targeted molecular imaging for noninvasive diagnosis and surgical guidance in basal cell carcinoma

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Abstract: Poly(ADP-Ribose) Polymerase 1 (PARP1) is a key DNA repair enzyme and therapeutic target in cancer, with overexpression observed in several cancers, including basal cell carcinoma (BCC). Conventional diagnostic methods for BCC lack specificity and are invasive, highlighting the need for noninvasive alternatives. PARP-targeted molecular imaging, particularly with fluorescence probes, has shown strong potential for tumor detection and real-time visualization. PARPi-FL, a fluorescent derivative of Olaparib, enables rapid, specific, and high-contrast imaging of BCC in preclinical and *ex vivo* human studies. Optimized application protocols confirm its safety and translational promise for noninvasive diagnosis and image-guided surgery.

Keywords: Poly(ADP-Ribose) Polymerase 1 (PARP1), basal cell carcinoma (BCC), positron emission tomography (PET), fluorescence imaging

Introduction

The Poly(ADP-Ribose) Polymerase (PARP) family, containing 18 nucleoprotein members, plays an essential role in cellular processes, including DNA damage repair, genome stability, and apoptosis regulation [1]. Among these, only PARP1 and PARP2 contain DNA-binding domains capable of recognizing damaged DNA and initiating repair via base excision repair (BER) pathways [2]. As the predominant member of the PARP family, PARP1 mediates over 90% of its catalytic activity. PARP1 consists of six domains: three zinc fingers (Zn1, Zn2, Zn3), a BRCA1 C-terminus (BRCT) domain, a WGR domain, and a catalytic (CAT) domain, which together enable its function in single-strand break repair [3]. Upon DNA damage, PARP1 first recognizes and binds to the lesion through its zinc finger domains. This binding activates PARP1, which catalyzes the transfer of ADP-ribose units from NAD^+ to synthesize poly (ADP-ribose) chains (PARylation). The modification serves as a signal to recruit key repair proteins, including XRCC1, DNA ligase III, and DNA polymerase β, thereby facilitating efficient DNA repair (**Figure 1**). PARP1 is recognized as a promising therapeutic target based on the principle of synthetic lethality. In homologous recombination (HR)-deficient cancer cells, such as those harboring BRCA mutations, PARP1 inhibition prevents BER, ultimately inducing tumor cell death. At present, many inhibitors targeting PARP have been developed and approved for the treatment of various tumors, such as breast cancer, ovarian cancer, and BRCA mutated associated cancer [4, 5]. Recent studies also indicate that PARP is overexpressed in basal cell carcinoma (BCC), the most common form of skin cancer. Current diagnostic approaches for BCC, including dermoscopy and biopsy, are limited by low specificity, potential false positives, and invasive procedures. Therefore, there is a pressing need for noninvasive and precise diagnostic methods. Molecular imaging has attracted increasing attention as it enables real-time, noninvasive visualization with high spatiotemporal resolution [6, 7]. Given the elevated expression of PARP in BCC compared with nonmalignant lesions, PARP-targeted contrast agents represent a promising approach for improving the diagnosis of BCC.

Development PARP1-targeted probes

Positron emission tomography (PET) is a powerful molecular imaging modality with excellent translational potential due to its real-time, quantitative, noninvasive capabilities and relatively low radiation dose [8-10]. A number of radiolabeled probes derived from FDA-approved PARP inhibitors have been developed to assess PARP expression, stratify tumor stage, and monitor therapeutic response. To name a few, examples include [^{18}F]Olaparib, [^{18}F]Rucaparib, [^{18}F]Talazoparib, [^{18}F]Pamiparib, [^{18}F]FTT, [^{18}F]F-PARPi and the most recent [^{11}C]PyBic [11] and [^{18}F] AZD9574 [12-15]. These discoveries highlight that PET probes targeting PARP can achieve excellent tumor imaging performance in both preclinical and clinical settings. Nevertheless, challenges of PET imaging remain, including limited spatial resolution, radiation exposure, and the inability to provide intraoperative tumor guidance. Fluorescence imaging offers an attractive complementary approach to overcome these drawbacks, enabling non-radioactive, real-time, and high-resolution tumor visualization. The prototypical PARP-targeted fluorescent probe, PARPi-FL, was first synthesized in 2012 by conjugating the FDA-approved inhibitor Olaparib to the BODIPY dye [16]. In U87 glioblastoma xenografts, PARPi-FL demonstrated strong nuclear accumulation within tumor cells (mean AU/px = 20.49) compared to brain (0.13) and mus-

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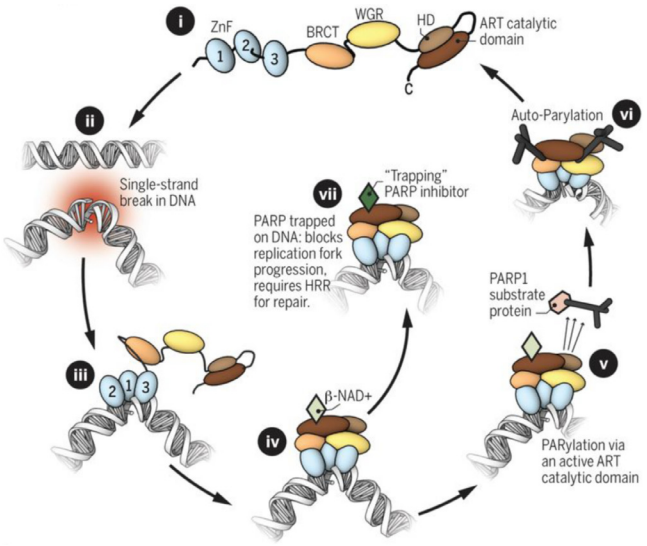

Figure 1. Mechanism of PARP repair single-strand breaks. The PARP protein first recognizes and binds to the damaged site at high speed and affinity through zinc finger. Then, the activated PARP1 catalyzes NAD^+ to synthesize poly ADP ribosylation (PARylation) through the CAT, and finally recruits repair protein XRCC1, DNA ligase III, and DNA polymerase β to the damaged site for DNA repair. Panels reproduced with permission from ref 1 (Copyright 2017, American Association for the Advancement of Science).

cle (3.45), resulting in a high tumor-to-background ratio [17]. Preblocking with excess inhibitor or using U251 cells with low PARP expression significantly reduced tumor signal, confirming specificity. Fluorescence microscopy further revealed robust nuclear localization of PARPi-FL in tumor tissue, consistent with the known subcellular distribution of PARP1. In orthotopic glioblastoma models, tumor-selective uptake was similarly observed, with surrounding normal brain displaying only background signal. Pharmacokinetic evaluation showed that 80.3% of PARPi-FL remained intact within 5 minutes post-injection, but more than 45% was metabolized by 30 minutes. Despite this, PARPi-FL has demonstrated utility across multiple tumor models. In oral squamous cell carcinoma, which exhibits approximately 7.8-fold higher PARP1 expression than normal mucosa (confirmed by IHC) [18], PARPi-FL accumulated strongly in tumor nuclei with a Pearson correlation coefficient of 0.97 for colocalization. Topical application studies revealed rapid and selective tumor uptake, providing high-contrast visualization suitable for intraoperative use.

Literature highlight: PARPi-FL for the diagnosis of BCC

In previous studies, PARP1 was found to be highly expressed in BCC, serving as a reliable tumor marker for distinguishing BCC from normal tissue. The fluorescent probe PARPi-FL has been shown to enhance diagnostic accuracy by enabling real-time visualization of tumor margins and by permeating both *ex vivo* human tissue and *in vivo* pig skin models [19]. Building upon these findings, further optimization of probe concentration and incubation time demonstrated improved diagnostic performance. Specifically, PARP1 expression was detected in more than 87.7% of BCC lesions, a statistically significant difference compared with benign lesions (24.8%) (**Figure 2A**) [20]. *Ex vivo* human skin samples exhibited a strong fluorescence signal within 2-5 minutes of topical application using 10 μM PARPi-FL. *In vivo* fluorescent confocal microscopy (FCM) imaging further confirmed bright, uniform fluorescence in BCC tumor nodules, which appeared as round-to-oval clusters within 5 minutes of topical application. By contrast, benign lesions showed weaker and more heterogeneous signals (**Figure 2B**). While some nonspecific binding to corneocytes was observed in both malignant and benign lesions, the cellular morphology, epidermal thickness, and basal layer architecture visualized with FCM were highly consistent with hematoxylin and eosin (H&E)-stained sections. In transgenic B6 K5-Gli2 mice, FCM imaging demonstrated comparable fluorescence outcomes between 5 μM PARPi-FL applied for 15 minutes and 1 μM PARPi-FL applied for 30 minutes (**Figure 2C**). Tumor-specific fluorescence was observed within 70-100 μm beneath the skin surface, exceeding background signal from basal epidermal nuclei and control groups. Importantly, no evidence of systemic or local toxicity was detected: body weight remained stable, skin morphology appeared normal, and both H&E histology and serum biochemistry revealed no pathological changes or organ damage. Moreover, systematic evaluation of application parameters demonstrated that fluorescence intensity correlated positively with dye concentration during short application times (**Figure 2D**). These results highlight the strong translational potential of PARPi-FL for the non-invasive, rapid, and precise diagnosis of BCC.

Conclusion

PARP has emerged as a promising target for both tumor imaging and therapy, particularly in the context of BCC. Fluorescent probes derived from PARP inhibitors offer significant advantages for noninvasive, high-contrast imaging of BCC lesions, enabling more accurate detection and characterization compared with conventional approaches. Beyond diagnostic applications, PARP-targeted fluorescent agents hold great potential as transformative technologies for preoperative lesion mapping and intraoperative image-guided surgery, thereby improving surgical precision and patient outcomes. Despite these advances, several challenges remain before broad clinical adoption can be realized. In particular, optimization of the imaging window is essential to ensure consistent and reliable visualization across different clinical scenarios. Furthermore, the development of next-generation probes with emission in the near-infrared or shortwave infrared range is expected to improve tissue penetration and significantly enhance the signal-to-background ratio. These improvements will be critical for achieving deeper *in vivo* tumor visualization and maximizing the clinical utility of PARP-targeted fluorescence imaging.

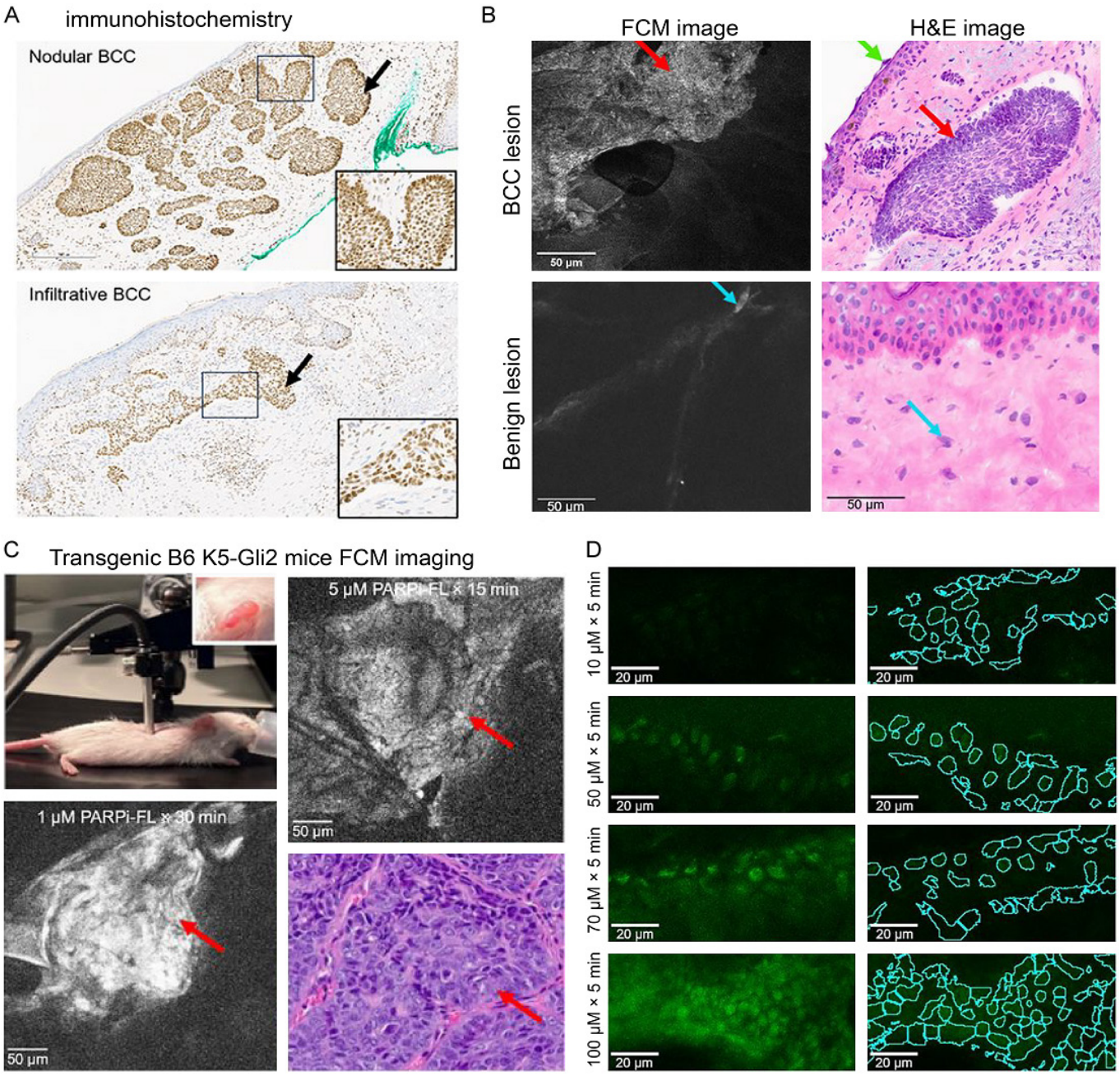

Figure 2. Tumor imaging of basal cell carcinoma (BCC). A. Immunohistochemistry images of BCC and benign lesions. B. The FCM images and H&E images of excised human BCC lesions and benign lesions after topical application 5 min. C. The *in vivo* FCM images and H&E images of transgenic B6 K5-Gli2 mice. D. The human skin FCM images treated with different concentrations of PARPi-FL for 5 min. Panels A-D were reproduced with permission from ref 20 (Copyright 2025 by the Society of Nuclear Medicine and Molecular Imaging).

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Disclosure of conflict of interest

None.

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