Scleroderma spectrum disorders range from primary Raynaud's phenomenon through to the complex connective tissue disorders of diffuse and limited cutaneous systemic sclerosis (SSc) (Figure 1). Both subsets of SSc can be complicated by significant organ-based morbidity and mortality. The pathology involves a functional and structural vasculopathy causing early endothelial cell injury, inflammation (initially perivascular but followed by more diffuse inflammatory changes) and, later, changes of fibrosis, resulting in the morbidity associated with these conditions.

The complex interaction between the fibroblast and its environment in these conditions is likely to underpin this. Fibroblasts themselves are derived from mesenchymal progenitor cells, which differentiate depending on fibroblast growth factors, platelet derived growth factor and endothelin-1. Wound healing requires differentiation to myofibroblasts, so termed as they express elevated levels of α-smooth muscle actin and consequently display a markedly enhanced ability to contract extracellular matrix (ECM) [1]. In normal scarring, apoptosis is responsible for depletion of activated fibroblasts, resulting in healing rather than hypertrophic scarring. Disproportionate fibroblast activity is due to alteration of the normal extracellular milieu of profibrotic and antifibrotic cytokines and secreted proteins [2].

It is known that fibroblasts in patients with SSc produce excessive quantities of ECM components, resulting in a profibrotic phenotype. Proposed defects in SSc have included fibrillin protein abnormalities, autoantibody formation (including antifibrillin-1 antibodies), excessive endothelial response to injury and increased transforming growth factor (TGF)-β bioactivity [3-5].

Rationale for TGF-β blockade in systemic sclerosis

Significant in vitro and in vivo evidence exists that TGF-β signaling pathways are key positive mediators of tissue fibrosis that, with altered control, have the consequence of excessive ECM formation. The TGF-β superfamily regulates cell growth, death and apoptosis, differentiation and synthesis of the ECM in vivo, and is known to induce expression of ECM proteins in mesenchymal cells. In addition, it induces production of protease inhibitors to prevent the enzymatic breakdown of ECM, which may otherwise occur during inflammation.

The possibility that altered TGF-β bioactivity could be implicated in the pathogenesis of SSc was first suggested in 1989 by Carwile LeRoy of the University of South Carolina (SC, USA) [6]. Since then, significant evidence has been obtained suggesting that it is a pivotal upstream mediator of many of the adverse tissue characteristics seen in SSc. Given the known properties of TGF-β, particular interest lies in the fact that it is active in early disease and, therefore, is a potentially powerful target for therapy prior to permanent tissue damage by fibrosis. The three mammalian isofoms, TGF-β1, -2 and -3, are important regulators of embryonic and postnatal cell differentiation and proliferation. They are also potent profibrotic factors in vitro. Mice lacking any one of the TGF-β isofoms will all show perinatal lethal phenotypes, but each one will be different, suggesting somewhat distinct biological functions in vivo [7].

There have been a number of studies examining the TGF-β ligand in SSc. One unexpected finding revealed that active TGF-β1 levels in the plasma or serum of patients with early diffuse cutaneous SSc was lower than in controls or
those with limited cutaneous SSc. One possibility is that, in this highly inflammatory stage of disease, available TGF-β1 is sequestered in lesional skin. Indeed, studies revealed that both TGF-β1 and TGF-β2 ligand expression are increased in early lesional skin in SSc (Figure 2). Furthermore, the gene and protein expression profile of lesional SSc fibroblasts is reminiscent of TGF-β1-activated control cells [8–10].

The TGF-β superfamily signal through a pathway involving two high-affinity receptors, TβRI and II, both with serine/threonine kinase activity, and a family of downstream mediator proteins, termed Smads. The process of TGF-β activation has been extensively reviewed elsewhere [2,11]. Increased TβRI and -II expression is seen in SSc fibroblasts, as is transcriptional activation of TβRI and TβRII receptors, both suggesting enhanced activity. Perturbed TGF-β signaling in SSc fibroblasts is also demonstrated by altered smad7 and smurf1 and smurf2 expression (which are negative regulators of the signaling pathway). α(v)β3 integrin is an active receptor for latent TGF-β1, which shows increased expression in SSc fibroblasts. Transient overexpression of α(v)β3 integrin in normal fibroblasts induced promoter activity of human α2(I) collagen gene and decreased mmp-1 gene [12,13]. Other investigations into downstream signals from TGF-β demonstrate that procontractile signals from TGF-β were integrated through syndecan-4 and mitogen-activated protein kinase/extracellular signal regulated kinase (MEK/ERK) (Figure 3) [14].

Although some of the aforementioned data are contradictory, there is overall evidence that TGF-β overexpression exerts downstream effects resulting in the profibrotic phenotype. It appears to be an ideal target for immunotherapy. However, as TGF-β is such a ubiquitous molecule, there are, of course, potential pitfalls in such a nonspecific block. Virtually every cell in the body is capable of producing TGF-β and carries receptors for it. It regulates the proliferation and differentiation of cells, embryonic development, wound healing and angiogenesis. In normal cells, TGF-β acts as a tumor suppressor. Its main role in the cell cycle is to arrest the G1 phase by stimulating production of the cyclin-dependent protein kinase inhibitor p15 and inhibiting essential cell cycle regulators, such as cyclins A and E. These result in decreased phosphorylation of the retinoblastoma gene product and enable it to bind to members of the E2F family of transcription
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Factors. Sequestered E2F is then unable to stimulate expression of genes that regulate progression through the cell cycle, such as c-myc and b-myc. Cancer cells carrying mutations in TGF-β pathways that confer resistance to growth inhibition show uncontrolled proliferation. TGF-β also plays a role in metastasis, with increased TGF-β production by cancer cells, higher proteolytic activity (noted through changes in the ECM) and increased cell-adhesion molecule presentation. Stimulation of angiogenesis is also important. In vivo, the importance of the TGF-β signaling pathway is demonstrated when human pancreatic and colon cancers are studied. A total of 100% and 83%, respectively, carry a TGF-β pathway mutation [15].

All leukocytes produce TGF-β, and it promotes their differentiation, while inhibiting their proliferation and activation. It is also a chemotactic stimulus. Mice deficient in TGF-β1 die from cardiac, pulmonary and gastric inflammation and Smad3-deficient mice develop chronic mucosal infections due to impairment of T-cell activation. Production of TGF-β1 by cancer cells limits host inflammation and, hence, helps them escape immunosurveillance [15].

Mouse studies exist that suggest a role for the TGF-β pathway in inhibition of atherosclerosis. Serum levels are low in those with atherosclerosis, and tamoxifen may work by increasing serum TGF-β levels [15]. Mouse models of fibrillino-pathies, as well as human genetic investigations, reveal that some critical and life-threatening aspects of the Marfan syndrome phenotype result from abnormal TGF-β signaling [16]. There is also evidence that the TGF-β3 isoform may confer an antifibrotic effect, through differential signaling through the TβR. Nonspecifically blocking the function of TGF-β could theoretically enhance the profibrotic phenotype, as well as exerting a range of effects as described above, including cell proliferation and risk of tumorigenesis, increased propensity to atherosclerosis and a contribution to mucosal inflammation.

Strategies for blockade of the TGF-β signaling axis
In theory, multiple routes for blocking TGF-β exist. Antisense oligonucleotides exist to bind complementary mRNA sequences and block translation of TGF-β mRNA itself, hence, preventing its production. Synthesized TGF-β exists in the extracellular environment in a latent form anchored to the cell surface or ECM by associating noncovalently with latency-associated peptide (LAP). Together these are termed the small latent complex (SLC) and are usually joined by latent TGF-β binding protein to form the large latent complex (LLC). This complex is able to bind to the ECM. TGF-β is activated in cases of extreme pH, high temperatures, radiation and the presence of thrombospondin-1, which binds LAP and induces a conformational change in the LLC, releasing the cytokine. Decorins and other small molecules, such as betaglycan and endoglin, inhibit this process. Commercially available monoclonal anti-TGF-β antibody has been shown to be efficacious. Alternatives include sequestration of the cytokine by soluble receptors or using naturally occurring TGF-β inhibitors, such as decorins, which have been shown to block TGF-β effects in vivo. Most other soluble proteins that bind TGF-β extracellularly have not been shown to block its action in vivo.

The most well-studied signaling pathway for TGF-β involves the Smad proteins. There have been eight discovered in vertebrates, divided into those activated by the receptor, R-Smad (Smad 1, 2, 3, 5 and 8), common mediator Smad, C-Smad (Smad 4) and inhibitory or I-Smad (Smad 6 and 7). Smad 2 and 3 are activated through the TβR. They then detach and form a heterotrimer with Smad 4 and the complex exerts gene transcription effects by translocating into the nucleus. There are many chaperones to Smad recruitment and binding. Alternative pathways are known to exist: studies in Smad4-deficient cancer cell lines still demonstrate the ability to respond to TGF-β [17]. αvβ6 integrin is able to bind the TGF-β–LAP
complex. LAP-β1 is a ligand for αvβ6 integrin and can result in activation of integrin-signaling complexes when combined with the actin cytoskeleton. Hence, this is a Smad-independent means of TGF-β signaling, which, in theory, could be separately targeted [18,19].

The TβRI, -RII and -RIII transmembrane receptors themselves can be modulated, preventing further downstream signaling, either Smad-dependent or independent. For instance, the small inhibiting molecule, SB431542, decreases TβRI kinase activity [20]. Inhibiting TGFβRII kinase using a specific inhibitor, SD208, reduced the expression of a cohort of fibrotic markers by dermal fibroblasts from patients with diffuse cutaneous SSc, and attenuated the elevated adhesive and contractile abilities of dendritic cell SSc fibroblasts [21]. Administration of recombinant adenovirus vector carrying cDNA of the TβRII decreases the availability of TGF-β [22]. Gene therapy using inhibitory Smad7 blocks the signaling cascade and inhibits bleomycin-induced fibrosis in animal models [23]. Connective tissue growth factor (CTGF) is a mitogenic peptide secreted by fibroblasts in response to TGF-β. In mammalian cells, it acts as a downstream mediator of TGF-β action on connective tissue cells only,

Active TGF-β is released from the latent form when LTBP/LAP is cleaved. TGF-β is then available to bind to the TGF-β receptor. The activated receptor is then able to phosphorylate Smad3, which binds Smad4. The resultant complex migrates to the nucleus, where it has effects on gene transcription and extracellular matrix synthesis. Transcription is also affected by other signaling complexes. Smad7 has an inhibitory effect on this process. Sites marked with a black cross in red circle denote sites of TGF-β inhibitors currently in development.

ERK: Extracellular signal-regulated kinase; LAP: Latency-associated peptide; LTBP: Latent transforming growth factor-β complex; MEK: Mitogen-activated protein kinase; TGF: Transforming growth factor; TSP: Thrombospondin.
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where it stimulates cell proliferation and ECM synthesis. CTGF does not. However, act on immune cells or epithelial cells. Monoclonal antibodies to CTGF may act as a more specific target for selective intervention in processes such as scleroderma fibrosis, without acting on the other homeostatic or immune effects of TGF-β [24–26].

Efficacy in animal models
None of the currently available animal models for scleroderma exhibit all the clinical characteristics of the disease. Each model can provide insight into the pathogenesis and potential therapeutic strategies when investigated.

The murine graft-versus-host-disease (GVHD) model accurately represents the skin and lung histopathology seen in human scleroderma patients, with this form of GVHD being mainly fibrotic rather than cytotoxic (Scl GVHD). It is known that cutaneous TGF-β and collagen are upregulated in this model. BALB/c mice, lethally irradiated, were transplanted with B10.D2 (H H2d) bone marrow and spleen cells across minor histocompatibility loci. The study mice were sacrificed at intervals up to day 75 (36–50 animals per experiment) and their back skin harvested for RNA extraction, flow cytometry, immunostaining and routine histologic staining. By day 21, sclerodermatous skin thickening was detectable on routine histopathological sections in the experimental group and absent in the controls. Increased TGF-β1 mRNA and collagen mRNA were confirmed in the experimental group, with increased CD11b+ mononuclear cell infiltrates, particularly in the deep dermis. In order to determine whether anti-TGF-β therapy could prevent skin thickening in the experimental group, these mice were then injected with a standard dose of anti-pan TGF-β antibodies on days 1 and 6 post bone marrow transplant. They were sacrificed on day 21, when all parameters of Scl GVHD were demonstrable. The anti-TGF-β antibody treatment did not prevent successful transplantation, but did prevent the skin thickening seen in Scl GVHD. The administration of an antagonist to the fibrogenic cytokine TGF-β can prevent the cutaneous fibrotic process in early Scl GVHD, presumably by blocking TGF-β. Although this murine model is less frequently used to study lung fibrosis, similar prevention of lung fibrosis was noted in the treatment group at day 21 [27].

Bleomycin is an established antitumor agent that is in widespread clinical use. Bleomycin hydrolase is present in most tissues, behaving as an inactivating enzyme, but is absent in the lungs and skin, hence the well-described side effect of bleomycin-induced fibrosis. This is an established rodent model for pulmonary fibrosis. Local bleomycin treatment has been found to induce dermal sclerosis that mimicked the histology of human scleroderma. Distant skin sites were not affected, and visceral involvement, other than in the lung, was absent. Autoantibodies were also detected in the serum after treatment [28,29]. TGF-β is known to play an important part in collagen production in bleomycin-induced fibrosis. In the model of bleomycin-induced scleroderma, TGF-β was detected on the infiltrating macrophages, as well as in the lesional skin. In several experimental animal models, antibodies to TGF-β or soluble TGF-βR inhibit the development of tissue fibrosis, either in the lung or skin [30]. Furthermore, trials in Smad3 null mice, using the above model to induce sclerodermatous skin change, revealed similar degrees of early inflammatory change but attenuated fibrosis, lower synthesis and accumulation of collagen and reduced collagen gene transcription in situ on day 28 compared with wild-type. This implies that ablation of Smad3 confers partial resistance to bleomycin-induced injury, without an early change in the inflammatory response [31].

A kinase-deficient mutant Type II TGF-βR, which encodes the extracellular and transmembrane portion of human TβRII, has been developed that can therefore engage free TGF-β ligand, but not initiate downstream signaling by phosphorylation. This has previously been shown to act as a competitive antagonist to TGF-β1 and, when expressed at high levels in vitro, operates as a dominant-negative inhibitor of TGF-β activity [32]. A fibroblast-specific expression of this mutant TGF-β receptor should selectively disrupt TGF-β signaling through these cells without disrupting other lineages or nonfibroblast functions of TGF-β. As expected, fibroblasts cultured from these mice were refractory to exogenous TGF-β; however, in vivo, adult transgenic mice, somewhat surprisingly, developed dermal and pulmonary fibrosis. The dominant-negative inhibitor effect found during high levels of expression in vitro obviously exerted more complex effects at the lower gene expression levels necessary for survival in vivo. Nonetheless, the unexpected development of fibrosis in this model provided strong direct evidence for the role of TGF-β-dependent signaling pathways in the development of fibrosis, and the potential importance of non-signaling ligand-binding proteins in modulating TGF-β receptor function in vivo [33].
Clinical development of TGF-β compounds in SSc

Preclinical development of TGF-β inhibitors is underway, with the indications including treatment of malignant processes and glaucoma in addition to the fibrotic diseases. Some of the agents under investigation are listed in Table 1, and described in greater detail below. Monoclonal antibodies with variable affinity for each of the TGF-β isoforms or, in fact, targeting all three, exist. Betaglycan, a recombinant form of soluble TβRII, is still at the preclinical stage, as are small-molecule inhibitors of the TβRI. An antisense TGF-β2 has undergone Phase II trials for glioblastoma [34]. Those trials involving SSc are detailed in Table 1. The first clinical trial of a neutralizing substance to TGF-β, CAT-192, was a human recombinant immunoglobulin (Ig)G4 antibody against TGF-β1. It was evaluated for safety and efficacy in humans with diffuse cutaneous SSc. Four groups, totaling 45 patients, were randomized into a placebo and three treatment groups: 0.5, 5 and 10 mg/kg. The medication was infused four-times in an 18-week period. Primary outcomes were safety and pharmacokinetics. Secondary outcomes included skin score, health assessment questionnaire, organ disease severity and biomarkers. Four scleroderma-associated deaths occurred, which were not thought to be treatment related. The study was not powered to assess efficacy for skin disease and no significant differences were seen either in secondary outcomes or adverse events between the groups. The treatment effects could not be demonstrated on skin biopsy specimens, but the primary outcome was achieved with the antibody appearing to be safe and reasonably well tolerated [35].

More recently, human monoclonal antibodies active against all three isoforms of TGF-β have been developed, and are currently undergoing Phase I trials in idiopathic pulmonary fibrosis. The lead candidate is GC1008. Its murine equivalent has provided promising data, which demonstrate reduction in fibrosis with preservation of organ function. Results of the Phase I safety study in idiopathic pulmonary fibrosis are due for publication at the end of 2006.

Small-molecule inhibition of TGF-β signaling is an alternative therapy that may gain widespread clinical use. Halofuginone, a plant alkaloid, was previously in use as an antiparasitic drug for animals, and is now recognized as an inhibitor of collagen Type I synthesis in various disease states characterized by excess collagen deposition. The mechanism of action is thought to be due to inhibition of TGF-β-dependent Smad3 phosphorylation. In vitro studies suggest it also inhibits angiogenesis through thrombospondin-1 expression and by inhibiting cell proliferation, which is being investigated as a potential therapy for treating malignant angiogenesis. An early Phase II trial in 13 patients with early diffuse cutaneous SSc used topical preparations of halofuginone hydrochloride and demonstrated a modest reduction in skin fibrosis. More recent Phase I studies have demonstrated that an orally administered formulation has achieved expected plasma therapeutic levels and is well tolerated. Primary uses of the oral medication include sclerodermatous GVHD and, potentially, the internal fibrotic complications of scleroderma itself [36,37]. Other small molecules are also being developed, in particular, agents that block ATP binding to the TβRI kinase (ALK5) are now available. These have been tested in animal models [38] and also appear to normalize some of the profibrotic features of SSc fibroblasts in vitro [39].

Patients with SSc often experience a skin-softening effect when being administered their iloprost infusions to treat the complications of their Raynaud’s phenomenon. This synthetic prostacyclin analog has also been shown to be

Table 1. Clinical development of transforming growth factor-β compounds in systemic sclerosis and related fibrotic conditions in humans.

<table>
<thead>
<tr>
<th>Product name</th>
<th>Mode of action</th>
<th>Disease studied</th>
<th>Phase</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAT-192</td>
<td>Anti-TGF-β1 antibody</td>
<td>Diffuse cutaneous systemic sclerosis</td>
<td>I and II</td>
<td>[35]</td>
</tr>
<tr>
<td>GC1008</td>
<td>Anti-pan-TGF-β antibody</td>
<td>Idiopathic pulmonary fibrosis</td>
<td>I</td>
<td>Results awaited</td>
</tr>
<tr>
<td>Halofuginone</td>
<td>Inhibition of TGF-β-dependent Smad3 phosphorylation</td>
<td>Diffuse cutaneous systemic sclerosis</td>
<td>III (topical preparation)</td>
<td>[36,37]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>I (oral preparation)</td>
<td></td>
</tr>
<tr>
<td>Iloprost</td>
<td>Synthetic prostacyclin analog, downstream inhibition of CTGF</td>
<td>Systemic sclerosis</td>
<td>Widespread clinical use</td>
<td>[40,41]</td>
</tr>
</tbody>
</table>

CTGF: Connective tissue growth factor; TGF: Transforming growth factor.
beneficial for intravenous treatment of pulmonary arterial hypertension. Prostanoids have been shown to exert an inhibitory effect on the synthesis of collagen by fibroblasts in vivo and studies suggest that downstream inhibition of TGF-β by iloprost may be responsible. Using wound chambers implanted into the back of rats, it was demonstrated that administration of TGF-β did indeed enhance the production of type I collagen. Iloprost markedly reduced this TGF-β-mediated induction of collagen protein, although it did not reduce basal levels in dimethyl sulfoxide (DMSO) controls. In a separate experiment, scleroderma dermal fibroblasts were found to secrete greater levels of basal CTGF than controls, and the addition of iloprost in vitro reduced the secretion by scleroderma fibroblasts but not the controls. Of interest, when TGF-β was used to stimulate CTGF production, both sets of fibroblasts responded similarly and coadministration of iloprost had a marked inhibitory action in both cases. In summary, iloprost appears to suppress the profibrotic effect of excess TGF-β while leaving the normal wound-healing process unaltered [40,41].

Future perspective
The future of TGF-β therapy of fibrotic conditions, of which SSc is a prototype, lies in the targeted suppression of TGF-β-mediated excessive fibrosis, ideally without interference into the other homeostatic functions of the cytokine. Interference into the role of TGF-β meditated cell cycle control is obviously a concern, hence using downstream mediators, such as CTGF, may be a safer and more specific option. Small-molecule inhibitors, again of the TGF-β signaling pathway through the Smads, also show promise in early clinical trials, both in fibrotic and nonfibrotic conditions.

Late-stage scleroderma with end-organ damage, such as lung or gut disease, is unlikely to respond to the TGF-β-based therapies, where the mechanism of action appears to rely on prevention of the early deposition of collagen and ECM. The significant mortality and morbidity due to the condition in the long term will not be addressed. However, the awareness of scleroderma as a prototype for fibrotic diseases has helped the research interest into this field enormously. Until the trials of endothelin antagonists into connective tissue disease-related pulmonary hypertension, there were no licensed therapies available for SSc at all. The US FDA decision to grant orphan status to some of these medications will allow further clinical audit and research and further advance the field.

In summary, TGF-β remains the molecular target of choice in SSc based upon preclinical studies in animal models and on ex vivo analysis of SSc fibroblasts. However, safety remains a major concern and the extent to which TGF-β bioactivity may be safely blocked remains uncertain. Biological agents are more likely to be of benefit in vivo since, whilst potent inhibitors are being developed, they may not completely block TGF-β. In addition plasma concentrations may be difficult to achieve in patients.

### Executive summary

#### Background
- The spectrum of disease discussed in this article ranges from Raynaud's phenomenon to limited and diffuse cutaneous systemic sclerosis (SSc). The latter two result in significant morbidity and mortality due to vasculopathy, inflammation and fibrosis. Disproportionate fibroblast activity results in a profibrotic phenotype in these patients.

#### Rationale for transforming growth factor-β blockade in systemic sclerosis
- There is good evidence that transforming growth factor (TGF)-β is a pivotal upstream mediator of the adverse tissue characteristics seen in SSc.
- Smads are the main intracellular molecules responsible for downstream signaling of TGF-β. There are also Smad-independent signaling pathways.
- TGF-β is a ubiquitous molecule and is responsible for cell cycle control and cell differentiation. It may also inhibit atherosclerosis. Blocking this molecule would potentially have far wider consequences than the control of fibrosis alone.

#### Strategies for blockade of the TGF-β-signaling axis
- Theoretically, strategies for blockade of the TGF-β-signaling axis exist at each level in the signaling cascade. They include using both monoclonal antibodies and naturally occurring inhibitors.
- Connective tissue growth factor is secreted by fibroblasts in response to TGF-β and is more specific since it acts only on connective tissue cells, causing cell proliferation and extracellular matrix synthesis.
Executive summary

Efficacy in animal models

- Several murine models for SSc exist, none of which exhibit all the characteristics of the disease.
- The murine graft-versus-host disease (GVHD) model represents the skin and lung pathology seen in SSc. When TGF-β antibodies are injected, skin, thickening is prevented.
- TGF-β antibodies inhibited lung and skin fibrosis in the bleomycin-induced fibrotic lung disease model. Smad3-deficient mice were resistant to bleomycin-induced injury.
- The dominant-negative inhibitor effect caused lung and skin fibrosis in a mouse with a mutant TGF-β receptor due to deficient kinase activity. In vitro, their fibroblasts had been refractory to the higher levels of TGF-β used.

Clinical development of TGF-β compounds in systemic sclerosis

- CAT-192 is a human recombinant immunoglobulin G4 antibody against TGF-β1, which was shown to be safe and well tolerated in Phase II trials in diffuse cutaneous SSc.
- GC1008 is the lead candidate blocking all three isoforms of TGF-β. Phase I trials in idiopathic pulmonary fibrosis have commenced.
- Halofuginone is a plant alkaloid thought to inhibit TGF-β signalling. Topical preparations show a modest reduction in skin thickness in diffuse disease.
- Agents that block ATP binding to the TβR1 kinase are available. These normalize some of the profibrotic features of SSc fibroblasts in vitro.
- Iloprost is a synthetic prostacyclin analog that markedly reduced TGF-β1-mediated induction of Type I collagen.

Bibliography

Papers of special note have been highlighted as either of interest (*) or of considerable interest (**) to readers.
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