Supplementary Table S1. Detailed Preclinical Evidence for Nanomedical Strategies in Calcium Oxalate Stone Models

This table provides the detailed formulation, model, dosing, comparator, efficacy, targeting, safety, and limitation data underlying the concise comparison in Table 1 of the main manuscript.

Platform, formulation, and size	Model, route, dose, and timing	Key comparators	Principal outcomes and carrier contribution	Targeting, safety, and interpretation
NM@CPBzyme [8] Biomimetic antioxidant nanozyme Neutrophil-membrane-coated citrate-modified Prussian blue nanozyme; core ~37 nm; hydrodynamic diameter ~50 nm (CPBzyme ~40 nm). Zeta potential: -20.1 +/- 3.1 mV (CPBzyme: -32.5 +/- 0.4 mV).	Male C57BL/6J mice; glyoxylate (Gly) 75 mg/kg i.p. daily on days 1-7; acute CaOx nephrocalcinosis/crystal-injury model. 2 mg/kg i.v. (tail vein) on days 2, 4, and 6; assessed on day 8. Intervention occurred during crystal induction (preventive/early therapeutic design).	PBS; Gly; Gly + PBzyme; Gly + CPBzyme (all nanoparticles 2 mg/kg).	Versus Gly and precursor controls, NM@CPBzyme most strongly reduced polarized-light/Von Kossa crystal burden, PAS tubular injury, OPN/KIM-1/gamma-H2AX, renal ROS, NETosis, and NLRP3-caspase-1-GSDMD pyroptosis. The stepwise PBzyme -> CPBzyme -> NM@CPBzyme comparison supports contributions from citrate modification and membrane coating, although most in vivo results were reported as relative/semiquantitative rather than absolute effect sizes.	Cy5.5 signal peaked at 6 h; membrane coating increased injured-kidney/proximal-tubule accumulation and reduced off-target liver signal relative to CPBzyme. Daily 2-10 mg/kg i.v. for 7 days caused no reported major-organ histology, blood-count, ALT/AST, BUN/creatinine, or hemolysis abnormality. Limitation: one short glyoxylate mouse model; no formed-stone clearance, recurrence, long-term safety, or clinical data.
Se@CQ [9] Drug-loaded selenium nanoparticle Chloroquine encapsulated in chitosan-stabilized selenium nanoparticles; spherical, ~80 nm; measured CQ concentration 1.015 mg/mL from a theoretical 2 mg/mL (~50.8% loading by concentration).	Two models: (1) C57BL mice, Gly 65 mg/kg i.p. daily for 7 days; (2) male SD rats, 1% ethylene glycol (EG) in drinking water for 4 weeks plus 1% NH4Cl (2 mL) on days 1-3 and 15-17. Mouse: Se@CQ 40 microg/kg i.p. on days 0, 2, 4, and 6. Rat: Se@CQ 90 microg/kg by oral gavage every other day from day 0 to day 28; assessed day 29. Both were concurrent/preventive regimens.	Model controls; Se-NPs at matched Se@CQ dose; free CQ (2 mg/kg in mice; 45.6 mg/kg in rats).	Se@CQ outperformed Se-NPs and free CQ in reducing tubular injury, CaOx crystal deposition, KIM-1, MCP-1/F4/80 recruitment, NF-kappaB/NLRP3/ASC/caspase-1 signaling, IL-1beta, OPN, and CD44. In vitro viability reached 86.46% at 25 micromol/L Se@CQ after oxalate injury. Component controls support an added formulation-specific benefit over either component alone, but formal pharmacological interaction or synergy was not tested and no clinical stone endpoint was evaluated.	Oral ICG-Se@CQ reached kidney by 12 h; pharmacokinetic study after 10 mg/kg i.v. estimated t1/2 ~58 h. No group differences were reported for liver indices, serum ions, or major-organ histology. Important reporting issue: biodistribution dose is 40 microg/kg in Methods but 80 microg/kg in Results. No long-term accumulation study or treatment of established stones.
RBCM@CeO2/TAK-242 [10] | ROS-responsive biomimetic combination | RBC-membrane-coated CeO2 nanozyme containing the TLR4 inhibitor TAK-242; H2O2-responsive release; hydrodynamic size approximately 107 nm; zeta potential -10.90 mV (RBC membrane: -10.49 mV).	C57BL/6J mice; Gly 75 mg/kg i.p. daily for 7 days; acute CaOx nephrocalcinosis model. Equivalent to CeO2 5 mg/kg and TAK-242 1 mg/kg i.v. (200 microL) on days 2, 4, and 6; assessed day 8. Intervention occurred during induction.	Saline; CeO2; TAK-242; uncoated CeO2 + TAK-242; RBCM@CeO2/TAK-242.	The coated combination reduced CaOx deposition, PAS/TUNEL injury, KIM-1/NGAL, NOX2/IL-1beta/ROS, TNF-alpha/IL-6, and M1 markers while increasing M2 markers; it also inhibited TLR4/NF-kappaB. The uncoated combination and single-component arms support added value of co-delivery/coating, but exact between-group effect sizes were not consistently reported in text.	Cy5 studies showed greater injured-kidney fluorescence than CeO2 alone and than coated particles in healthy mice. RBC membrane supports prolonged circulation/immune evasion; it is not itself evidence of leukocyte-like inflammatory homing. Short-term histology and renal/hepatic indices were unremarkable at tested concentrations (exact safety doses NR in text). Limitation: one acute model, limited pharmacokinetic/immune characterization, and no long-term safety.

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MOF-818 [11] Antioxidant metal-organic-framework nanozyme Cu/Zr-based MOF-818 with SOD- and CAT-like activity; octahedral; average diameter 220 nm.	Male SD rats; 1% EG in drinking water for 3 weeks plus 1% NH4Cl by gavage (2 mL/day) during the first 3 days of weeks 1 and 3. MOF-818 0.5 or 1.5 mg/kg by oral gavage daily (2 mL/animal/day) throughout the 3-week model; concurrent preventive regimen.	Normal control; EG + NH4Cl model; model + two MOF doses; healthy + MOF-818 0.5 mg/kg.	Renal tubular injury score fell from 3.50 +/- 0.51 in the model to 2.73 +/- 0.45 and 1.03 +/- 0.32 at 0.5 and 1.5 mg/kg, respectively; the 1.5 mg/kg arm also markedly reduced Pizzolato-positive crystals, apoptosis, creatinine/BUN, TIM-1/OPN/CD44, TNF-alpha/IL-6, and M1 polarization while increasing SOD/CAT and M2 polarization. Dose response was demonstrated, but there was no standard-drug comparator.	ICG-labeled MOF-818 reached kidney by ~2 h after gavage and was largely metabolized by 60 h. Major-organ histology, serum ALT/ALB/TP/ions, and Cu/Zr measurements did not indicate cumulative toxicity over 3 weeks. Limitation: one preventive rat model, no component/active comparator, and no long-term metal fate or human data.
PDA@PPy@HA nanomotor (PYA) [12] NIR-driven active renal delivery Polydopamine/polypyrrole core with hyaluronic-acid surface; average particle size ~200 nm; zeta potential -17.7 mV.	Male C57BL/6J mice; Gly 80 mg/kg i.p. daily on days 1-7; acute renal CaOx crystal-deposition model. PYA 3 mg/kg i.v. on days 2, 4, and 6; NIR applied to the kidney region ~1 h after injection (808 nm, 0.5 W reported for targeting experiments); assessed day 8. Concurrent intervention.	Control; healthy + PYA; Gly; Gly + PYA; Gly + PYA + NIR.	PYA reduced crystal deposition, tubular injury/apoptosis, BUN/creatinine, ROS/NOX2, and OPN/CD44 while restoring antioxidant and mitochondrial indices; NIR activation further improved renal enrichment and efficacy versus PYA alone, supporting a propulsion contribution. No free-drug comparator applies because the material itself is therapeutic.	HA-CD44 interaction plus NIR propulsion increased injured-kidney uptake; Cy5 signal was present in kidney by 1 h and diminished substantially by 24-48 h. Repeated 3 mg/kg i.v. every other day for 7 days caused no reported organ-histology or ALT/AST/BUN/creatinine abnormality. Limitations acknowledged by authors: ~200-nm size, only 7-day safety, external irradiation requirement, and preclinical proof-of-concept stage.
ZnO@CP nanoemulsion [13] Plant-extract/lipid-coated ZnO formulation ZnO nanoparticles coated with Cymbopogon proximus extract/lipid layer; TEM mean 142.35 nm; DLS 145.8 nm; PDI 0.281; zeta potential -23.4 mV.	Male Wistar rats (250-270 g; n=6/group); 1% EG model for 4 weeks. ZnO@CP NEs 250 microg/mL orally in two daily administrations for 4 weeks, apparently concurrent with EG. Because administered volume/body-weight dose was not reported, systemic exposure cannot be reconstructed.	Saline; EG model; cystone 100 mg/kg; CP extract; unloaded ZnO NPs 200 microg/mL.	ZnO@CP NEs reduced urinary crystal density and improved renal histology and serum indices versus untreated EG rats. Reported creatinine/urea/uric acid were 0.95 +/- 0.01, 46.5 +/- 1.63, and 3.8 +/- 0.08 mg/dL, respectively; unloaded ZnO produced numerically lower values for these three markers, so superiority of the combined formulation was not established across outcomes. Crystal burden was shown mainly by representative images rather than blinded quantitative morphometry.	No biodistribution, renal-targeting, clearance, or dedicated in vivo dose-ranging study. L929 viability remained ~76.9% at the highest tested concentration and efficacy-study histology/biochemistry suggested tolerability. Major limitations: concentration-based dosing without administered volume, internal CP-dose discrepancy (0.05 vs 5 mg/kg), limited quantitative crystal analysis, and no proof that coating adds efficacy over unloaded ZnO.
Ce-CDs@Cel [14] Drug-carrier-integrated carbon-dot nanodrug Cerium-doped glutathione carbon dots loaded with celastrol; Ce-CDs ~3 nm by FETEM and remained similar after loading; hydrodynamic diameter NR in main text.	C57BL/6J mice; Gly 75 mg/kg i.p. daily for 7 days; acute CaOx crystal-deposition model. Human CaOx stones were also tested ex vivo. Daily i.v. during the 7-day induction: Ce-CDs 100 mg/kg/day; Ce-CDs@Cel 100 mg/kg/day Ce-CDs + 3 mg/kg/day Cel; free Cel 3 mg/kg/day; assessed day 8.	Saline/Gly controls; Ce-CDs alone; free Cel; Ce-CDs@Cel; citrate comparator in the ex vivo dissolution experiment.	Ce-CDs@Cel outperformed either component in reducing crystal area, OPN, KIM-1, PAS injury, apoptosis, inflammation, and ferroptosis, supporting combined carrier and cargo activity. Ex vivo, Ce-CDs produced 6.02 +/- 0.50% human-stone weight loss, approximately twice that of equimolar potassium sodium hydrogen citrate. In vivo endpoints remained crystal deposition/injury, not expulsion of formed stones.	Ce6-labeled Ce-CDs accumulated in liver and kidney, with higher damaged-kidney retention and CaOx colocalization in model mice; biodistribution used 10 mg/kg tracer. A separate single-dose 175 mg/kg i.v. 14-day study showed 100% survival and no reported organ, blood-count, inflammatory, renal, or hepatic abnormality. Limitations: concurrent acute model, small safety cohorts, tracer-based targeting, and no chronic pharmacokinetic/toxicity or clinical validation.

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tFNA-polydatin (tFNA-P) [15] DNA nanocarrier targeting ferroptosis Polydatin complexed with tetrahedral framework nucleic acid; hydrodynamic diameter 18.17 +/- 2.2 nm (tFNA 14.21 +/- 1.2 nm); zeta potential -11.6 +/- 3.72 mV.	Male C57BL/6 mice; Gly 80 mg/kg i.p. daily for 7 days. Treatment began after crystals had been documented by day 3, creating a delayed-intervention acute crystal model rather than a clinical recurrence model. tFNA or tFNA-P, 80 microL of 1 micromol/L i.v., single dose starting on day 4; assessed day 8. Separate safety study: 80 microL of 1 micromol/L daily for 7 days.	Sham/model; polydatin alone; tFNA alone; tFNA-P; ferrostatin-1 in mechanistic experiments.	tFNA and tFNA-P reduced crystal area (both P<0.0001), whereas polydatin alone did not; polydatin and tFNA-P reduced tubular injury, whereas tFNA alone did not. tFNA-P gave the strongest renal-function protection and suppressed iron accumulation, lipid peroxidation, and ferroptosis. These complementary component effects support the rationale for conjugation.	Whole-body fluorescence peaked at 1 h, with predominant liver and secondary kidney accumulation; kidney sections showed proximal-tubule localization. Seven-day repeated dosing caused no reported blood-count, ALT/AST, BUN/creatinine, or major-organ histology abnormality. Limitations: short single-model study; no established-stone removal or true postsurgical recurrence; dose expressed as concentration/volume rather than mass exposure.
LEVNs [16] Naturally derived oral nanovesicles Lemon-derived extracellular vesicle-like nanoparticles; NTA mean ~165 nm; zeta potential -22.4 mV; citric acid content 16.70 +/- 2.67%.	EG-induced nephrolithiasis in rats. Early treatment began day 1; delayed treatment began day 14. Exact induction and treatment doses are reported in Supporting Information, not the supplied main article. Primarily oral gavage; early and delayed regimens; an i.v. LEVN arm was also tested. Exact dose/frequency: NR in the supplied main article.	EG model; early/delayed potassium citrate; early/delayed LEVNs; i.v. LEVNs.	Early oral LEVNs inhibited micro-CT/Von Kossa renal calcification more strongly than early potassium citrate and delayed treatments. In vitro, LEVNs shifted CaOx toward 55.06% COD, reduced crystal-cell adhesion to 25.7% (vs 64.6% with citric acid), lowered ICAM-1/VCAM-1 by 33.5%/53.8%, LDH release by 48.6%, and TNF-alpha/IL-6 by 50.6%/37.1%, while suppressing ER stress and restoring Ca2+/mitochondrial homeostasis.	After oral dosing, renal signal appeared at 1 h, peaked at 12 h, localized mainly to tubules, and retained FRET evidence of vesicle integrity. Supporting data reported no major-organ lesions or liver/electrolyte abnormalities. Limitations: exact regimen is NR in the supplied main article and full safety details require the Supporting Information; no vesicle-depleted or citrate-matched control, uncertain active cargo, one rat model, and no human efficacy.
HCeY [17] | ROS-responsive oral biomimetic delivery | HPBTEa-celastrol nanoparticles encapsulated in beta-glucan yeast microcapsules; spherical particles approximately 150 nm; numeric zeta potential NR in the article text.	C57BL/6 mice; glyoxylate model, days 1-7. HCeY was given by oral gavage at 3 mg/kg/day celastrol equivalent for 7 days and assessed on day 8. Treatment occurred during induction. Safety was evaluated at the same oral dose daily for 1 or 4 weeks in healthy mice.	Control; glyoxylate model; free celastrol; HCeY. Distribution controls included free ICG and macrophage depletion. Yeast-microcapsule-only and HCe controls were absent.	HCeY reduced intrarenal deposits, OPN, tubular injury, and KIM-1 more than free celastrol. Plasma celastrol Cmax and AUC were 14.7- and 3.16-fold higher, respectively. The absence of yeast-microcapsule-only and HCe controls limits attribution of the effect to individual carrier components.	Peyer's-patch uptake, F4/80-positive renal colocalization, and reduced kidney signal after macrophage depletion support a macrophage-associated transport contribution. Kidney fluorescence Cmax and AUC were 1.76- and 1.93-fold higher than those of free ICG. Four-week safety findings were unremarkable. No urine mass balance, long-term clearance, recurrence data, or human efficacy evidence was reported; preclinical.

Notes: CaOx, calcium oxalate; COD, calcium oxalate dihydrate; HCeY, HPBTEa-celastrol nanoparticles encapsulated in yeast microcapsules; i.p., intraperitoneal; i.v., intravenous; NIR, near-infrared; NR, not numerically reported in the supplied main article text; ROS, reactive oxygen species. 'Targeting' denotes comparative renal or lesion-associated distribution evidence; fluorescence signal alone does not establish intact-particle delivery or active molecular targeting. All platforms are at the preclinical stage.