The Saga of Recombinant Human Pentraxin-2 as a Potential Therapeutic Agent for Pulmonary Fibrosis

Keith C Meyer

Department of Medicine, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA

Serum amyloid P (SAP) is an endogenous protein of hepatic origin that is constitutively present in the peripheral circulation and a member of the pentraxin family of proteins. Preclinical studies in animal models suggested that SAP (pentraxin-2) could blunt or prevent tissue fibrosis, including bleomycin-induced pulmonary fibrosis. Recombinant human pentraxin-2 was termed PRM-151 when it entered clinical trials for patients with idiopathic pulmonary fibrosis (IPF) or myelofibrosis over a decade ago. Despite the potential promise of PRM-151 (now known as zinpentraxin alfa) as a therapeutic intervention to treat fibrotic diseases and its potential efficacy for patients with IPF as suggested by a phase II randomized clinical trial (RCT), interim analyses of the data from the phase III RCT (STARSCAPE) in patients with IPF showed a lack of efficacy. The purpose of this article is to review the properties of pentraxin-2 and the promising findings on PRM-151 as an anti-fibrotic drug in preclinical studies and early-phase RCTs that supported its advance to a phase III RCT.

Keywords

Animal models, human recombinant pentraxin 2, idiopathic pulmonary fibrosis, macrophages, pentraxin-2, PRM-151, pulmonary fibrosis, randomized clinical trial, serum amyloid P, zinpentraxin alfa

Disclosures: Keith C Meyer has no financial or non-financial relationships or activities to declare in relation to this article.

Review Process: Double-blind peer review.

Compliance with ethics: This article involves a review of the literature and did not involve any studies with human or animal subjects performed by any of the authors.

Data availability: Data sharing is not applicable to this article as no datasets were generated or analyzed during the writing of this article.

Authorship: The named author meets the criteria of the International Committee of Medical Journal Editors for authorship for this manuscript, takes responsibility for the integrity of the work as a whole and has given final approval for the version to be published.

Received: 29 September 2023

Accepted: 12 February 2024

Citation: *touchREVIEWS in Respiratory & Pulmonary Diseases.* 2024;9(1):Online ahead of journal publication

Corresponding author: Keith C Meyer, Department of Medicine, University of Wisconsin School of Medicine and Public Health, Madison, WI 53792, USA.
E: kcm@medicine.wisc.edu

Support: No funding was received in the publication of this article.

Pentraxin-2 is a member of the pentraxin family of proteins, which includes C-reactive protein (CRP), pentraxin-2 and pentraxin-3.[1–3] When initially discovered and characterized, pentraxin-2 was known as serum amyloid P (SAP) due to its isolation from amyloid deposits in humans; subsequently, SAP was found to be in the sera from circulating blood and, hence, its designation as SAP.[4–6] Subsequent research revealed multiple biological properties and functions of SAP (*Table 1*). SAP is produced in the liver by hepatocytes and secreted into the circulating blood.[6] As SAP is an acute-phase protein in mice, its serum levels can increase by up to 20-fold in response to an inflammatory stimulus; however, SAP is not an acute-phase protein in humans.[7] SAP and CRP have similar structures, having circular pentamers shaped like a flat disc with a gap in the middle.[1–3,8] As each SAP molecule binds to two Ca^{2+} atoms, the pentamer displays a total of 10 Ca^{2+} atoms on one side of its disc-like structure.[1–3] Ca^{2+} cations facilitate the binding to various moieties, including amyloid deposits, toxins and polysaccharides from bacteria and debris from apoptotic cells.[9–11]

Patients with idiopathic pulmonary fibrosis (IPF) progressively and irreversibly lose lung function over time, although there is considerable variability among patients in the pace of lung function decline, with a 5-year survival rate estimated to range from 20 to 40%.[12] The elderly population (especially males) is predominantly affected by IPF, with an incidence ranging from three to nine cases per 100,000 person-years.[13] The anti-fibrotic drugs, pirfenidone and nintedanib, have been shown to significantly attenuate the rate of decline in lung function over time for patients with IPF, and more recent clinical trial results show the efficacy of these agents for other forms of progressive fibrosing interstitial lung disease, such as that associated with scleroderma, rheumatoid arthritis and other autoimmune disorders.[14–18] However, while decline in lung function may be slowed by anti-fibrotic therapy, not all patients benefit from such anti-fibrotic pharmacotherapies, resulting in declining lung function in these patients. These drugs can have significant side effects, leading some patients to be unable to tolerate them. There remains an urgent need for anti-fibrotic drug therapies that can be both effective and well tolerated by patients.

Numerous early investigations indicated that SAP can modulate wound healing and can have an inhibitory effect on various forms of fibrosis that lead to organ dysfunction. Such findings fostered numerous clinical studies to assess the ability of SAP to inhibit scar tissue formation in animal models and humans. Forms of fibrosis that can cause severe morbidity and lead to death range from cardiac fibrosis, cirrhosis of the liver and end-stage diabetic kidney disease to various forms of pulmonary fibrosis (PF).[19]

Preclinical investigations

Studies on the role that SAP may play in wound healing and tissue fibrosis have led to important insights supporting its efficacy as an anti-fibrotic moiety.[20–23] Fibrocytes, which promote scar formation and stimulate resident fibroblasts to produce excessive collagen, are found in high numbers in healing wounds, fibrotic lesions in patients with PF and animal models of pulmonary and other forms of fibrosis.[2,24,25] SAP has been shown to be an endogenous inhibitor of fibrocyte

Table 1: Characteristics and functions of serum amyloid P (pentraxin-2)

• MW 127,310 Da
• Five pentameric subunits are arranged in a planar symmetrical pattern
• Structurally similar to CRP
• Circulates in the blood as a single pentamer
• Pattern-recognition molecule
• Ca^{2+} atoms (two per molecule) facilitate the binding of SAP to multiple moieties: – Bacterial polysaccharides – Deposited amyloid – Bacterial toxins – Apoptotic debris (opsonizes bacteria and cell debris to promote phagocytosis)
• Binds multiple plasma proteins
• SAP complexed by debris bound by phagocytic cells (monocytes and macrophages)
• Constitutively produced in the liver and secreted into the circulation
• Macrophage immunoregulator (promotes the generation of M1 phagocytic macrophages and immunoregulatory macrophages)
• Suppresses the differentiation of monocytes into tissue fibrocytes
• Acute-phase reactant in mice (not in humans)
• Serum SAP levels in humans: – Are unaffected by inflammation – Range from 20 to 60 µg/mL – Are low in patients with fibrotic disorders (e.g. pulmonary fibrosis, renal fibrosis and connective tissue disease)
• Inhibits the adhesion of neutrophils to the extracellular matrix and neutrophil transmigration into tissues
• Exogenous SAP inhibits fibrosis in multiple models of pulmonary and other forms of fibrotic disease

CRP = C-reactive protein; MW = molecular weight; SAP = serum amyloid P.

differentiation.[26] Additionally, SAP has an inhibitory effect on pro-fibrotic macrophages and has been shown to promote the formation of immune-regulatory macrophages.[27] Bleomycin has been found to induce a heightened and persistent inflammatory response accompanied by increased fibrosis in an SAP-knockout mouse model, and exogenous SAP blunted the accumulation of pro-inflammatory macrophages and attenuated PF.[20,22,28]

Preclinical studies summarized in *Table 2* support the notion that SAP/pentraxin-2 has the ability to suppress fibrotic responses that can be triggered by injury and inflammation.[20–22,28–33] In a model of bleomycin-induced PF, Pilling et al. found that intraperitoneal injections of SAP reduced leucocyte and fibrocyte accumulation and attenuated PF in both rats and mice.[21] This line of research was extended by Murray et al. by assessing the effect of SAP on bleomycin-induced PF in mice and measuring SAP levels in human subjects with IPF versus controls.[28] They found that SAP significantly diminished tissue fibrosis and collagen deposition in their mouse model, which was associated with a reduction in pro-inflammatory M2 macrophages and a probable increase in M1 regulatory macrophages. Additionally, SAP levels in circulating venous blood from patients with usual interstitial pneumonia (UIP)/IPF were lower than those in controls, and levels of specific plasma proteins were consistent with a skewing of macrophages from M1 to M2 phenotypes. Subsequently, Murray et al. examined SAP levels in human subjects with UIP/IPF and the effect of SAP treatment on fibrocyte accumulation in their bleomycin/PF mouse model in which transforming growth factor (TGF)-β1 could be overexpressed.[22] As reported previously, plasma levels of SAP were significantly lower in patients with UIP/IPF versus control subjects and correlated inversely with the degree of forced vital capacity (FVC) impairment. When human monocytes were cultured *in vitro*, SAP exposure reduced the secretion of M2 macrophage-associated proteins and promoted the emergence of M1 macrophage responses. In the mouse model, SAP attenuated collagen accumulation in a dose-dependent fashion and was associated with decreased fibrocytes in both bronchoalveolar lavage and lung tissue. Further experiments by Pilling et al. using a bleomycin/PF mouse model, in which the SAP gene was knocked out, showed that bleomycin induced a persistent inflammatory response and increased PF in the knockout mice.[20] Treatment with exogenous SAP reduced the accumulation of inflammatory macrophages and prevented the fibrotic change in both knockout and wild-type mice exposed to bleomycin.

In addition to preclinical studies of SAP in models of PF, numerous studies have examined the effects of SAP on experimental models of non-pulmonary tissues/organs. Murray et al. examined experimental radiation-induced damage in a hamster cheek pouch model and reported that intraperitoneally administered SAP delayed the onset of oral mucositis, diminished myofibroblast infiltration into tissues, reduced collagen deposition and gene expression and promoted injury resolution.[29] Moreira et al. examined the effects of SAP on airway inflammation and remodelling in a murine model that used *Aspergillus fumigatus* conidia to induce airway sensitivity, performing both *in vivo* and *in vitro* experiments to determine the effects of SAP on monocyte/macrophage in Fcγ chain receptor-deficient mice versus wild-type mice.[30] They reported that SAP suppressed M2 macrophage activation via an FcγR-dependent mechanism, inhibited an increase in airway resistance induced by methacholine challenge and reduced airway inflammation and remodelling but did not impair the clearance of fungi. Haudek et al. examined the effects of SAP on cardiac fibrosis in a mouse model of ischaemia/reperfusion cardiomyopathy induced by intermittent coronary artery occlusion.[31] They reported that SAP significantly reduced fibroblast flux into tissue and completely prevented ischaemia/reperfusion-induced fibrosis and ventricular dysfunction. Additional experiments reported by Haudek et al. using the murine cardiomyopathy model in $Fc\gamma R^{-/-}$-knockout mice showed that SAP provided protection against ischaemia/reperfusion fibrotic injury and cardiac dysfunction in wild-type mice but not in the knockout mice, but SAP had to be present prior to monocyte trans-endothelial migration when applied to an *in vitro* membrane model.[32] Finally, Castaño et al. examined the effect of SAP administration in a mouse model of kidney fibrosis caused by unilateral ureteric obstruction while also measuring SAP serum concentrations in patients with chronic kidney disease.[33] Human SAP (hSAP) given intraperitoneally every 48 h suppressed kidney fibrosis at days 7 and 14, and myofibroblast activation was markedly inhibited. hSAP induced an anti-inflammatory cellular signature in macrophages that infiltrated inflamed tissue, concentrations of hSAP were markedly increased in injured kidneys and predominantly associated with apoptotic/necrotic cells and hSAP was shown to bind to Fcγ receptors. It was also found that patients with more severe kidney diseases had lower SAP levels in circulating blood.

Clinical development and regulatory trials of PRM-151

As pentraxin-2 had been shown to potently inhibit the differentiation of monocytes into pro-inflammatory macrophages and profibrotic fibrocytes and suppress the production of TGF-β1, a key mediator of tissue fibrosis, IPF, was considered as one form of fibrotic disease that could be targeted in a clinical trial. Furthermore, preclinical studies suggested that patients with IPF as well as other fibrotic disorders appeared to have deficient circulating levels of SAP. As SAP was often confused with another protein,

Table 2: Preclinical investigations[20–22,28–33]

Reference (year)	Type of model	Methods/intervention	Observations
Pilling et al. (2007)[21]	Bleomycin-induced PF in mice and rats	• Bleomycin instilled intratracheally • SAP purified from serum (rat and mouse) and given intraperitoneally • Lung collagen content assessed in minced lungs and by examining lung tissue sections	• SAP (including delayed injections of SAP) diminished PF in the rat model • SAP reduced bleomycin-induced leucocyte accumulation in rat lungs • SAP decreased fibrocyte accumulation in rat lungs • SAP attenuated PF in mouse lungs
Murray et al. (2010)[28]	• Intratracheal bleomycin-induced PF in mice • Observational study of SAP levels in human subjects with IPF versus controls	Murine model: • SAP administered intraperitoneally • Lung tissue stained for collagen deposition • Tissue sections examined for M2 macrophage content Human study: • SAP level measured in patients with UIP/IPF versus normal subjects • M2 macrophage-associated proteins measured in plasma and lysed whole lung tissue from biopsy specimens	Mouse model: • SAP significantly reduced tissue fibrosis and collagen deposition • Decrease in IL13Ra2+ alveolar macrophages (M2 phenotype) in the lungs of SAP-treated mice versus controls • SAP reduced the expression of M2-associated proteins (MARCO, ST2 and FIZZ-1) • SAP attenuated profibrotic mediators (CCL2 [MCP1/JE]) and oncostatin M • SAP increased the level of IP10/CXCL10 and NOS2 production versus control (consistent with an increase in the M1 macrophage phenotype) Human study: • Protein levels in the lungs and peripheral blood reflect skewing towards an alternatively activated, pro-fibrotic M2 macrophage phenotype • SAP levels reduced in the circulating peripheral blood from patients with UIP/IPF versus control patients
Murray et al. (2011)[22]	Lung-specific TGF-β1 transgenic mouse model exposed to intratracheal bleomycin	Mouse model: • Mice (C57BL/6 background) with chronic TGF-β1 overexpression • BAL cells and lung tissues analysed to determine macrophage-associated gene transcript levels Human study: • Patients with UIP/IPF compared with age-matched controls • Monocytes cultured *in vitro* to assess cell-derived cytokines associated with M1 versus M2 monocyte/macrophage phenotypes	Mouse model: • SAP treatment reduced lung collagen accumulation in a dose-dependent manner but had no effect on TGF-β1 levels in BAL • Flow cytometry indicated significantly decreased fibrocyte accumulation in BAL with SAP treatment • SAP-treated mice had reduced TGF-β1-induced pulmonary fibrocyte accumulation in lung tissue Human study: • Plasma levels of SAP were significantly lower in UIP/IPF versus control subjects • Plasma SAP levels significantly correlated with the degree of FVC impairment (inversely) • *In vitro* SAP reduced the secretion of the M2-associated protein PARC/CCL18 by activated CD14+ monocytes from patients with UIP/IPF • *In vitro* SAP treatment increased IL-14 production by CD14+ cells from patients with UIP/IPF (consistent with the restoration of an M1 phenotype)
Pilling et al. (2014)[20]	Bleomycin aspiration in SAP-knockout mice	• Bleomycin administered via oropharyngeal aspiration to *Apcs*$^{-/-}$ mice (SAP knockouts) and wild-type C57Bl/6 mice (controls) • Inflammation and fibrosis assessed • SAP derived from human sera administered	• Bleomycin aspiration caused a persistent inflammatory response and increased fibrosis in the lungs of *Apcs*$^{-/-}$ mice versus C57Bl/6 • Initial inflammatory response cells in the lungs of knockout mice were similar to those in C57Bl/6 wild-type mice • Injections of exogenous SAP reduced the accumulation of inflammatory macrophages and prevented fibrotic change in both knockout and wild-type mice.

Continued

Table 2: Continued

Reference (year)	Type of model	Methods/intervention	Observations
Murray et al. (2010)[29]	Hamster cheek pouch irradiation model	• OM induced by single radiation dose (40 Gy) everted left cheek pouch • Fibrotic remodelling histologically visualized and quantified via collagen gene expression	• SAP treatment (intraperitoneal injection) delayed the onset of OM and enhanced injury resolution • SAP inhibited the extent of tissue remodelling, diminished myofibroblast infiltration and lessened collagen deposition and gene expression
Moreira et al. (2010)[30]	Murine model of airway sensitization to *Aspergillus fumigatus* conidia antigens	• Female C57BL/6 FcγR2/2 (λ chain subunit-deficient FcγR2/2) mice versus C57BL/6 wild-type mice • *In vitro* experiments with bone marrow-derived or interstitial lung macrophages with M2-skewing culture media • *In vivo* experiments with examination of BAL and lung tissue sections • Effects of SAP compared with CRP	• SAP potently inhibited alternative activation of M2 macrophages *in vivo* and *in vitro* (CRP had only a minor effect) via an FcγR-dependent mechanism • SAP completely inhibited STAT6 phosphorylation in M2 macrophages • SAP inhibited airway resistance induced by methacholine • SAP inhibited airway inflammation and remodelling • SAP did not impair fungal clearance or nitric oxide generation
Haudek et al. (2006)[31]	Cardiomyopathy/fibrosis model in mice	• I/RC induced by daily episodes of brief coronary artery occlusion causing fibrotic cardiomyopathy • SAP (isolated and purified from mouse sera) administered *in vivo* (daily)	• I/R caused sustained elevation of MCP-1 and the appearance of highly proliferative fibroblasts, spindle-shaped fibroblasts expressing collagen I and α-smooth muscle actin • SAP markedly reduced fibroblast number and completely prevented I/R-induced fibrosis and ventricular dysfunction • SAP did not suppress inflammation and chemokine expression seen in the I/RC model
Haudek et al. (2008)[32]	• Cardiomyopathy/fibrosis model in mice • *In vitro* transendothelial monocyte migration model	• 10–12-week-old $Fc\gamma R^{-/-}$ chain KO mice (C57BL/6) and wild-type controls subjected to intermittent coronary occlusion to cause I/RC • SAP (isolated and purified from mouse sera) administered *in vivo* (daily) • Human monocytes used for *in vitro* transendothelial migration studies	• SAP given *in vivo* protected against I/RC in wild-type mice but not in $Fc\gamma^{-R/-}$ KO mice • SAP profoundly inhibited monocyte-to-fibroblast transition *in vitro* if present prior to the transendothelial migration • Conclusion: *In vivo* SAP suppressed the transition of a monocyte subpopulation into fibroblasts through action on cellular FcγRs
Castaño et al. (2009)[33]	• Mouse kidney fibrosis model • SAP serum concentrations in patients with chronic kidney disease	• Unilateral ureteric obstruction used to induce mechanical kidney injury and interstitial fibrosis • hSAP given intraperitoneally (q48h) • Fibrotic change and myofibroblast activation assessed in tissue sections • Unilateral kidney injury also caused by ischaemia–reperfusion injury (second model)	• Mouse kidney fibrosis inhibited at days 7 and 14 • Myofibroblast activation markedly diminished by SAP • hSAP concentrations were markedly increased in injured kidneys (mostly associated with apoptotic/necrotic cells) • hSAP shown to bind all mouse FcγRs • hSAP induced an anti-inflammatory signature in infiltrating macrophages • Patients with more severe kidney disease had lower SAP serum levels

BAL = bronchoalveolar lavage; C57Bl/6 = C57 black 6 mouse strain; CCL2 (MCP1/JE) = chemokine (CC-motif) ligand 2/monocyte chemoattractant protein 1; CD14+ = cluster of differentiation 14; CRP = C-reactive protein; FcR = Fc receptor; FIZZ-1 = resistin-like alpha; FVC = forced vital capacity; IL = interleukin; IL13Ra2+ = interleukin-13 receptor subunit alpha 2; IP10/CXCL10 = C-X-C motif chemokine 10; I/R = ischaemia/reperfusion; I/RC = ischaemia/reperfusion cardiomyopathy; KO = knockout; MARCO = macrophage receptor with collagenous structure; MCP = monocyte chemotactic protein; NOS2 = nitric oxide synthase 2; OM = oral mucositis; PARC/CCL18 = pulmonary and activation-regulated chemokine; PF = pulmonary fibrosis; q48h = once every 48 hours; SAP = serum amyloid P (pentraxin-2); ST2 = interleukin 1 receptor-like 1; STAT6 = signal transducer and activator of transcription 6; TGF = transforming growth factor; UIP/IPF = usual interstitial pneumonia/interstitial pneumonia fibrosis.

serum amyloid A, the nomenclature of SAP was changed to pentraxin-2, and the recombinant SAP used for clinical trials was named PRM-151.[2]

The results of the first study in normal volunteers and patients with IPF (*Table 3*) were published in 2013.[34–37] This blinded, placebo-controlled, randomized clinical trial (RCT) was performed to evaluate the safety, tolerability and pharmacokinetics of PRM-151 using single ascending doses (range 0.1–20 mg/kg) of PRM-151 administered via continuous intravenous (IV) infusion over 30 min while fasting. While mostly healthy subjects were evaluated, a modest number of patients with IPF were also studied. Plasma concentrations of SAP were elevated with the 5, 10 and 20 mg/kg protocols and persisted for up to 72 h, and pharmacokinetic profiles for 10 mg/kg dosing were similar for both healthy volunteers and patients with IPF. Fibrocyte percentages (CD45+/procollagen-1+ cells in whole blood samples) declined by 30–50% at 24 h following PRM-151 administration.

The results of the subsequent phase Ib RCT were published in 2016.[35] Three successive cohorts of patients with IPF received multiple ascending doses of PRM-151 (1, 5 or 10 mg/kg versus placebo) on

Table 3: Clinical trials of PRM-151 (recombinant human pentraxin-2)[34–37]

Trial/reference	Design	Observations/outcomes
First-in-human study of IV PRM-151 in normal volunteers and patients with IPF (phase I open label)[34]	• Randomized, blinded, placebo-controlled design used to assess the safety, tolerability and pharmacokinetics of PRM-151 • Single ascending doses (range 0.1–20 mg/kg) of PRM-151 administered via continuous IV infusion over 30 min while fasting • Healthy subject cohorts (2:1 ratio for drug versus placebo); three patients with IPF included for comparison • Percentage of fibrocytes (CD45+/procollagen-1+ cells) in whole blood samples assessed to demonstrate the biological activity of PRM-151	• Adverse events were mild and transient • Mean baseline plasma SAP concentrations were 20.4 ± 6.7 mg/mL in normal volunteers (n=24) versus 15.0 ± 7.5 in subjects with IPF (n=3) • SAP plasma concentrations increased with 5, 10 and 20 mg/kg dosing and persisted for up to 72 h (13-fold increase for 20 mg/kg) in healthy volunteers • Pharmacokinetic profiles for SAP were similar for healthy volunteers and patients with IPF receiving 10 mg/kg • Fibrocyte percentage declined by 30–50% at 24 h post PRM-151 administration in subjects with IPF
A phase Ib study of IV PRM-151 in patients with IPF (PRM-151F-12GL) (ClinicalTrials.gov identifier: NCT01254409)[35]	• Randomized, double-blind, placebo-controlled study to assess tolerability, pharmacokinetics and pharmacodynamics • Multiple ascending doses of PRM-151 administered IV to patients with IPF • Three successive cohorts (1, 5 or 10 mg/kg versus placebo) given the study drug on days 1, 3, 5, 8 and 15 • Recipients followed up to day 57	• PRM-151 well tolerated at all dose levels • No serious adverse reactions • Two- to eightfold dose-dependent increases in circulating pentraxin-2 levels over plasma baseline values observed • Substantial interindividual variability in PRM-151 half-life observed • Trend towards improvement in FVC and 6MWT distance for combined groups receiving PRM-151 (n=14) versus placebo recipients (n=6) • Thoracic HRCT showed stable or improved lung volume unoccupied by interstitial lung abnormality for some PRM-151 recipients (n=5) versus subjects given placebo on day 57
A trial (phase II) to evaluate the efficacy of PRM-151 in subjects with IPF (ClinicalTrials.gov identifier: NCT02550873)[36]	• Randomized, double-blind, placebo-controlled (18 sites in seven countries) • Designed to evaluate the efficacy and safety of PRM-151 for subjects with IPF (age 40–80 years) • Drug versus placebo administered IV every 4 weeks for 24 weeks (10 mg/kg IV infusion over 60 min on days 1, 3 and 5 and then one infusion every 4 weeks) • Concurrent use of nintedanib or pirfenidone allowed • Primary outcome measure: least-squares mean change in FVC% predicted from baseline to week 28 • Secondary outcome measures included change in 6MWT distance, change in HRCT appearance, various composite scores and all-cause mortality	• Mean age =68.6 years (81% male and mean time from IPF diagnosis =3.8 years) • 117 patients randomized; 116 given one dose or more of the study drug or placebo (77 given PRM-151 and 39 received placebo) • 111 (96%) completed the study • Majority of subjects received concurrent anti-fibrotic therapies (n=61 for PRM-151 and n=30 for placebo recipients) • Change in FVC% predicted was -2.5 versus -4.8 for treated versus placebo groups (p=0.001); slowing of FVC decline was also noted for a small number of subjects not receiving concomitant anti-fibrotic agents (n=16 for PRM-151 and n=9 for placebo) • No significant difference between groups for total lung volume, ILAs or DLCO changes from baseline to 28 weeks • Change in 6MWT distance was -0.5 m versus -31.8 m for treated versus placebo groups (p<0.001) • Most common adverse events for treated patients were cough, fatigue and nasopharyngitis
A study (phase III) to evaluate the efficacy and safety of recombinant rhPTX-2 (PRM-151) in participants with idiopathic pulmonary fibrosis (STARSCAPE) (ClinicalTrials.gov identifier: NCT04552899)[37]	• Randomized, double-blind, placebo-controlled trial • Documented diagnosis of IPF per the 2018 ATS/ERS/JRS/ALAT Clinical Practice Guideline • Age 40–85 years • Main inclusion criteria: 6MWT distance ≥150 m; FVC ≥45% predicted; DLCO ≥30% but ≤90% predicted; can concurrently be taking pirfenidone or nintedanib • Main exclusion criteria: presence of extensive emphysema; taking high-dose corticosteroids or other immunomodulatory/cytotoxic drugs; presence of heart failure or significant pulmonary hypertension • Primary endpoint =absolute change in FVC from baseline to week 52	• IV infusion of PRM-151 (10 mg/kg) based on the weight of the participants (or placebo depending on randomization) administered on days 1, 3 and 5 followed by infusions Q4W to week 48 • Study terminated in the fourth quarter of 2022 and announced by Roche on 02 February 2023 (interim data analysis revealed a lack of efficacy)

ALAT = Latin American Thoracic Association; ATS = American Thoracic Society; DLCO = diffusion capacity of the lung for carbon monoxide; ERS = European Respiratory Society; FVC = forced vital capacity; HRCT = high-resolution computed tomography; ILA = interstitial lung abnormality; IPF = idiopathic pulmonary fibrosis; IV = intravenous; JRS = Japanese Respiratory Society; 6MWT = 6-min walk test; Q4W = every 4 weeks; rhPTX-2 = recombinant human pentraxin-2; SAP = serum amyloid P (pentraxin-2).

days 1, 3, 5, 8 and 15, and recipients were followed up to day 57. No serious adverse reactions to the study drug were observed, and SAP levels in plasma increased in a dose-dependent fashion up to eightfold, although considerable interindividual variability in drug half-life was observed. Although subject numbers were limited, a trend towards an improvement in 6MWT distance and stabilization of interstitial changes on high-resolution computed tomography (HRCT) occurred in some participants.

The results of the phase I studies set the stage for a phase II efficacy and safety trial, the results of which were reported in 2018.[36] The phase II RCT enrolled eligible patients aged 40–80 years, with 111 of the 116 randomized patients (96%) completing the study at 28 weeks with 77 randomized to PRM-151 and 39 receiving placebo. Drug (10 mg/kg IV infusion over 60 min on days 1, 3 and 5 and then one infusion every 4 weeks) or placebo infusions were administered every 4 weeks for 24 weeks, and the majority of study participants were also receiving nintedanib or pirfenidone. The FVC% predicted showed a significantly less decline at week 28 for the PRM-151 recipients versus those given placebo (-2.5 versus -4.8 for treated versus placebo groups, p=0.001), and this trend was also noted for the subset of patients not receiving pirfenidone or nintedanib. The change in 6MWT distance was also attenuated (-0.5 m versus -31.8 m for treated versus placebo groups, p<0.001), but there was no significant difference in diffusion capacity of the lung for carbon monoxide or changes in HRCT appearance for drug versus placebo.

Nearly all study subjects (111 of 116) opted to enter the long-term extension study; the 37 subjects who had been on placebo began taking PRM-151, and the 74 subjects who had been randomized to PRM-151 continued to receive the drug.[38] The open-label extension participants were followed up to week 128. Although treatment-emergent adverse events (TEAEs) led to permanent discontinuation of the study drug in 28 (25%) participants prior to week 128, PRM-151 was relatively well tolerated, and its safety profile was acceptable; no serious TEAEs were found to be related to the drug.[38,39] While the trajectory of decline in FVC and 6MWT distance suggested a sustained effect of PRM-151 over time as noted in the initial RCT, participant numbers were too limited to allow conclusive evidence of a sustained drug effect.[39]

The positive results (attenuation of FVC decline and stabilization of 6MWT distance as compared with patients who received placebo) in the phase II study compelled the US Food and Drug Administration to fast-track PRM-151 for a phase III trial (A Study to Evaluate the Efficacy and Safety of Recombinant Human Pentraxin-2 (rhPTX-2; PRM-151) in Participants With Idiopathic Pulmonary Fibrosis [STARSCAPE]; ClinicalTrials.gov identifier: NCT04552899) with recombinant human pentraxin-2 (PRM-151 relabelled as zinpentraxin alfa).[37] Change in FVC from baseline was chosen as the primary endpoint, and enrolment was initiated in 2021 following the dosing regimen used in the phase II RCT. An open-label extension study (A Study to Evaluate Long Term Safety and Efficacy of Recombinant Human Pentraxin-2 [rhPTX-2; PRM-151] in Participants With Idiopathic Pulmonary Fibrosis [STARSCAPE-OLE]; ClinicalTrials.gov identifier: NCT04594707) enrolling both phase II and phase III participants was also planned in anticipation of positive results from the phase III RCT.[40] Unfortunately, interim data analyses of phase III RCT results showed a lack of efficacy, and the trial was terminated by the sponsor in the fourth quarter of 2022.

Whether pentraxin-2 may yet be found to have efficacy in treating fibrotic disorders other than IPF remains to be seen. Although PRM-151 (zinpentraxin alfa) had also advanced to phase II status for the treatment of anaemia caused by bone marrow fibrosis, these myelofibrosis trials in Canada, France and the USA have been discontinued.[41]

Serum amyloid P/pentraxin-2 as a treatment for fibrotic disorders in perspective

Despite the potential utility of SAP as a treatment for fibrotic diseases as suggested by preclinical studies and the potential efficacy and an acceptable safety profile of recombinant human pentraxin-2 for patients with IPF as suggested by the early RCT results, interim data analyses did not support efficacy. Considering the apparent lack of benefit for zinpentraxin alfa, it is unlikely that the drug will be further studied in any RCT for fibrosing lung disease or other fibrotic disorders. However, this is not to say that pentraxin-2 lacks anti-fibrotic properties. Even well-powered phase III RCTs can go off the rails for a multitude of reasons, including skewed participant randomization or the impact of confounding variables.

Many potential therapies for the treatment of idiopathic pulmonary fibrosis (other than pentraxin 2) that have made it to phase III status when the phase II RCT outcomes suggested possible efficacy and acceptable safety profiles have been abandoned due to interim data analyses showing a lack of efficacy. One potential pitfall of using pentraxin-2 to treat IPF is that virtually all patients enrolled in an RCT have well-established and fairly advanced diseases. The preclinical study using the cardiomyopathy model suggested that pentraxin-2 had to be administered prior to the trans-endothelial migration of pro-inflammatory monocyte/macrophages to prevent tissue invasion and transformation of these cells to pro-fibrotic, tissue-resident fibrocytes to attenuate fibrosis.[32] This observation may, in part, explain why pentraxin-2 infusions in patients with IPF with established, advanced disease did not appear to have a significant effect on the primary endpoint of FVC in the STARSCAPE RCT. Additionally, the burden of monthly IV infusions with associated costs and inconvenience would need to be outweighed by a definitive, robust therapeutic response that prevents the loss of lung function over time to justify the use of PRM-151/zinpentraxin alfa as a stand-alone agent or an adjunctive therapy combined with pirfenidone or nintedanib use.

Although PRM-151 (*aka* SAP, pentraxin-2 or zinpentraxin alfa) had a good safety profile in the phase II RCT (A Phase 2 Trial to Evaluate the Efficacy of PRM-151 in Subjects With Idiopathic Pulmonary Fibrosis [IPF]; ClinicalTrials.gov identifier: NCT02550873) and in the long-term extension follow-up studies, as with many phase III RCTs of promising drug therapies for IPF, efficacy was not supported by the interim data analysis of the phase III STARSCAPE trial.[36,38,39] Nonetheless, the basic and clinical research into this endogenous modulator of fibrotic pathways as described in this review provides valuable information concerning the difficulties involved in developing effective pharmacotherapeutic agents for IPF.

Key points

- Preclinical investigations in various models of fibrosis, including the bleomycin mouse model, supported pentraxin-2 as a relatively potent inhibitor of tissue fibrosis.
- The phase II trial of PRM-151 in patients with idiopathic pulmonary fibrosis showed a significant impact on both forced vital capacity decline (primary endpoint) and 6MWT distance (secondary endpoint); these outcomes were observed even when patients were receiving the US Food and Drug Administration-approved anti-fibrotic agents nintedanib or pirfenidone.

- Significant changes in DLCO, total lung volume or HRCT imaging were not observed over a 28-week treatment course in the phase II RCT.
- Long-term follow-up of patients enrolled in the phase II trial showed a good safety profile for PRM-151.
- An interim analysis of the data from the phase III (STARSCAPE) trial revealed a lack of efficacy, which led to its early termination.
- Zinpentraxin alfa is no longer a candidate drug for the treatment of pulmonary fibrosis and is unlikely to enter clinical trials targeting other forms of tissue/organ fibrosis in humans. ❑

1. Du Clos TW. Pentraxins: Structure, function, and role in inflammation. *ISRN Inflamm*. 2013;2013:379040. DOI: 10.1155/2013/379040.
2. Pilling D, Gomer RH. The development of serum amyloid P as a possible therapeutic. *Front Immunol*. 2018;9:2328. DOI: 10.3389/fimmu.2018.02328.
3. Pepys MB. The pentraxins 1975-2018: Serendipity, diagnostics and drugs. *Front Immunol*. 2018;9:2382. DOI: 10.3389/fimmu.2018.02382.
4. Levin M, Franklin EC, Frangione B, Pras M. The amino acid sequence of a major nonimmunoglobulin component of some amyloid fibrils. *J Clin Invest*. 1972;51:2773–6. DOI: 10.1172/JCI107098.
5. Benson MD, Skinner M, Lian J, Cohen AS. "A" protein of amyloidosis. Isolation of a cross-reacting component from serum by affinity chromatography. *Arthritis Rheum*. 1975;18:315–22. DOI: 10.1002/art.1780180404.
6. Hutchinson WL, Hohenester E, Pepys MB. Human serum amyloid P component is a single uncomplexed pentamer in whole serum. *Mol Med*. 2000;6:482–93.
7. Pepys MB, Baltz M, Gomer K, et al. Serum amyloid P-component is an acute-phase reactant in the mouse. *Nature*. 1979;278:259–61. DOI: 10.1038/278259a0.
8. Emsley J, White HE, O'Hara BP, et al. Structure of pentameric human serum amyloid P component. *Nature*. 1994;367:338–45. DOI: 10.1038/367338a0.
9. Pepys MB, Booth SE, Tennent GA, et al. Binding of pentraxins to different nuclear structures: C-reactive protein binds to small nuclear ribonucleoprotein particles, serum amyloid P component binds to chromatin and nucleoli. *Clin Exp Immunol*. 1994;97:152–7. DOI: 10.1111/j.1365-2249.1994.tb06594.x.
10. Pepys MB, Dyck RF, de Beer FC, et al. Binding of serum amyloid P-component (SAP) by amyloid fibrils. *Clin Exp Immunol*. 1979;38:284–93.
11. Bharadwaj D, Mold C, Markham E, Du Clos TW. Serum amyloid P component binds to FC gamma receptors and opsonizes particles for phagocytosis. *J Immunol*. 2001;166:6735–41. DOI: 10.4049/jimmunol.166.11.6735.
12. Hutchinson J, Fogarty A, Hubbard R, McKeever T. Global incidence and mortality of idiopathic pulmonary fibrosis: A systematic review. *Eur Respir J*. 2015;46:795–806. DOI: 10.1183/09031936.00185114.
13. Raghu G, Chen SY, Hou Q, et al. Incidence and prevalence of idiopathic pulmonary fibrosis in US adults 18-64 years old. *Eur Respir J*. 2016;48:179–86. DOI: 10.1183/13993003.01653-2015.
14. Noble PW, Albera C, Bradford WZ, et al. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): Two randomised trials. *Lancet*. 2011;377:1760–9. DOI: 10.1016/S0140-6736(11)60405-4.
15. Richeldi L, du Bois RM, Raghu G, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. *N Engl J Med*. 2014;370:2071–82. DOI: 10.1056/NEJMoa1402584.
16. Distler O, Highland KB, Gahlemann M, et al. Nintedanib for systemic sclerosis-associated interstitial lung disease. *N Engl J Med*. 2019;380:2518–28. DOI: 10.1056/NEJMoa1903076.
17. Matteson EL, Kelly C, Distler JHW, et al. INBUILD trial investigators. Nintedanib in patients with autoimmune disease-related progressive fibrosing interstitial lung diseases: Subgroup analysis of the INBUILD trial . *Arthritis Rheumatol*. 2022;74:1039–47. DOI: 10.1002/art.42075.
18. Matteson EL, Aringer M, Burmester GR, et al. Effect of nintedanib in patients with progressive pulmonary fibrosis associated with rheumatoid arthritis: Data from the INBUILD trial. *Clin Rheumatol*. 2023;42:2311–9. DOI: 10.1007/s10067-023-06623-7.
19. Wynn TA, Ramalingam TR. Mechanisms of fibrosis: Therapeutic translation for fibrotic disease. *Nat Med*. 2012;18:1028–40. DOI: 10.1038/nm.2807.
20. Pilling D, Gomer RH. Persistent lung inflammation and fibrosis in serum amyloid P component (Apcs-/-) knockout mice. *PLoS One*. 2014;9:e93730. DOI: 10.1371/journal.pone.0093730.
21. Pilling D, Roife D, Wang M, et al. Reduction of bleomycin-induced pulmonary fibrosis by serum amyloid P. *J Immunol*. 2007;179:4035–44. DOI: 10.4049/jimmunol.179.6.4035.
22. Murray LA, Chen Q, Kramer MS, et al. TGF-beta driven lung fibrosis is macrophage dependent and blocked by serum amyloid P. *Int J Biochem Cell Biol*. 2011;43:154–62. DOI: 10.1016/j.biocel.2010.10.013.
23. Nakagawa N, Barron L, Gomez IG, et al. Pentraxin-2 suppresses C-Jun/AP-1 signaling to inhibit progressive fibrotic disease. *JCI Insight*. 2016;1:e87446. DOI: 10.1172/jci.insight.87446.
24. Bucala R, Spiegel LA, Chesney J, et al. Circulating fibrocytes define a new leukocyte subpopulation that mediates tissue repair. *Mol Med*. 1994;1:71–81.
25. Mehrad B, Burdick MD, Zisman DA, et al. Circulating peripheral blood fibrocytes in human fibrotic interstitial lung disease. *Biochem Biophys Res Commun*. 2007;353:104–8. DOI: 10.1016/j.bbrc.2006.11.149.
26. Pilling D, Buckley CD, Salmon M, Gomer RH. Inhibition of fibrocyte differentiation by serum amyloid P. *J Immunol*. 2003;171:5537–46. DOI: 10.4049/jimmunol.171.10.5537.
27. Pilling D, Galvis-Carvajal E, Karhadkar TR, et al. Monocyte differentiation and macrophage priming are regulated differentially by pentraxins and their ligands. *BMC Immunol*. 2017;18:30. DOI: 10.1186/s12865-017-0214-z.
28. Murray LA, Rosada R, Moreira AP, et al. Serum amyloid P therapeutically attenuates murine bleomycin-induced pulmonary fibrosis via its effects on macrophages. *PLoS One*. 2010;5:e9683. DOI: 10.1371/journal.pone.0009683.
29. Murray LA, Kramer MS, Hesson DP, et al. Serum amyloid P ameliorates radiation-induced oral mucositis and fibrosis. *Fibrogenesis Tissue Repair*. 2010;3:11. DOI: 10.1186/1755-1536-3-11.
30. Moreira AP, Cavassani KA, Hullinger R, et al. Serum amyloid P attenuates M2 macrophage activation and protects against fungal spore-induced allergic airway disease. *J Allergy Clin Immunol*. 2010;126:712–21. DOI: 10.1016/j.jaci.2010.06.010.
31. Haudek SB, Xia Y, Huebener P, et al. Bone marrow-derived fibroblast precursors mediate ischemic cardiomyopathy in mice. *Proc Natl Acad Sci USA*. 2006;103:18284–9. DOI: 10.1073/pnas.0608799103.
32. Haudek SB, Trial J, Xia Y, et al. Fc receptor engagement mediates differentiation of cardiac fibroblast precursor cells. *Proc Natl Acad Sci U S A*. 2008;105:10179–84. DOI: 10.1073/pnas.0804910105.
33. Castaño AP, Lin SL, Surowy T, et al. Serum amyloid P inhibits fibrosis through FC gamma R-dependent monocyte-macrophage regulation in vivo. *Sci Transl Med*. 2009;1:5ra13. DOI: 10.1126/scitranslmed.3000111.
34. Dillingh MR, van den Blink B, Moerland M, et al. Recombinant human serum amyloid P in healthy volunteers and patients with pulmonary fibrosis. *Pulm Pharmacol Ther*. 2013;26:672–6. DOI: 10.1016/j.pupt.2013.01.008.
35. van den Blink B, Dillingh MR, Ginns LC, et al. Recombinant human pentraxin-2 therapy in patients with idiopathic pulmonary fibrosis: Safety, pharmacokinetics and exploratory efficacy. *Eur Respir J*. 2016;47:889–97. DOI: 10.1183/13993003.00850-2015.
36. Raghu G, van den Blink B, Hamblin MJ, et al. Effect of recombinant human pentraxin 2 vs placebo on change in forced vital capacity in patients with idiopathic pulmonary fibrosis. *JAMA*. 2018;319:2299. DOI: 10.1001/jama.2018.6129.
37. ClinicalTrials.gov. A Study to Evaluate the Efficacy and Safety of Recombinant Human Pentraxin-2 (rhPTX-2; PRM-151) in Participants With Idiopathic Pulmonary Fibrosis (STARSCAPE). ClinicalTrials.gov identifier: NCT04552899. 2024. Available at: www.clinicaltrials.gov/study/NCT04552899 (Date last accessed: 23 April 2024).
38. Raghu G, van den Blink B, Hamblin MJ, et al. Long-term treatment with recombinant human pentraxin 2 protein in patients with idiopathic pulmonary fibrosis: An open-label extension study. *Lancet Respir Med*. 2019;7:657–64. DOI: 10.1016/S2213-2600(19)30172-9.
39. Raghu G, Hamblin MJ, Brown AW, et al. Long-term evaluation of the safety and efficacy of recombinant human pentraxin-2 (rhPTX-2) in patients with idiopathic pulmonary fibrosis (IPF): An open-label extension study. *Respir Res*. 2022;23:129. DOI: 10.1186/s12931-022-02047-0.
40. ClinicalTrials.gov. A Study to Evaluate Long Term Safety and Efficacy of Recombinant Human Pentraxin-2 (rhPTX-2; PRM-151) in Participants With Idiopathic Pulmonary Fibrosis (STARSCAPE-OLE). ClinicalTrials.gov identifier: NCT04594707. 2023. Available at: www.clinicaltrials.gov/study/NCT04594707 (Date last accessed: 23 April 2024).
41. Adis Insight. Drugs - Zinpentraxin alfa - Roche. 2023. Available at: https://adisinsight.springer.com/drugs/800030617 (Date last accessed: 25 September 2023).