

AC-SDKP

Historical clinical exposure 850 mcg or 4.2 mg daily for four days

AC-SDKP is being investigated for limiting pathological fibrosis and inflammatory remodeling in the heart, kidneys, liver, and lungs, with effects demonstrated in specific animal models. [8,9,12–16,22–24] AC-SDKP (N-acetyl-seryl-aspartyl-lysyl-proline), also called goralatide, is an endogenous tetrapeptide corresponding to the N-terminal residues 1–4 of thymosin beta 4. [5,6] Sequential cleavage involving meprin- α and prolyl oligopeptidase releases it, and angiotensin-converting enzyme (ACE) degrades it. [5,6] It also stimulates angiogenesis and reversibly inhibits primitive hematopoietic progenitor proliferation in experimental systems. [10,26] Antifibrotic effects in humans are biologically plausible, supported by human-cell experiments and convergent animal findings, but clinical benefit from administered AC-SDKP has not been established. [7–9,12–16]

 Brief clinical exposure was generally well tolerated. [1] Longer-term safety is unknown. Pro-angiogenic activity creates a plausible concern in active malignancy. [10,25]

  Antifibrotic activity is reproducible across several animal injury models. Corresponding human antifibrotic effects are plausible. [7–9,12–16,22–24]

Disclaimer: These notes are not authoritative and should not be interpreted as definitive scientific guidance. They are summaries, compilations and plausible extrapolations drawn from the most relevant research I was able to locate, and may omit nuances, conflicting data, or emerging evidence. The material reflects an attempt to organize and understand complex topics, not to provide clinical recommendations or expert interpretation.

How AC-SDKP Fits Within Thymosin Beta 4 and TB-500 Biology

Full-length thymosin beta 4 contains multiple biologically active regions. AC-SDKP is its N-terminal 1–4 fragment, with experimentally demonstrated antifibrotic, anti-inflammatory, angiogenic, and hematopoietic-regulatory activities. [5–10,26] TB-500 is Ac-LKKTETQ, a synthetically N-acetylated version of the 17–23 region. [19]

AC-SDKP is an endogenous human peptide and an ACE substrate. ACE inhibitors raise plasma AC-SDKP concentrations in humans. [2,3] This establishes exposure to increased endogenous AC-SDKP, but ACE inhibitors have multiple actions, so their clinical benefits or safety cannot be assigned to AC-SDKP.

Dosing Patterns

Human studies demonstrate rapid clearance of administered AC-SDKP. [18] ACE inhibition and impaired renal function can increase exposure, so endogenous peptide status does not establish a safe therapeutic regimen. [2–4]

No evidence-based human antifibrotic dose or therapeutic SC interval has been established. [18] Several animal efficacy experiments used continuous infusion rather than intermittent

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injections. [8,13,16,22,24] Translating these findings into community injection schedules remains speculative.

Documented Clinical Exposure

Historical goralatide trial: An 84-patient randomized oncology trial evaluated the following experimental daily regimens on days 1–4 of chemotherapy cycles: [1]

- **12.5 or 62.5 mcg/kg daily on days 1–4 [1]**

These were myeloprotection regimens used with carboplatin and fluorouracil, not recommended antifibrotic doses; the trial did not demonstrate hematologic benefit. [1]

Research Administration

Continuous infusion was used in cardiac, renal, and pulmonary animal experiments.

[8,13,16,22,24] An oral dose also improved renal fibrosis endpoints in diabetic mice. [23]

Combination Context

ACE inhibitors reduce AC-SDKP degradation and raise circulating concentrations in humans.

[2,3] Concurrent synthetic AC-SDKP could plausibly increase or prolong exposure. An oral mouse study investigated AC-SDKP with and without imidapril in type 2 diabetes and as an imidapril add-on in type 1 diabetes. [23] A separate neuroinflammation study investigated AC-SDKP and TB-500; its abstract does not establish a synergistic combination regimen. [17]

Benefits

The most reproducible findings concern reduced inflammatory-cell infiltration, fibroblast activation, myofibroblast differentiation, and extracellular-matrix deposition in the experimental systems studied. [7–9,12–16,24] These findings support a plausible human antifibrotic effect, but reduced fibrosis does not invariably improve organ function. [8]

- **Cardiac antifibrotic effects:** AC-SDKP reduced inflammation and fibrosis in rodent hypertension, myocardial infarction, and radiation-injury models. [8,9,22,24,27] Functional effects differed: one rat infarction study found worse systolic function with preventive treatment and no functional improvement with later treatment, whereas a mouse infarction study and a rat irradiation study found functional benefit. [8,9,22]
- **Renal protection:** AC-SDKP reduced inflammation and fibrosis in rat nephritis and ureteral-obstruction models. [12,13] In established nephritis it also improved proteinuria and renal-function measures. [12] Oral treatment reduced fibrosis in diabetic mice, with the type 1 model studied as an ACE-inhibitor add-on. [23]
- **Hepatic antifibrotic effects:** AC-SDKP reduced liver injury, inflammation, collagen deposition, and TGF-beta/Smad signaling in a carbon-tetrachloride rat model, with related inhibition of hepatic stellate-cell activation in vitro. [14]

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- **Pulmonary antifibrotic effects:** AC-SDKP reduced collagen deposition, myofibroblast differentiation, and epithelial-to-mesenchymal transition-associated changes in rat silicosis experiments. [15,16]. A later experimental study linked its antifibrotic effects to ALKBH1 and miR-129-5p regulation. [21]
- **Inflammatory signaling regulation:** Reduced macrophage infiltration and inflammatory signaling were observed in injured cardiac, renal, and hepatic tissue. [8,12–14,22,24] In cultured human cardiac fibroblasts, AC-SDKP also reduced ER-stress-associated NF-kappa B signaling, IL-6, and collagen production. [20]
- **Angiogenesis:** AC-SDKP stimulated endothelial migration and capillary-like structures in vitro and new-vessel formation in chicken and rat experimental systems. [10] Whether this produces beneficial or undesirable effects depends on the tissue and disease context.
- **Hematopoietic progenitor quiescence:** AC-SDKP directly and reversibly inhibited proliferation of primitive human CD34+ progenitors in vitro. [26] This supports the rationale for myeloprotection, but the randomized chemotherapy trial found no significant improvement in the measured hematologic nadirs or toxicity duration. [1]
- **Neuroinflammatory support:** A study investigating AC-SDKP and TB-500 reported reduced inflammatory and neuronal-injury markers in cell models and improved memory-test performance in 5xFAD mice. Hippocampal amyloid burden was unchanged. [17].

Potential Applications

- **Cardiac remodeling:** Human antifibrotic benefit is plausible from rodent and human-cell findings, but effects on cardiac function are model-dependent and cannot be assumed from collagen reduction alone. [7–9,22,24,27]
- **Progressive kidney fibrosis:** Reduced inflammatory and fibrotic remodeling in nephritis, obstruction, and diabetic models supports plausible human renal benefit. [12,13,23]
- **Chronic liver fibrosis:** Reduced stellate-cell activation and fibrogenic signaling support plausible benefit in chronic liver injury. [14]
- **Fibrotic lung disease:** Silicosis-model findings support plausible antifibrotic activity. [15,16,21]
- **Ischemic tissue repair:** Endothelial and animal angiogenesis findings make improved microvascular repair plausible. [10]
- **Bone-marrow protection:** Reversible progenitor quiescence provides a plausible protective mechanism against cell-cycle-dependent injury. [26] Clinical myeloprotection was not demonstrated in the randomized chemotherapy trial, so it should not be described as likely effective in that setting. [1]

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Cautions

- **Active or previous malignancy:** Pro-angiogenic activity raises a plausible concern about supporting an existing tumor's blood supply. [10].
- **Anemia or marrow suppression:** AC-SDKP inhibits primitive human progenitor proliferation in vitro. [26] Anemia and lymphopenia occurred more frequently in the randomized chemotherapy trial. [1]
- **ACE inhibitor use:** ACE inhibitors increase endogenous AC-SDKP concentrations. [2,3]
- **Impaired renal function:** AC-SDKP levels can increase in renal failure, particularly during ACE inhibition. [2,4]
- **Pregnancy and breastfeeding:** Reproductive, developmental, and lactation safety has not been established.

Potential for Diminishing Benefit

A fully characterized receptor mechanism and clinically relevant desensitization have not been established. [16,20] Rapid clearance is demonstrated in humans, but it does not itself determine how long downstream effects last or whether repeated administration loses effectiveness. [18]

Biological Mechanism

AC-SDKP is released from the N-terminus of thymosin beta 4 through sequential proteolysis involving meprin-alpha and prolyl oligopeptidase. [5,6] It is hydrolyzed predominantly by the N-domain of ACE; ACE inhibition raises endogenous concentrations without direct peptide administration. [2,3,27]

Its antifibrotic effects involve several context-dependent pathways. In human cardiac fibroblasts, AC-SDKP reduced TGF-beta1-induced Smad2 and ERK1/2 activation, myofibroblast differentiation, and collagen production; Smad7 was unchanged in that experiment. [7] Smad7 increased in nephritic rat kidneys, while TGF-beta/Smad signaling decreased. [12] Rat liver findings included lower phosphorylated Smad2/3, and hypertensive rat hearts showed lower TGF-beta and connective-tissue growth factor expression. [14,27]

Anti-inflammatory effects include reduced macrophage infiltration, MCP-1 expression, and NF-kappa B signaling in experimental injury. [8,13,24] Human cardiac fibroblast experiments linked reduced collagen production to attenuation of ER-stress responses, including CHOP/NF-kappa B signaling; persistence of effects after CHOP knockdown suggests additional mechanisms. [20] AC-SDKP also directly promoted endothelial migration, tube formation, and experimental angiogenesis. [10]

In hematopoiesis, AC-SDKP directly and reversibly limits proliferation of primitive human progenitors in vitro. [26] Quiescence could protect against some cell-cycle-dependent insults,

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but suppression may also impair recovery under other conditions. The chemotherapy trial's blood-cell findings and the renal-failure association warrant caution when extrapolating to sustained exposure. [1,4]

AC-SDKP and Cancer Risk

AC-SDKP stimulates experimental angiogenesis, creating a plausible tumor-vascularization concern. [10] Human tumor-tissue overexpression is associative evidence, not proof of a causal effect of treatment. [25]

Conclusions

Short clinical exposure provides limited reassurance about general tolerability, alongside observed anemia and lymphopenia signals. [1] Hepatic and renal injury-model findings support plausible tissue protection, but do not establish chronic human organ safety. [12–14,23] Cardiovascular inference is constrained by differing functional results across models. [8,9,22] Cancer-related and blood-cell risks require separate consideration. [1,4,10,25,26]

AC-SDKP has demonstrated anti-inflammatory and antifibrotic activity in multiple experimental systems. [7–9,12–16,22–24] Translation to human antifibrotic benefit is plausible, while clinical functional benefits, an intermittent SC therapeutic regimen, and cycling practices remain unestablished. Human PK data exist and should inform future clinical development rather than be replaced by animal dose scaling. [18]

References

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