SunAct

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OncoVantage

Insights into global breakthroughs in cell-based therapies

IN-VIVO CAR ENGINEERING | KRAS G12D DEGRADER TRIAL | SMM EARLY TREATMENT APPROVAL | AI NANO LIQUID BIOPSY

Programmable *In-Vivo* Hematopoietic Stem Cell (HSC) Engineering via Virus-Like Particles Produces Lineage-Specific Multiplexed CAR Effector Cells for Robust Tumour Control

This study demonstrates a novel *in-vivo* multicellular CAR therapy in which hematopoietic stem cells (HSCs) are genetically engineered directly in the body using a high-capacity virus-like particle (VLP) platform to generate lineage-restricted HER2 CAR macrophages, CAR-NK cells, and CAR-T cells. By targeting CD46-expressing primitive HSCs and enabling stable transgene integration, a single *in-vivo* intervention produced durable, multi-lineage CAR immune cells for at least five months, with evidence of long-term HSC engraftment shown by secondary transplantation. Functionally, these HSC-derived CAR-M, NK, and T cells cooperated to infiltrate tumours, remodel the tumour micro-environment, and suppress solid tumour growth in immunocompetent models.

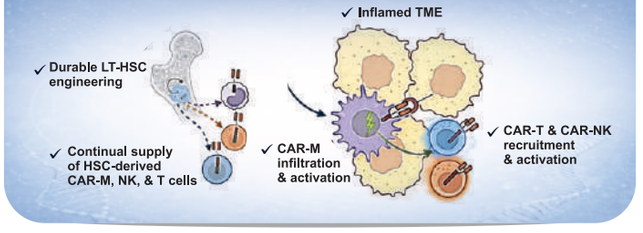
Clinical Implications

- **Durable efficacy:** Self-renewing HSCs act as a long-term reservoir of CAR immune cells, supporting sustained anti-tumour activity without repeated dosing.
- **Improved solid tumour control:** Combined CAR-M, CAR-NK, and CAR-T activity addresses poor trafficking, immunosuppressive TME, and antigen heterogeneity.
- **Reduced manufacturing burden:** Eliminates complex *ex-vivo* cell production and may reduce or even avoid the need for lymphodepletion.
- **Broader patient access:** An *in-vivo*, off-the-shelf–like approach could significantly lower cost and expand eligibility.

Why It Matters

- **Durable multi-lineage immunity:** HSC-derived CAR-M, CAR-NK, and CAR-T cells co-operate for long-term solid tumour control.
- **Overcomes major solid tumour barriers:** Addresses poor trafficking, immunosuppressive TME, and limited persistence.
- **Simplified and scalable therapy:** *In-vivo* engineering bypasses complex *ex-vivo* manufacturing, lowering cost and expanding patient access.
- **Potential paradigm shift:** Converts the patient's hematopoietic system into a renewable source of anti-tumour immunity.

***In-vivo* engineering of HSC to generate multi-lineage CAR immune cells**



Reference: Zhao Y *et. al. J Immunother Cancer* 2025;13(Suppl 2)

Phase 1/2 Study of ARV-806, A Proteolysis Targeting Chimera (PROTAC) KRAS G12D Degrader, in KRAS G12D Mutated Advanced Solid Tumours, including Pancreatic Cancer

ARV-806 is a first-in-class proteolysis targeting chimera (PROTAC) designed to selectively degrade KRAS G12D, the most prevalent KRAS mutation in cancer and a major unmet need in pancreatic ductal adenocarcinoma (PDAC). Unlike conventional KRAS inhibitors, ARV-806 induces proteasomal degradation of both GTP- and GDP-bound KRAS G12D. Robust preclinical activity including >25-fold higher anti-proliferative potency versus existing KRAS inhibitors and tumour regressions in xenograft and PDX models supports clinical evaluation. The ongoing first-in-human, multicentre phase 1/2 trial (NCT07023731) is assessing safety, pharmacokinetics, and preliminary efficacy in KRAS-G12D-mutant advanced solid tumours, with phase 2 focused on previously treated pancreatic ductal adenocarcinoma (PDAC).

Clinical Implications

- **Addresses a critical unmet need:** Currently, there are no approved therapies for KRAS G12D-mutant cancers, particularly PDAC.
- **Mechanistic advantage:** Degradation (not inhibition) of KRAS G12D may overcome limitations of target occupancy and signalling rebound.
- **Broad applicability:** Potential utility across pancreatic, colorectal, and lung cancers harbouring KRAS G12D.
- **Favourable dosing paradigm:** Low-dose IV, intermittent schedules with strong preclinical efficacy.

Why It Matters

- **Novel breakthrough strategy:** ARV-806 uses targeted protein degradation to eliminate KRAS G12D, overcoming a major limitation of traditional KRAS inhibitors.
- **High clinical relevance:** It addresses a critical unmet need in KRAS G12D–mutant cancers, particularly pancreatic ductal adenocarcinoma, where no targeted therapies exist.
- **Strong translational potential:** Compelling preclinical efficacy and a rational phase 1/2 design position ARV-806 as a potentially first-in-class therapy if clinical benefit is confirmed.

Reference: Murciano-Goroff YR, *et al J Clin Oncol.* 2026;44(2_suppl): TPS792

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First Approved Treatment for Smouldering Multiple Myeloma on January 27, 2026

On January 27, 2026, daratumumab and hyaluronidase (Darzalex Faspro) became the first FDA-approved therapy for high-risk smouldering multiple myeloma (SMM). SMM has historically been managed with observation alone despite a substantial risk of progression to active multiple myeloma. This approval marks a major Shift toward early therapeutic intervention. Daratumumab, an anti-CD38 monoclonal antibody, induces immune-mediated death of malignant plasma cells, while hyaluronidase enables subcutaneous delivery by enhancing tissue permeability, improving convenience and feasibility for long-term treatment in asymptomatic patients.

Why It Matters

- **First-in-class milestone:** DARZALEX FASPRO® is the first approved therapy for high-risk smouldering multiple myeloma.
- **Shift to early intervention:** Validates disease-interception as a new paradigm in multiple myeloma management.
- **Clinical impact:** Offers a well-tolerated, targeted option that may meaningfully delay progression to active disease.

Clinical Implications

- **Practice-changing approval:** Introduces active treatment for high-risk SMM, replacing watchful waiting in a defined patient population.
- **Disease interception strategy:** Early targeting of CD38-positive clonal plasma cells may delay or prevent progression to symptomatic multiple myeloma.
- **Patient-friendly regimen:** Subcutaneous administration supports outpatient use and better adherence in asymptomatic individuals.

Reference: AACR, FDA Approvals in Oncology: October-December 2025

Intelligent Nano-Fingerprinting: An Efficient and Precise Approach for Liquid Biopsy

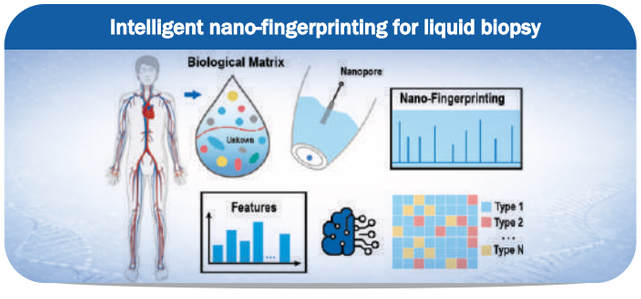
A group of scientists at the Zhejiang University, China has developed a novel technology for disease detection using liquid biopsy. This work introduces an intelligent nano-fingerprinting strategy for liquid biopsy that leverages single-molecule nano-pore technology combined with AI-based classification to analyse complex plasma matrices holistically. Instead of targeting predefined biomarkers, the approach captures global molecular fingerprints of blood in a label-free, amplification-free, and minimal-processing manner. Using only microlitre-scale volumes and simple dilution, nano-pore signals reflecting the intrinsic molecular heterogeneity of plasma are generated and accurately classified by intelligent algorithms, enabling efficient and potentially scalable disease detection.

Why It Matters

- **Addresses a core limitation of liquid biopsy:** Overcomes the specificity and information-loss issues inherent to single-biomarker and heavily processed multi-omics approaches.
- **Captures system-level biology:** Reflects the true molecular complexity of blood as an integrated network rather than isolated components.
- **Enables early and accessible detection:** The simplicity and efficiency of nanopore-AI profiling lower barriers to clinical adoption, supporting earlier intervention and better allocation of healthcare resources.

Clinical Implications

- **Holistic diagnostics:** Moves beyond single or multi-biomarker assays to capture integrated molecular changes that better reflect systemic disease states.
- **Simplified workflow:** Eliminates complex extraction, enrichment, and multi-omics preprocessing, reducing variability, cost, and sample requirements.
- **Scalable screening potential:** Label-free, low-volume, and rapid testing makes it suitable for large-scale population screening and longitudinal monitoring.
- **Adjunct to precision medicine:** Can complement existing diagnostics to improve early detection, stratification, and understanding of disease mechanisms.



Reference: Yuxin Yang *et. al.*, 2026 physics.bio-ph doi.org/10.48550/arXiv.2601.11947

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