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HIGHLIGHT

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Innovative integration of plant photosynthetic system for targeted restoration of NAD+/NADPH imbalance in acute kidney injury

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Acute kidney injury (AKI) is a life-threatening clinical syndrome characterized by metabolic imbalance of renal proximal tubular cells (PTCs), including ATP depletion, nicotinamide adenine dinucleotide (NAD+) deficiency, and NADPH exhaustion, and current therapies such as NAD+ precursors fail to address this multi-target metabolic disorder. This highlight integrates two innovative plant photosynthesis-based systems—nanothylakoid units coated with chondrocyte membranes (CM-NTU, Chen *et al.*, *Nature*, 2022, **612**, 546–554) and ultrasound-responsive thylakoid-integrating liposomes (LipTk-AA, Lei *et al.*, *Nat Biomed Eng.*, 2025, **9**(10), 1740–1757)—to propose a synergistic fused platform that overcomes the limitations of individual systems. By combining CM-NTU's modular membrane camouflage and light-driven NADPH/ATP production with LipTk-AA's ultrasound deep-tissue activation and NAD+ *de novo* synthesis, the fused system achieves precise targeting, spatiotemporal control, and comprehensive metabolic repair encompassing ATP, NAD+, and NADPH; we elaborate on their metabolic cross-talk, material design, and clinical translation prospects, highlighting how this fusion drives the field of metabolic-regulatory therapy beyond single-system capabilities.

Acute kidney injury (AKI) is a common and fatal clinical syndrome that occurs frequently in hospitalized patients, often leading to high mortality rates and adverse outcomes, such as progression to chronic kidney disease (CKD), which significantly increases the disease burden.[1] The core pathology of AKI lies in the metabolic imbalance of PTCs—mitochondrial dysfunction impairs the tricarboxylic acid (TCA) cycle to reduce ATP generation, enhanced glycolysis and the inhibited pentose phosphate pathway (PPP) cause reactive oxygen species (ROS) accumulation, and diminished NAD+ biosynthesis due to downregulated quinolinate phosphoribosyltransferase (QPRT) further disrupts redox homeostasis, creating a "metabolic vicious cycle" that current therapies cannot break.[2,3] NAD+ and NADPH are central to resolving this cycle: NAD+ activates sirtuin 1 (SIRT1)/peroxisome proliferator-activated receptor-γ coactivator 1α (PGC1α) to repair mitochondria and drive ATP synthesis, while NADPH regenerates glutathione (GSH) to scavenge ROS, and their cross-talk is critical—NAD+ serves as a precursor for NADPH *via* NAD kinase (NADK)-catalyzed phosphorylation, and NADPH protects NAD+ from oxidative degradation. In AKI, NAD+ depletion directly reduces NADPH production, and ROS-induced NAD+ degradation exacerbates this imbalance, making dual targeting of NAD+/NADPH essential for effective therapy.[4–6] Plant photosynthesis provides a natural prototype for metabolic repair: light-driven electron transport in thylakoid membranes reduces NAD+ to NADPH (photosystem I) and synthesizes ATP (ATP synthase), maintaining redox and energy homeostasis,[7,8] and by engineering thylakoid components into nanocarriers, we can replicate this process in mammalian cells to directly correct metabolic defects.

Based on the above research background, recent innovative therapies such as the plant-based photosynthetic system developed by Pengfei Chen *et al.* (2022)[9] and the ultrasound responsive liposome strategy proposed by Yao Lei *et al.* (2025)[10] provide new intervention methods for targeting NAD+/NADPH imbalance. Chen *et al.*'s research focuses on enhancing light driven synthetic metabolism, attempting to compensate for energy deficiency by improving cellular basal metabolic functions. Lei *et al.* focused on targeted delivery of mitochondrial

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repair and NAD+ biosynthesis, aiming to restore the redox homeostasis of renal tubular cells. The emergence of these new strategies provides new possibilities for correcting the metabolic imbalance of NAD+/NADPH in the pathological process of AKI. This Highlight focuses on the synergistic fusion of two plant-derived systems (CM-NTU and LipTk-AA), demonstrating how their complementary strengths address AKI's multi-target disorder better than individual strategies or traditional therapies.

Chen *et al.* (2022)[9] developed CM-NTU, a nanosized system based on spinach-derived nanothylakoid units (NTUs) coated with chondrocyte membranes (CM), to improve cell anabolism in osteoarthritis (OA), with its material design enabling targeted delivery and light-driven metabolic regulation: NTUs, isolated from spinach thylakoids *via* ultrasound homogenization and extrusion through 100-nm polycarbonate membranes, retain photosynthetic proteins and catalyze light-dependent ATP/NADPH production, while the CM coating, prepared *via* physical extrusion of CM (isolated from chondrocytes) and NTUs through 1000/400/200 nm membranes, retains vesicle targeting and membrane fusion proteins to enable homologous fusion with chondrocytes, achieving higher uptake than lipid nanoparticle-coated NTUs and avoiding lysosomal degradation. In OA models, CM-NTU combined with red light restores ATP/NADPH in degenerated chondrocytes, upregulates extracellular matrix (ECM) synthesis, and downregulates degradation (Fig. 1), but it has limitations: light penetration restricts deep-tissue use (*e.g.*, kidneys) and it lacks NAD+ synthesis capacity, critical for AKI's NAD+ deficient microenvironment.

Lei *et al.* (2025)[10] developed LipTk-AA, ultrasound-responsive liposomes integrating spinach thylakoid fragments (Tk) and L-ascorbic acid (AA), to target AKI's metabolic imbalance, with its material design optimizing deep-tissue delivery and multi-metabolite repair: liposomes are prepared *via* thin-layer evaporation of lipids with Tk fragments and AA, where Tk retains QPRT and photosynthetic electron transport proteins, and the lipid coating enhances accumulation in injured kidneys *via* the enhanced permeability and retention (EPR) effect, while ultrasound excitation of chlorophyll a (Chla) in Tk triggers electron transfer from AA to NAD+ to form NADH, which restores ATP *via* the malate-aspartate shuttle (MAS) bypassing impaired TCA cycles, and AA redirects glycolysis to PPP to boost NADPH. In cisplatin-induced AKI mice, LipTk-AA combined with ultrasound reduces serum creatinine (CRE) and blood urea nitrogen (BUN) to near-normal levels, inhibits PTC apoptosis, and prevents AKI-to-CKD transition (Fig. 2), yet it lacks active targeting (relying on passive EPR) and its NADPH production is constrained by PPP efficiency in severely injured PTCs. As summarized in Table 1, the two systems exhibit striking complementarity: CM-NTU's modular membrane camouflage resolves LipTk-AA's lack of active targeting, while LipTk-AA's ultrasound activation overcomes CM-NTU's deep-tissue penetration barrier. Metabolically, CM-NTU's light-driven direct NADPH production complements LipTk-AA's PPP-constrained NADPH supply, and LipTk-AA's QPRT-mediated NAD+ synthesis fills CM-NTU's gap in NAD+ generation. This complementarity serves as the foundational rationale for a fused system, where integrating their core strengths would enable precise cell targeting, deep-tissue activation, and comprehensive metabolic repair (ATP/NAD+/NADPH) unattainable by either system alone.

The fusion of CM-NTU and LipTk-AA is a paradigm shift that resolves individual limitations, integrating modular targeting, dual activation, and multi-metabolite supply to achieve comprehensive metabolic repair for AKI. A major bottleneck in metabolic nanotherapeutics is balancing ''cell-specific targeting'' and ''deep-tissue activation'': CM-NTU's membrane camouflage enables precise targeting but relies on light with poor deep penetration, while LipTk-AA's ultrasound activation reaches deep organs but lacks active targeting. The fused system addresses this by coating LipTk-AA with PTC-derived membranes (sourced from healthy donors or induced pluripotent stem cells, iPSCs), a strategy validated by CM-NTU's chondrocyte membrane camouflage, enhancing PTC uptake and reducing off-target accumulation in the liver/spleen while retaining ultrasound activation to trigger AA electron transfer for NADH/ATP production in deep renal tissue,[11] a critical synergy for AKI as PTCs are the primary injured cells and active targeting lowers the required dose to reduce potential toxicity. NADPH depletion in AKI arises from NAD+ deficiency (reducing NADK activity) and PPP inhibition (limiting glucose flux), with individual systems addressing only one cause: CM-NTU produces NADPH *via* photosynthesis bypassing PPP but lacks NAD+ support, and LipTk-AA boosts NADPH *via* PPP but is constrained by NAD+ levels. The fused system combines direct photosynthetic NADPH from CM-NTU's NTUs and intrinsic PPP NADPH from LipTk-AA's AA—NTUs integrated into LipTk-AA produce NADPH under red light bypassing impaired PPP, while AA inhibits glycolysis and activates PPP to increase key metabolites in AKI PTCs—markedly enhancing NADPH levels, reducing ROS, and inhibiting PTC apoptosis compared to either

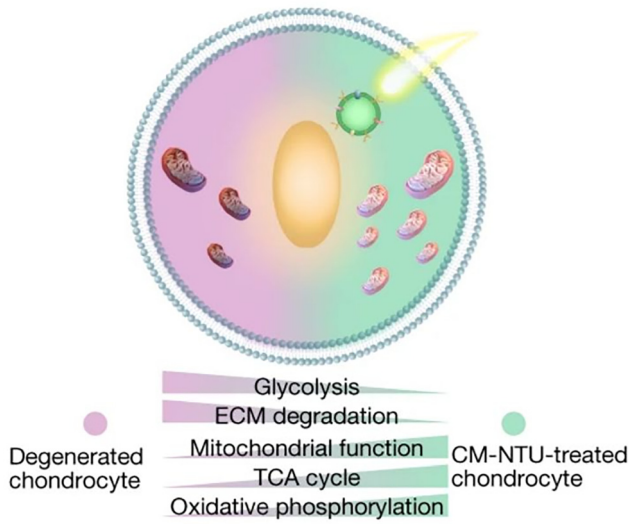

Fig. 1 Schematic diagram of CM-NTU-driven metabolic reprogramming in degenerated chondrocytes.

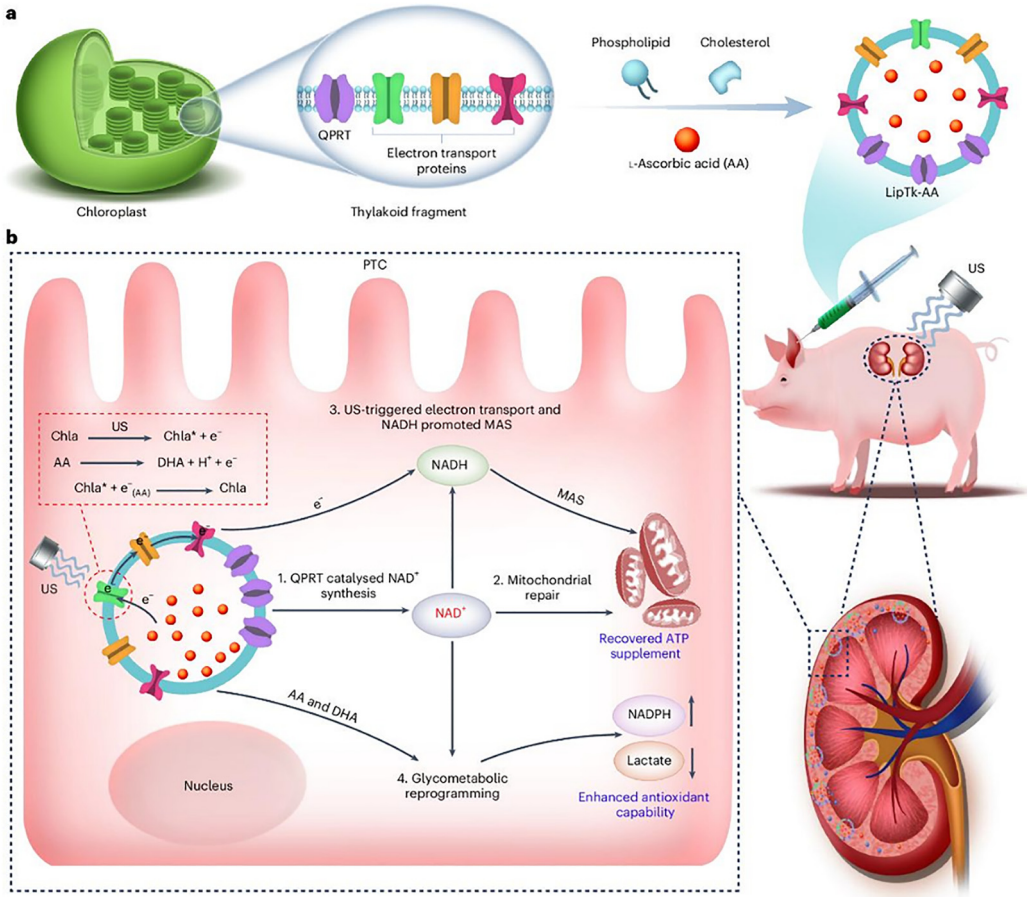

Fig. 2 (a) Preparation of LipTk-AA. (b) Mechanism of LipTk-AA boosted NAD+ generation and NAD+ centred metabolic reprogramming under US condition.

Table 1 Compares the key dimensions of these two systems

Comparison dimension	CM-NTU (Chen *et al.*, 2022)[9]	LipTk-AA (Lei *et al.*, 2025)[10]
Core design	Spinach-derived nanothylakoid units (NTUs) coated with chondrocyte membranes (CM)	Spinach thylakoid fragments (Tk) integrated into ultrasound-responsive liposomes, loaded with L-ascorbic acid (AA)
Activation mode	Red light (630 nm, 80 μmol photons m^{-2} s^{-1})	Ultrasound (1 W cm^{-2}, 5 min)
Targeting strategy	Modular homologous cell membrane camouflage (chondrocyte membrane); mediates homologous fusion with target cells	Passive targeting *via* enhanced permeability and retention (EPR) effect in injured kidneys; no active cell-type recognition
Key metabolites produced	ATP, NADPH (light-driven direct synthesis)	NAD+ (QPRT-catalyzed *de novo* synthesis), ATP (malate-aspartate shuttle), NADPH (pentose phosphate pathway activation)
Core Advantages	High biocompatibility (CM camouflage reduces macrophage clearance)	Deep-tissue penetration (ultrasound avoids light limitation)
	Modular membrane design for cell-type specificity	NAD+ synthesis addresses AKI-specific deficiency
	Light-controllable on/off metabolite production	Multi-pathway metabolic regulation (NAD+/ATP/NADPH)
Inherent limitations	Poor deep-tissue penetration (light cannot reach organs like kidneys)	Lack of active targeting (relies on passive EPR)
	No NAD+ synthesis capacity	NADPH production constrained by intrinsic PPP activity in severely injured cells
	Limited to superficial tissue diseases (*e.g.*, osteoarthritis)	Dependence on ultrasound equipment
Applicable disease models	Osteoarthritis (OA, superficial connective tissue disease)	Acute kidney injury (AKI, deep organ disease); effective in cisplatin/sepsis/rhabdomyolysis-induced AKI models

system alone. AKI's metabolic disorder requires targeting three core nodes: ATP (energy), NAD+ (mitochondrial repair), and NADPH (antioxidant), which individual systems fail to cover, while the fused system achieves "full-network repair" by integrating ultrasound-activated MAS (from LipTk-AA) and light-driven photosynthesis (from CM-NTU) for ATP production, QPRT-catalyzed *de novo* synthesis (from LipTk-AA) plus NADPH protection (from CM-NTU) for NAD+ homeostasis, and dual NADPH sources for antioxidant defense, activating downstream protective signals such as SIRT1/PGC1α and NRF2 to prevent AKI progression to CKD. The fused system's efficacy also relies on reinforcing NAD+/NADPH cross-talk: restored NAD+ activates NADK to convert NAD+ to NADPH, enhancing PPP-derived NADPH, and NADPH regenerates GSH to scavenge ROS and prevent NAD+ degradation *via* oxidative stress, breaking AKI's metabolic vicious cycle and making dual targeting far more effective than single-pathway strategies

The fused system's success relies on advanced material engineering that aligns with the core focus of relevant fields on functional nanomaterials. The fused system's success depends on advanced material engineering aligning with *Journal of Materials Chemistry B*'s focus on functional nanomaterials. For targeting, CM-NTU's CM coating—isolated from chondrocytes *via* centrifugation and validated by western blot—retains membrane fusion proteins that mediate homologous fusion with chondrocytes, while the fused system's PTC coating, isolated from human PTCs *via* the same protocol, retains proximal tubular markers and targeting proteins to enhance PTC-specific uptake, and this modular design allows swapping membranes for other diseases such as astrocyte membranes for neurodegeneration or muscle satellite cell membranes for myopathy. For spatiotemporal control, the fused system integrates dual responsive mechanisms: red light activates photosystem II in NTUs to trigger electron transport for ATP/NADPH production in a strictly light-dependent manner enabling on/off control, and ultrasound excites Chla to transfer electrons from AA to NAD+ forming NADH, avoiding off-target activation and ensuring deep-tissue efficacy, providing flexibility for use in superficial tissues (*e.g.*, OA with light) or deep organs (*e.g.*, kidneys with ultrasound).

The fused system outperforms traditional NAD+ precursors (*e.g.*, nicotinamide riboside, NR; nicotinamide mononucleotide, NMN) in effectiveness, targeting, and safety: it directly produces ATP/NAD+/NADPH bypassing impaired metabolic pathways in AKI, achieves higher restoration of normal metabolite levels compared to precursors that rely on cellular metabolism, offers active membrane coating for enhanced PTC uptake *versus* systemic distribution of precursors, requires a much lower dose to reduce adverse effects, and shows no organ toxicity in preclinical studies unlike high-dose precursors that may burden the liver.[12] Several potential barriers exist but have feasible solutions: scaling high-purity thylakoid isolation requires standardization, which Lei *et al.*[10] (2025) optimized *via* ultrasound homogenization and extrusion to achieve low batch-to-batch variation; plant-derived components may trigger immune responses, but CM/lipid coating reduces macrophage uptake and avoids elevating pro-inflammatory cytokines; and thylakoid proteins may induce antibodies, though preclinical studies show no antibody production after repeated doses. The fused system is highly replicable due to accessible materials (commercially available spinach thylakoids, lipids, and cell membranes isolated *via* standard centrifugation), established protocols for NTU preparation, LipTk-AA synthesis, and membrane coating from both cited studies, and routine techniques for quality control such as dynamic light scattering for particle size, assay kits for chlorophyll content, and ELISA for QPRT activity. Clinical translation prospects are promising: preclinical studies show no toxicity in mice and piglets with normal structure of major organs confirmed by H&E staining, red light and ultrasound devices are clinically approved for other applications ensuring accessibility, and trial design can proceed with Phase I trials in healthy volunteers to assess safety followed by Phase II trials in AKI patients to evaluate CRE/BUN reduction and PTC protection.

The synergistic fusion of CM-NTU and LipTk-AA creates a universal metabolic-regulatory platform that overcomes the limitations of individual systems, integrating modular membrane targeting, dual light/ultrasound activation, and multi-metabolite supply to resolve AKI's multi-target disorder and break the NAD+/NADPH metabolic vicious cycle. Future directions include combining the system with gene editing to deliver CRISPR-Cas9 for knocking down CD38 (a NAD+ consuming enzyme) to enhance NAD+ retention, optimizing activation *via* developing near-infrared (NIR)-responsive NTUs for deeper penetration and self-powered ultrasound devices for point-of-care use, and expanding to other diseases by adapting the platform to OA (chondrocyte coating + light) and neurodegeneration (astrocyte coating + ultrasound). While limitations remain—such as light penetration for deep tissues and ultrasound equipment dependence—this fusion represents a transformative step toward precision metabolic therapy, offering new hope for AKI and other degenerative diseases.

Author contributions

Jinxin Zhang: conceptualization, data curation, investigation, writing – original draft, writing – review & editing. Jihong Chen: conceptualization, funding acquisition, supervision, writing – review & editing. Pengfei Zhang: funding acquisition, supervision, writing – review & editing.

Conflicts of interest

There are no conflicts to declare.

Data availability

This study was carried out using publicly available data from A plant-derived natural photosynthetic system for improving cell anabolism Nature at https://doi.org/10.1038/s41586-022-05499-y and NAD+ biosynthesis and mitochondrial repair in acute

kidney injury *via* ultrasound-responsive thylakoid-integrating liposomes Nature Biomedical Engineering at https://doi.org/10.1038/s41551-025-01402-y.

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