



# Breaking Through Oral Gene Delivery Barriers: Peptide Nanocarriers Delivering CAR Genes for Targeted Pancreatic Cancer Therapy

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A recently published study (Xin *et al.*, *Prog Biochem Biophys*, 2026, **53**(2): 431-441. DOI: 10.3724/j.pibb.2025.0508) addresses the therapeutic challenges of pancreatic ductal adenocarcinoma (PDAC) by innovatively developing an orally administered nanogene delivery system. Designed to achieve *in situ*, efficient delivery of chimeric antigen receptor (CAR) genes to tumor sites, this approach offers a novel strategy for CAR-macrophage (CAR-M) based immunotherapy. Its key highlights are as follows.

## 1 Conceptual innovation: revolutionizing the traditional CAR–M production process by pioneering a novel approach to *in vivo* engineering *via* oral administration

Current CAR-M therapies rely on complex, time-consuming *in vitro* cell modification and reinfusion. This study proposes and validates a novel paradigm for the targeted delivery of orally administered nanoparticles within the body. This strategy holds promise for significantly simplifying treatment protocols, reducing preparation costs and risks, and represents a major breakthrough in delivery methods for cell-based immunotherapies.

## 2 Exquisite delivery system design: combining high–efficiency payload delivery, stable transport, and active targeting capabilities

### 2.1 High–efficiency core

The cationic peptide carrier (PNP) efficiently

compresses the loaded CAR plasmid (pCAR) to form a nanoscale complex (PNP/pCAR) with excellent stability.

### 2.2 Key modification

Surface modification with  $\beta$ -glucan serves as the crowning touch.  $\beta$ -Glucan can be recognized by specific receptors on the surface of macrophages, enabling nanoparticles to target pancreatic tumor sites after oral administration.

### 2.3 Intelligent escape

The system demonstrates robust lysosomal escape capability within cells, ensuring CAR genes enter the cytoplasm and express effectively, thereby overcoming a critical bottleneck in nucleic acid delivery.

## 3 Comprehensive experimental validation system: multi–level confirmation of system effectiveness from cells to living organisms

### 3.1 Cellular level

Low toxicity, high uptake, and efficient transfection (with transfection rates superior to the commonly used reagent Lipofectamine 2000) were demonstrated in RAW 264.7 macrophages.

### 3.2 Animal level

In an orthotopic pancreatic cancer mouse model, *in vivo* imaging technology dynamically and visually demonstrated that orally administered  $\beta$ -glucan-modified nanoparticles specifically accumulated at pancreatic tumor sites. The expression of the reporter protein (GFP) was successfully detected within tumor

tissues, achieving full-process validation of the “oral administration-targeting-expression” pathway.

#### **4 Significant application potential: providing a key technological foundation for overcoming the challenges in PDAC treatment**

The fibrotic matrix and immunosuppressive microenvironment of PDAC represent major therapeutic barriers. The system developed in this study delivers CAR genes directly to tumor sites, aiming to *in situ* reprogram macrophages within the tumor microenvironment to acquire dual functions: tumor killing and immune microenvironment remodeling. Theoretically, this approach could more effectively overcome PDAC's defense mechanisms.

In summary, this study transcends conventional drug delivery frameworks, representing a cross-disciplinary innovation that integrates nanotechnology

and immunotherapy. It not only develops a novel nanodelivery platform but also has the potential to pioneer a more convenient and efficient “*in vivo* CAR-M” therapeutic model, opening an attractive new avenue for conquering intractable solid tumors such as pancreatic cancer. Future research should focus on evaluating its *in vivo* antitumor efficacy and long-term safety following loading with therapeutic CAR genes.

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