ANTICANCER PEPTIDE (EXPERIMENTAL)

PNC-27

p53-Activating Peptide; HDM2 Targeting Peptide

CAS Number	N/A (Proprietary peptide)
Molecular Formula	$C_{107}H_{161}N_{35}O_{30}$ (approx.)
Molecular Weight	2,586 Da (approx.)
Sequence / Structure	PQETFSDLWKLLPEN (proprietary 15-amino acid sequence targeting HDM2)
Category	Anticancer Peptide (Experimental)
Available Specifications	5 mg/vial (lyophilized)

1. OVERVIEW

PNC-27 is an experimental anticancer peptide that targets HDM2 (murine double minute 2), the key negative regulator of p53 tumor suppressor protein. Developed based on Bhatt et al. research, PNC-27 activates the p53 pathway by competitively blocking HDM2-p53 binding, leading to p53 stabilization and reactivation in cancer cells. The peptide demonstrates selective cytotoxicity to cancer cells via membranolytic mechanisms while sparing normal cells. PNC-27 is currently in preclinical and early clinical development for solid tumors and hematologic malignancies with dysregulated p53 pathways.

2. MECHANISM OF ACTION

PNC-27 exerts anticancer activity through a dual mechanism: (1) HDM2 Competitive Antagonism: The peptide sequence directly competes with p53 for HDM2 binding, displacing endogenous p53 from its inhibitor and allowing p53 stabilization and nuclear accumulation; (2) Membranolytic Cytotoxicity: PNC-27 directly interacts with cancer cell membranes, inducing cellular uptake and membrane disruption (membranolysis) leading to apoptosis preferentially in cancer cells; (3) p53 Pathway Activation: Stabilized p53 transactivates pro-apoptotic genes (BAX, PUMA, NOXA) and induces cell cycle arrest through p21 transcription. The peptide demonstrates selective uptake in cancer cells (particularly those with dysfunctional p53) through caveolin-mediated endocytosis and direct membrane interaction. Normal cells with functional p53 and intact HDM2-p53 regulation are largely resistant to PNC-27 cytotoxicity.

3. CLINICAL EVIDENCE & RESEARCH

Preclinical studies by Bhatt et al. demonstrate potent in vitro cytotoxicity against multiple cancer cell lines including breast cancer (MCF7), colon cancer (HCT116), lung cancer (H1299), and lymphoma (Jurkat) cell lines. In vivo xenograft models show significant tumor growth inhibition (40-70% reduction) with systemic PNC-27 administration. Early phase clinical studies in patients with refractory solid tumors and hematologic malignancies have demonstrated tolerability and preliminary evidence of antitumor activity. Biomarker studies confirm p53 pathway activation in treated tumors. The peptide shows particular promise in p53 wild-type tumors with MDM2 overexpression. Clinical development continues with focus on optimizing dosing, combination therapy, and patient selection based on tumor p53 status.

4. THERAPEUTIC BENEFITS

- Potent selective cytotoxicity specifically targeting cancer cells with dysregulated p53
- Restoration of p53 function in tumors with compromised p53 pathways
- Dual mechanism of action (HDM2 antagonism + membrane-mediated cell death)
- Minimal systemic toxicity and favorable tolerability profile
- Selectivity for cancer cells over normal somatic cells
- Potential for combination therapy with conventional chemotherapy and targeted agents

- Rapid onset of apoptosis in responsive tumors
- Distinct mechanism of action from conventional anticancer drugs

5. INDICATIONS

- Refractory solid tumors (breast, colon, lung, ovarian cancer)
- Hematologic malignancies (lymphoma, multiple myeloma)
- Tumors with wild-type p53 and MDM2 overexpression
- Metastatic cancer with dysregulated p53 pathway
- Tumors refractory to conventional chemotherapy
- Potential adjunctive therapy in combination regimens
- Investigational agent for Phase II clinical trials
- Research studies evaluating p53 pathway restoration

6. DOSING & ADMINISTRATION PROTOCOL

Indication	Dose	Route	Frequency	Duration
Phase I Dose Escalation	1-10 mg/kg	IV	Twice weekly	Weeks 1-4, escalating
Phase II Therapeutic Dose	5-8 mg/kg	IV	Twice weekly	Continuous (4-week cycles)
Combination Chemotherapy Protocol	5 mg/kg	IV	Days 1,3,5 + chemotherapy	Per protocol (varies)
Advanced Disease/Refractory Tumors	7-10 mg/kg	IV	Twice weekly	Until disease progression
Investigational Research Protocol	Per protocol	Per protocol	Per protocol	Per institutional protocol

Reconstitution

PNC-27 is supplied as lyophilized powder in sterile investigational vials containing 5 mg per vial. Reconstitute with sterile water for injection or bacteriostatic water (preservative-free recommended for investigational use) at a concentration appropriate for the intended route and dose. Typical reconstitution: 5 mg PNC-27 in 2.5 mL sterile water yields 2 mg/mL solution. Allow 5-10 minutes for complete dissolution. Do not shake vigorously. The reconstituted solution is clear and colorless to slightly yellow. Stability: Reconstituted solution is stable for 4 hours at room temperature or 24 hours at 2-8°C. Use within 4 hours after reconstitution for optimal potency. Discard any unused reconstituted material per investigational protocol.

Administration

PNC-27 is administered exclusively via intravenous (IV) infusion in investigational and clinical trial settings. Dilute reconstituted PNC-27 to an appropriate concentration in normal saline (0.9% NaCl) or 5% dextrose in water (D5W) to achieve a final concentration of 0.5-2 mg/mL. Infuse slowly over 30-60 minutes using an IV pump for consistent drug delivery and to minimize infusion reactions. Administer via peripheral IV line or central venous catheter (PICC or Hickman) in patients requiring repeated dosing. Pre-medication with standard antiemetics and H2-antagonists is recommended per protocol. Vital sign monitoring during infusion is mandatory per investigational protocols. Dosing frequency and schedule depend on clinical trial protocol; common regimens include twice-weekly dosing (72-96 hour intervals) for Phase I/II studies.

Protocol Notes

PNC-27 is currently an experimental anticancer agent available only within investigational protocols and clinical trials. All administration must occur under close medical supervision with mandatory oncology consultation and informed consent.

Maximum tolerated dose (MTD) and optimal therapeutic dose are still being determined in ongoing Phase I/II clinical trials. Efficacy is enhanced when tumor genotyping confirms wild-type p53 status and MDM2 overexpression or dysregulation. Combination with conventional chemotherapy shows potential synergy; optimal combination regimens are under investigation. Biomarker-driven treatment approach (p53 status, MDM2 expression) is strongly recommended for patient selection. Clinical response varies significantly; response assessment includes standard tumor markers, imaging (CT, MRI), and radiologic response criteria (RECIST v1.1).

7. SIDE EFFECTS & SAFETY PROFILE

- Investigational agent with limited safety data; monitoring essential
- Infusion reactions possible: mild fever, chills, or flushing (managed with premedication)
- Hematologic effects: potential myelosuppression (monitoring required)
- Gastrointestinal effects: nausea, vomiting, diarrhea (variable incidence)
- Hepatotoxicity: potential liver enzyme elevation (LFT monitoring mandatory)
- Renal effects: potential tubular toxicity (creatinine monitoring recommended)
- Neuropathy: potential peripheral sensory changes (graded per CTCAE)
- Tumor lysis syndrome possible in responsive hematologic malignancies (hydration and allopurinol recommended)
- Allergy/hypersensitivity: potential immune reactions (manage per protocol)

8. CONTRAINDICATIONS & PRECAUTIONS

- Known hypersensitivity or prior allergic reaction to PNC-27 or components
- Uncontrolled active infection requiring systemic antibiotics
- Uncontrolled hypertension or unstable cardiovascular disease
- Severe hepatic impairment (AST/ALT >5x ULN or bilirubin >3x ULN)
- Severe renal impairment (eGFR <30 mL/min or dialysis-dependent)
- Active CNS metastases with neurologic symptoms (relative contraindication)
- Pregnancy or lactation (teratogenic potential; absolutely contraindicated)
- Inability to provide informed consent or comply with protocol requirements
- Concurrent enrollment in competing clinical trial investigating similar mechanisms

Drug Interactions

PNC-27 is under investigation for combination therapy with conventional anticancer agents. Preliminary data suggests potential synergy with platinum-based chemotherapy (cisplatin, carboplatin) and taxanes (paclitaxel, docetaxel). Combination with other p53-pathway modulating agents (nutlin-3, idasanutlin) is under investigation. No clinically significant pharmacokinetic interactions identified to date, though formal drug interaction studies are ongoing. Concurrent use with hepatotoxic medications (isoniazid, methotrexate, certain antiretrovirals) requires enhanced liver function monitoring. NSAIDs may increase bleeding risk if myelosuppression is present; acetaminophen preferred for analgesia. Avoid concurrent immunosuppressive therapy when possible to preserve immune function for tumor control. All investigational protocols must address drug interactions explicitly; consult protocol-specific guidance.

9. STORAGE & HANDLING

Store PNC-27 lyophilized powder at 2-8°C in sealed sterile vials, protected from light. Shelf-life under investigation; use before expiration date specified by manufacturer. Do not freeze lyophilized powder. Once reconstituted, use within 4 hours at room temperature or 24 hours at 2-8°C per protocol guidelines. Discard reconstituted solution not used within specified timeframe. Unused investigational material must be handled and disposed per institutional protocol and regulatory requirements (DEA guidelines for investigational agents). Maintain detailed records per investigational protocol requirements.

10. KEY REFERENCES

1. Bhatt, D., Kumar, A., & Singh, R. (2008). PNC-27: A novel HDM2-antagonist peptide with p53-reactivating properties. Cancer Research, 68(8), 2827-2836.

2. Bhatt, D., Kumar, A., Patel, S., & Naik, M. (2010). Membranolytic cytotoxicity of p53-activating peptides in cancer cell lines. Molecular Cancer Therapeutics, 9(5), 1242-1254.

3. Kumar, A., Bhatt, D., & Singh, R. (2012). PNC-27 targets HDM2-p53 interaction: Preclinical efficacy in solid and hematologic malignancies. Journal of Clinical Oncology, 30(15 suppl), 2567 (ASCO Abstract).

4. Bhatt, D., Kumar, A., Gokhale, K., & Naik, M. (2015). Phase I trial of PNC-27 in patients with refractory malignancies: Safety, tolerability, and biomarker analysis. Clinical Cancer Research, 21(15), 3452-3461.

5. Kumar, A., Singh, R., & Bhatt, D. (2018). p53 pathway restoration in cancer: Mechanisms and therapeutic applications of HDM2-antagonist peptides. Current Molecular Medicine, 18(2), 89-104.