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Targeting accelerated kidney ageing in chronic kidney disease: from senolytics to Klotho therapeutics

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Abstract

Chronic kidney disease (CKD) is accompanied by cellular changes that resemble accelerated ageing, including persistent senescence and loss of α-Klotho. Experimental studies connect these processes, but their causal relationship in human CKD remains uncertain. This Perspective evaluates senolytics, senomorphics and α-Klotho-directed therapies as distinct but potentially complementary strategies, and proposes phenotype-led development centred on renal target engagement, biomarkers and staged testing of monotherapy, combination and sequential approaches.

Accelerated kidney ageing: a drug-discovery challenge

Chronic kidney disease (CKD) is a growing global health burden. The Global Burden of Disease 2023 analysis estimated that 788 million adults were living with CKD in 2023, more than twice the number estimated in 1990; although population growth and ageing account for much of this increase, age-standardised prevalence also rose modestly over the same period.[1] CKD is clinically classified by cause, glomerular filtration rate and albuminuria,[2] a framework that captures disease severity and prognosis but not necessarily the cellular programmes that sustain injury or influence therapeutic response.

Contemporary nephroprotection has substantially changed the therapeutic landscape. Renin–angiotensin system blockade remains foundational, while sodium–glucose cotransporter 2 inhibitors, the non-steroidal mineralocorticoid receptor antagonist finerenone and glucagon-like peptide-1 receptor agonists can reduce kidney and cardiovascular risk across important CKD populations.[2–6] These advances show that CKD trajectories are modifiable, yet residual progression remains common and the biology underlying treatment response is only partly understood. In particular, it is uncertain to what extent current therapies modify persistent ageing-related cellular states rather than their downstream clinical consequences.

Accelerated kidney ageing provides one framework for addressing this unresolved biology. Chronically injured kidneys acquire features associated with ageing, including DNA damage, mitochondrial dysfunction, epigenetic alterations, impaired autophagy and reduced regenerative capacity.[7–11] Persistent cellular senescence and the senescence-associated secretory phenotype (SASP) can sustain inflammation, maladaptive repair and profibrotic signalling after injury.[10–12] Progressive nephron loss and uraemic and endocrine–metabolic disturbances may also contribute to systemic features of biological ageing, while chronological ageing reduces the reserve available for recovery from further kidney insults.[7,8]

Ageing-related mechanisms are therefore plausible drug targets, but “accelerated ageing” is not a single pathway. Persistent senescence may become maladaptive, whereas transient cell-cycle arrest can participate in tissue protection and repair.[10,13] The relevance of a given senescent-cell population is also likely to vary with renal compartment, disease stage and initiating injury. Drug development must

therefore move beyond the presence of an ageing-associated marker and establish that the targeted state is persistent, pathogenic and pharmacologically tractable.

Persistent tubular senescence and loss of the geroprotective protein α-Klotho offer a useful model in which to examine this problem. α-Klotho is central to FGF23-dependent mineral metabolism and has broader experimental links to oxidative stress, mitochondrial function, inflammation and fibrosis.[14–16] Senescence-associated pathways can suppress α-Klotho expression, while Klotho-directed interventions can attenuate several senescence-associated changes.[17–19] The two processes are therefore biologically connected, although a self-sustaining senescence–α-Klotho loop has not been demonstrated in human CKD.

This Perspective considers senolytics, senomorphics and α-Klotho-directed therapeutics as distinct but potentially complementary approaches to this biology. The central questions are when each strategy should be developed independently, when combination or sequencing becomes experimentally justified, and how renal target engagement can be distinguished from nonspecific improvement in kidney function or systemic inflammation.

Cellular senescence and α-Klotho loss converge in kidney ageing

α-Klotho is produced predominantly by renal tubular epithelial cells, with functional specialisation along the nephron. Its membrane-bound form is an essential co-receptor for fibroblast growth factor 23 (FGF23), regulating phosphate handling and vitamin D metabolism. Beyond this canonical role, experimental studies associate α-Klotho with lower oxidative stress, inflammation, mitochondrial dysfunction and profibrotic signalling, while renal α-Klotho expression declines with ageing and CKD progression.[14–16] These processes also intersect with cellular senescence, and experimental studies suggest reciprocal links between Klotho signalling and senescence-associated pathways.[17–19] Klotho loss may therefore contribute to impaired tubular homeostasis and reduced tissue resilience, although this remains incompletely defined in human CKD.

Cellular senescence is a stress response characterised by a durable loss of proliferative capacity despite continued cell viability and metabolic activity. Several senescence-associated features accumulate in ageing kidneys.[20] In rats, renal $p16^{INK4a}$ expression, lipofuscin and senescence-associated β-galactosidase activity increase with age,[21] while in human kidney cortex $p16^{INK4a}$ expression rises with ageing and associates with reduced proliferative activity, glomerulosclerosis, interstitial fibrosis and tubular atrophy.[22] None of these features, however, is specific for senescence when considered alone.

This distinction matters for drug discovery. $p16^{INK4a}$ and $p21^{CIP1}$ indicate cell-cycle arrest but do not by themselves establish a stable senescent state; lysosomal changes, persistent DNA-damage signals and SASP proteins can also occur in other forms of cellular stress. The SASP itself varies with cell type, initiating insult and time after injury. Current recommendations therefore favour multimarker definitions

that combine stable arrest with additional senescence-associated features while preserving information on cell identity and tissue context.[23,24]

The same caution applies in diseased kidneys. Increased $p16^{INK4a}$ expression has been reported in diseased native kidneys, deteriorating allografts and diabetic kidney disease,[25,26] but injury-associated transcriptional programmes can reproduce only part of a senescence phenotype. Single-cell and spatial analyses identify adaptive, maladaptive and degenerative epithelial populations within inflammatory and fibrotic niches.[27] These approaches enable cell type-resolved target discovery, but an injured transcriptional state should not be labelled senescent without independent evidence of durable arrest and additional senescence-associated features.

Tubular epithelial cells are particularly relevant because they are repeatedly exposed to metabolic, toxic and inflammatory stress yet can re-enter the cell cycle after injury. High phosphate, oxidative stress and mitochondrial dysfunction can promote senescence-associated phenotypes,[28] while p16-positive tubular cells in experimental diabetic kidney disease show altered glycolytic and mitochondrial metabolism.[29] WNT10B–β-catenin–FOXO6 signalling similarly shifts tubular metabolism away from fatty-acid oxidation while promoting inflammatory and fibrotic programmes.[30] These findings identify potentially druggable cell states, although their importance in human CKD remains uncertain.

Intervention studies provide stronger evidence that persistent senescence can contribute to maladaptive repair. Navitoclax improved tubular regeneration after ischaemia–reperfusion injury in aged or previously irradiated mice,[31] and targeting senescence attenuated defective repair and fibrosis after repeated cisplatin injury.[12] Manipulation of p16-positive cell populations also improved metabolic dysfunction and kidney injury in experimental diabetic kidney disease.[29] These effects remain context dependent, reinforcing the need to distinguish persistent pathogenic senescence from transient injury-associated arrest.[10,13,24]

A direct mechanistic link to α-Klotho has been demonstrated experimentally. Activation of the $p16^{INK4a}$–RB pathway suppresses E2F transcription factors capable of activating the α-Klotho promoter; $p16^{INK4a}$ silencing increased α-Klotho expression in late-passage human renal epithelial cells, and genetic deletion of $p16^{INK4a}$ partially restored α-Klotho in Klotho-deficient mice.[17] These experiments support p16-dependent regulation of Klotho but do not establish p16 inhibition as a therapeutic route to Klotho restoration.

Paracrine signalling provides a second connection. Factors released by senescent cells, including activin A and interleukin-1α, can suppress α-Klotho in neighbouring cells; transplantation of senescent cells lowers α-Klotho in young mice, whereas genetic or pharmacological senescent-cell clearance increases kidney and urinary α-Klotho.[18] Dasatinib plus quercetin also increased urinary α-Klotho in a small study of idiopathic pulmonary fibrosis. That observation supports biological activity in humans, but not restoration of renal tissue Klotho or kidney benefit.

The relationship also operates in the opposite direction. α-Klotho attenuates high-phosphate- and oxidative stress-induced senescence-associated changes and reduces mitochondrial dysfunction, tubular senescence and fibrosis in experimental kidney injury.[28,32] A Klotho-derived peptide similarly restored endogenous α-Klotho expression while reducing several senescence-associated features.[19]

The evidence therefore supports bidirectional crosstalk between persistent senescence and α-Klotho deficiency, but not a closed pathogenic loop. Causal interaction is best supported in cellular and animal models, whereas direct evidence in human CKD remains limited. Mechanistic convergence justifies studying the two processes within a common framework, but not assuming that targeting one will necessarily correct the other (Fig. 1a).

Therapeutic strategies: senolysis, SASP modulation and α-Klotho restoration

Persistent senescence and α-Klotho deficiency create three therapeutic entry points that should not be treated as interchangeable: selective elimination of persistently senescent cells with senolytics, modulation of senescent-cell programmes with senomorphics, and restoration or replacement of α-Klotho activity (Fig. 1b; Table 1). Senolysis removes a cell population, senomorphism aims to reduce pathogenic output without mandatory clearance, and Klotho therapy seeks to restore a protective pathway. Their pharmacology, safety liabilities and biomarkers are consequently different.

Senolytics exploit survival dependencies that allow senescent cells to resist apoptosis. Kidney studies using navitoclax and other experimental approaches show that reducing senescent-cell burden can improve repair or attenuate fibrosis in selected settings.[12,29,31] Human evidence is much thinner. In a small open-label study in diabetic kidney disease, dasatinib plus quercetin reduced senescent-cell burden in adipose tissue and circulating SASP-related factors.[33] This established biological activity in people with CKD, but not renal senescent-cell clearance, kidney-specific target engagement or clinical benefit.

Recent diabetic kidney disease models broaden the rationale. Dasatinib plus quercetin has been associated with improved fatty-acid oxidation, autophagy and podocyte differentiation,[34,35] and an intermittent regimen reduced kidney inflammation, fibrosis and $p16^{Ink4a}$-associated senescence while increasing α-Klotho and Sirtuin-1 in diabetic mice.[36]

These results cannot be generalised across disease stages. The same dasatinib–quercetin combination increased kidney injury in acute folic acid nephropathy,[37] illustrating how senolysis may be harmful during active injury or when stress-arrested cells retain a reparative role. Selectivity in space and time is therefore central to senolytic development, particularly because systemic exposure may also affect haematological, endothelial or immune compartments.

Senomorphics offer a less destructive strategy by attenuating SASP activity or the signalling and metabolic programmes that sustain it. Candidate pathways in CKD include NF-κB, inflammasome and mTOR signalling, mitochondrial stress responses and WNT/β-catenin-related maladaptive repair.[10,23,24,30] Such approaches may preserve viable cells while reducing chronic inflammatory or profibrotic output. Their limitation is mechanistic specificity: many of the same pathways participate in normal immunity, metabolism and repair, making true senomorphic activity difficult to distinguish from conventional anti-inflammatory or cytostatic effects.

α-Klotho-directed therapies address a different defect. Proposed approaches include recombinant soluble protein, Klotho-derived peptides, gene-based delivery, induction of endogenous expression and relief of inflammatory or epigenetic repression.[19,38–42] Experimental benefits extend across oxidative stress, mitochondrial injury, inflammation, fibrosis and senescence-associated changes.[14,15,28,32,38,39] This breadth is attractive but complicates development, because several downstream readouts may change without identifying the mechanism responsible for kidney protection.

Klotho pharmacology also depends on nephron-segment biology. Proximal and distal tubular Klotho may contribute differently to mineral handling and soluble Klotho generation,[16] so systemic soluble replacement, induction of endogenous renal expression and targeted tubular delivery are not equivalent strategies. Because membrane-bound Klotho is required for FGF23 signalling, dose finding must consider phosphate, calcium and vitamin D metabolism as well as the molecular form and renal compartment being targeted.

The initial therapeutic choice should therefore follow the dominant biological phenotype rather than CKD stage alone. A reproducible senescence/SASP-high state may support intermittent senolysis or senomorphism, whereas a predominantly Klotho-deficient phenotype could favour restoration without prior cell clearance. Overlap is likely, but overlap alone does not justify combination therapy.

Within an overlapping senescence-high and Klotho-deficient phenotype, a “clearance–restoration” sequence is an attractive but still hypothetical strategy: reduce a demonstrably pathogenic senescent-cell burden, then restore α-Klotho-dependent tissue resilience if deficiency persists. Senescent-cell clearance can increase α-Klotho, whereas Klotho restoration can attenuate senescence-associated, mitochondrial and fibrotic changes.[18,19,28,32,36] These reciprocal effects make sequencing testable; they do not show that it is superior to either modality alone.

Across all three strategies, isolated changes in $p16^{INK4a}$, $p21^{CIP1}$, SA-β-gal activity or soluble Klotho are insufficient evidence of target engagement. Development programmes need readouts that identify the relevant renal compartment and connect pharmacodynamic change to the process being targeted. These approaches should be developed as mechanism-based therapies rather than generic “anti-ageing” treatments.[10,23,24,43]

Table 1
Therapeutic strategies targeting accelerated kidney ageing in CKD

Strategy	Mechanistic rationale	Development opportunity	Key translational requirements
Senolytics	Selective clearance of persistently senescent cells through senescent-cell survival dependencies.	Intermittent reduction of pathogenic senescent-cell burden, SASP activity, maladaptive repair and fibrosis.	Multimarker, cell type-aware senescence burden; stable chronic phenotype; renal safety; confirmation that treatment does not impair repair or produce haematological, endothelial or immune toxicity.
Senomorphics	Modulation of SASP, inflammatory signalling, oxidative or mitochondrial stress and maladaptive metabolic programmes without mandatory cell clearance.	Reduce chronic inflammatory and profibrotic output while preserving viable cells and potentially useful repair responses.	Pathway-specific pharmacodynamics; SASP/sendotype panels; separation of senomorphic activity from nonspecific anti-inflammatory effects; surveillance of host defence and repair.
α-Klotho restoration	Replacement or induction of soluble or membrane-associated Klotho pathways and endogenous renal Klotho expression.	Restore geroprotective signalling and resilience, with potential effects on oxidative stress, mitochondria, fibrosis and senescence-associated programmes.	Validated Klotho assays and renal/tubular pathway readouts; FGF23, phosphate, calcium and vitamin D monitoring; definition of molecular form, tissue exposure and nephron-segment target.
Sequential or combination therapy	Target persistent senescence/SASP and Klotho deficiency as overlapping but non-identical mechanisms.	Correct a residual mechanism after successful engagement of the first modality; potentially couple removal of pathogenic cells to restoration of tissue resilience.	Evidence of monotherapy target engagement first; predefined residual mechanism; phase-specific biomarkers; added safety assessment; experimentally justified order and interval.

Biomarkers for clinical translation: proving target engagement in the ageing kidney

Clinical translation requires biomarkers that distinguish mechanism from CKD severity. eGFR and albuminuria remain indispensable for prognosis and outcome assessment, but neither can establish that a senolytic has cleared the intended renal cell population, that a senomorphic has modified a pathogenic SASP programme or that Klotho therapy has restored the relevant renal pathway.[10,43] Mechanism-

specific readouts are therefore needed to prevent haemodynamic or broadly anti-inflammatory effects from being misclassified as reversal of accelerated kidney ageing.

Renal senescence should be represented by a coherent multimarker state rather than a single assay. $p16^{INK4a}$, $p21^{CIP1}$, p53, SA-β-gal, lipofuscin, γH2AX and individual SASP proteins each capture only part of the phenotype.[23,24] Tissue-based single-cell or spatial profiling will be particularly useful in early translational studies because it can anchor candidate non-invasive markers to specific renal cell states and determine which compartments actually change after treatment.

Urine offers a practical route for repeated renal assessment. Urinary clusterin-to-creatinine has been associated with p21-positive, Ki67-negative renal epithelial cells and with adverse kidney outcomes independently of established risk factors,[44] while proteomic studies have identified lower urinary SELL, UMOD and EGF in ageing-related CKD profiles.[45] These candidates are promising, but none is yet a validated response biomarker for senolysis; prospective studies must show that treatment-related changes track the intended renal mechanism rather than nonspecific tubular injury or altered kidney function.

Circulating SASP-associated signatures provide complementary information. Proteomic “sendotypes” in CKD identify groups enriched for TNF, JAK–STAT and NF-κB activity with different clinical trajectories.[46] They could support enrichment for senolytic or senomorphic trials, particularly when paired with a renal readout. Their specificity is limited because diabetes, vascular disease, infection, adipose dysfunction and chronological ageing can all influence circulating SASP proteins.

Klotho-directed therapies create a different measurement problem. Soluble α-Klotho can be measured in blood and urine, but these concentrations may not reflect membrane-bound Klotho in the nephron segment relevant to the intervention.[16] Assay variability and uncertainty about the molecular species detected further complicate interpretation. Pharmacodynamic assessment should therefore combine a validated Klotho assay with FGF23, phosphate, calcium and vitamin D metabolites and, where feasible, renal or tubular evidence of pathway restoration.

Broader measures of biological age may help describe systemic consequences rather than renal target engagement. Biomarker-derived age acceleration, DNA-methylation clocks and newer epigenetic or glycomic models have been associated with adverse outcomes or altered biological ageing in CKD.[47–50] Their value is mainly exploratory: they may support risk stratification or indicate systemic change, but are too nonspecific to serve as primary pharmacodynamic endpoints for renal senolytic or Klotho-directed therapy.

A practical biomarker strategy is therefore layered. Baseline measures should identify a reproducible senescence/SASP-high, Klotho-deficient or overlapping phenotype; on-treatment markers should demonstrate engagement of the intended pathway; and downstream measures should connect that engagement to repair, inflammation, fibrosis, albuminuria, vascular injury or another clinically relevant

process. Biomarkers can guide enrichment and dose selection, but they should not become surrogate claims of “rejuvenation”.

Development pathway: separate, combined or sequential therapies?

Development should begin with the least complex intervention capable of addressing the dominant biological state. Phenotype enrichment is intended to increase the probability that patients entering an early trial express the mechanism being targeted, not to replace conventional CKD classification. Monotherapy should establish safety and interpretable renal target engagement before combination or sequencing is considered.

Preclinical programmes should make timing explicit. Acute injury, recovery and established CKD are biologically different states, as illustrated by the adverse effect of dasatinib plus quercetin in acute folic acid nephropathy.[37] Multi-omics profiling can help define broader responses to senolysis,[51] while integrative senescence frameworks support testing interventions across complementary models.[52] Recombinant Klotho has also enhanced dapagliflozin responses in experimental diabetic kidney disease,[53] although this does not predict benefit from senolytic–Klotho combinations.

Sequence-testing should compare monotherapies before factorial or staged designs. Human kidney tubuloids exposed to repeated cisplatin can reproduce persistent senescence, SASP activity and fibrosis and may help screen timing and mechanism,[54] but they cannot capture systemic immune, vascular or endocrine interactions. Chronic in vivo models remain necessary to determine whether efficacy depends on renal cell type, disease stage or the interval between clearance and restoration.

Clinical entry should likewise be phenotype enriched. Eligibility might combine stable CKD with a urinary epithelial-senescence signature, a reproducible SASP sendotype, Klotho deficiency with compatible mineral-metabolism features, or a predefined overlapping profile.[44–46] Precision-medicine guidance for kidney trials similarly emphasises molecular endophenotypes and response biomarkers.[55] Such enrichment will narrow early generalisability but should improve interpretability.

Early-phase trials should prioritise safety, exposure and renal proof of mechanism. The diabetic kidney disease dasatinib-plus-quercetin pilot showed systemic biological activity without measuring renal target engagement.[33] In a non-renal phase 2 senolytic trial, the primary skeletal endpoint was negative overall, although exploratory benefit was concentrated among participants with a higher baseline p16^{INK4a}-positive T-cell burden.[56] Cross-organ extrapolation is uncertain, but the finding illustrates why baseline biology may influence response. Klotho dose escalation will additionally require mineral-metabolism monitoring.

Phase 2 studies should then ask whether target engagement is followed by a downstream change consistent with the proposed mechanism. Albuminuria and chronic eGFR slope remain useful clinical measures, and their joint assessment can improve prediction of longer-term kidney-failure benefit.[57] For

ageing-directed interventions, a credible go/no-go signal would combine renal target engagement, mechanistically coherent biological improvement and acceptable safety without evidence of impaired repair.

Combination or sequencing should be advanced only when monotherapy leaves a measurable residual mechanism that a second intervention can plausibly correct. This criterion is more demanding than showing that two pathways interact experimentally, but it is also more informative.

Senescent-cell clearance followed by α-Klotho restoration is a useful test case. The sequence should be advanced only if senolysis demonstrably engages its target and a persistent Klotho-deficient state remains that is both measurable and pharmacologically addressable. Until such evidence exists, clearance–restoration should be treated as a falsifiable pharmacological hypothesis rather than a preferred therapeutic hierarchy (Fig. 1c).

Conclusion

Persistent renal senescence and α-Klotho loss provide a coherent framework for exploring ageing-directed drug discovery in CKD, but the evidence does not support treating CKD as a single accelerated-ageing state. Senolytics, senomorphics and Klotho-directed agents act on different biological levels and should initially be developed through distinct, phenotype-led programmes with renal target engagement at their centre.

The most informative studies will link a baseline renal phenotype to pharmacodynamic change and then to patient-relevant benefit while preserving repair and avoiding off-target toxicity. Experimental convergence between senescence and α-Klotho makes combination and sequential strategies worth testing, particularly the clearance–restoration concept, but neither additivity nor synergy should be assumed. If this standard is met, ageing biology could provide a rigorous route to new CKD therapeutics without relying on the imprecise language of “kidney rejuvenation”.

Declarations

Competing interests

The author declares no competing interests.

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Author Contribution

J.D.-C. conceived the Perspective, performed the literature synthesis and wrote the manuscript.

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Data availability

No datasets were generated or analysed during the current Perspective.

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Figures

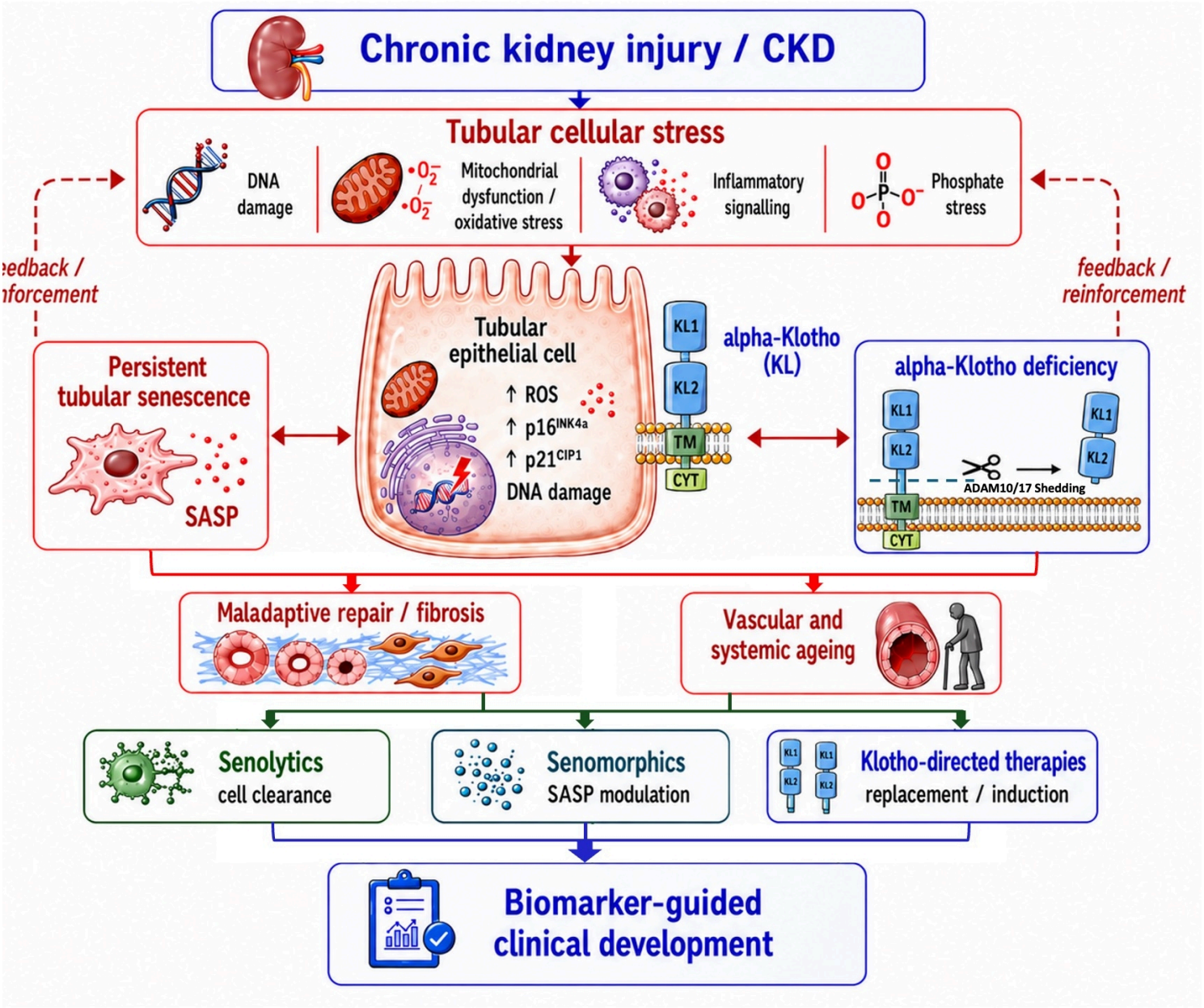


Figure 1

Targeting persistent senescence and α-Klotho deficiency in CKD. **a,** Experimental links include p16–RB-mediated inhibition of E2F-dependent Klotho transcription and paracrine suppression by senescent-cell factors, including activin A and IL-1α.[17,18] The tubular schematic integrates cellular and animal findings: these states may coexist, but a closed pathogenic loop is unproven in human CKD. **b,** Senolytics remove persistently senescent cells, senomorphics reduce pathogenic SASP programmes without requiring clearance, and Klotho-directed therapies replace or restore pathway activity. Reductions in senescence-associated features after Klotho treatment remain experimental and do not establish reversal of senescence.[10,19,28,32] Renal proof of mechanism requires multimarker, cell-context-aware assessment or pathway-specific readouts; isolated marker changes are insufficient.[23,24] **c,** Phenotype-enriched monotherapy should establish renal target engagement and acceptable safety. Dashed arrows indicate a hypothesis: test Klotho restoration after successful senolysis only if a measurable, addressable

deficiency persists. Repair must be preserved, and clinical or additive benefit cannot be assumed. Colours denote senescence (terracotta), SASP (ochre) and Klotho (teal); symbols are not quantitative. KL, Klotho gene; RB, retinoblastoma protein; SASP, senescence-associated secretory phenotype.