Published in final edited form as:
Int J Biochem Cell Biol. 2008 ; 40(3): 362–382.

The bleomycin animal model: a useful tool to investigate treatment options for idiopathic pulmonary fibrosis?

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Abstract

Different animal models of pulmonary fibrosis have been developed to investigate potential therapies for idiopathic pulmonary fibrosis (IPF). The most common is the bleomycin model in rodents (mouse, rat and hamster). Over the years, numerous agents have been shown to inhibit fibrosis in this model. However, to date none of these compounds are used in the clinical management of IPF and none has shown a comparable antifibrotic effect in humans. We performed a systematic review of publications on drug efficacy studies in the bleomycin model to evaluate the value of this model regarding transferability to clinical use. Between 1980 and 2006 we identified 246 experimental studies describing beneficial antifibrotic compounds in the bleomycin model. In 221 of the studies we found enough details about the timing of drug application to allow inter-study comparison. 211 of those used a preventive regimen (drug given ≤ day 7 after last bleomycin application), only 10 were therapeutic trials (> 7 days after last bleomycin application). It is critical to distinguish between drugs interfering with the inflammatory and early fibrogenic response from those preventing progression of fibrosis, the latter likely much more meaningful for clinical application. All potential antifibrotic compounds should be evaluated in the phase of established fibrosis rather than in the early period of bleomycin-induced inflammation for assessment of its antifibrotic properties. Further care should be taken in extrapolation of drugs successfully tested in the bleomycin model due to partial reversibility of bleomycin induced fibrosis over time. The use of alternative and more robust animal models, which better reflect human IPF, is warranted.

Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic progressive and ultimately fatal lung disease of unknown etiology. Its prognosis is poor and the outcome even worse than in many malignant diseases. IPF is one of the most frequent interstitial lung diseases and is characterized by the histological pattern of usual interstitial pneumonia (UIP) (ATS, 2000). The natural history of IPF is unknown and the onset of symptoms is gradual, starting usually with non-productive

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cough and exertional dyspnea. With involvement of larger areas of the lung, severe dyspnea at rest and signs of right heart failure develop (ATS, 2002). In some cases the clinical state is preserved for a period of several years, but the majority of patients deteriorate more rapidly. Mortality during acute exacerbation is high. The prevalence of IPF is estimated at 20/100,000 for males and 13/100,000 for females, and survival time from diagnosis ranges from 2 to 4 years (D. S. Kim, Collard, & King, 2006). Histological characteristics of UIP include remodeling of lung architecture with fibroblastic foci and “honeycombing”. The lung involvement is patchy with a predominantly basal and subpleural pattern of matrix deposition and tissue distortion (ATS, 2002). Most patients present at an advanced stage of disease. Treatment options for pulmonary fibrosis are limited. The clinical management focuses on treatment of complications (e.g. right heart failure, infections, etc.), supportive care and in few cases involves lung transplantation. Anti-inflammatory drugs such as prednisone may carry symptomatic relief, but they do not appear to halt progression of fibrosis, and their beneficial effects in IPF remain in question. Cytotoxic drugs (cyclophosphamide, azathioprin, etc) have not been shown to improve lung function or life expectancy and may be associated with harmful side effects.

The last two decades have markedly improved the knowledge about underlying mechanisms of pulmonary fibrosis and helped to identify potential targets for novel therapies. However, despite the large number of anti-fibrotic drugs being described in experimental pre-clinical studies, the translation of these findings into clinical practice has not been accomplished yet. This review will focus on the bleomycin model of pulmonary fibrosis, highlight its undisputable contribution to investigation of basic pathomechanism of disease and critically reflect its usefulness in determining efficacy of antifibrotic drugs.

Animal models of pulmonary fibrosis

Animal models play an important role in the investigation of diseases, and many models are established to examine pulmonary pathobiology. Chronic diseases are more difficult to model. The situation with IPF is even more complicated, since the etiology and natural history of the disease is unclear and no single trigger is known that is able to induce “IPF” in animals. Different models of pulmonary fibrosis have been developed over the years. Most of them mimic some, but never all features of human IPF, especially the progressive and irreversible nature of the condition. Common methods include radiation damage, instillation of bleomycin, silica or asbestos, and transgenic mice or gene transfer employing fibrogenic cytokines. So far, the standard agent for induction of experimental pulmonary fibrosis in animals is bleomycin.

Bleomycin

Bleomycin is a chemotherapeutic antibiotic, produced by the bacterium “Streptomyces verticillus” (Adamson, 1976; Umezawa, 1967). Its use in animal models of pulmonary fibrosis is based on the fact that fibrosis is one of the major adverse drug effects of bleomycin in human cancer therapy. Bleomycin plays an important role in the treatment of lymphoma, squamous cell carcinomas, germ cell tumors and malignant pleural effusion, where it is injected intrapleurally. It is believed that bleomycin acts by causing single and double-strand DNA breaks in tumor cells and thereby interrupting the cell cycle. This happens by chelation of metal ions, and reaction of the formed pseudoenzyme with oxygen, which leads to production of DNA-cleaving superoxide and hydroxide free radicals (Claussen & Long, 1999). An overproduction of reactive oxygen species can lead to an inflammatory response causing pulmonary toxicity, activation of fibroblasts and subsequent fibrosis (Chaudhary, Schnapp, & Park, 2006; Grande NR, 1998). Bleomycin hydrolase, a bleomycin-inactivating enzyme, critically influences the effects of this drug on different tissues. The lungs maintain low levels of the enzyme and therefore are more susceptible to bleomycin-induced tissue injury(Sebti, Mignano, Jani, Srimatkandada, & Lazo, 1989). Pulmonary side effects in patients are dose-dependent, age-related and occur more often in the presence of pre-existing pulmonary diseases or smoking. Lung toxicity develops in ~10% of patients receiving bleomycin, and is clinically associated with cough, dyspnea, fever, cyanosis, and deterioration of lung function parameters. Within weeks to months this response might progress to pulmonary fibrosis in ~1% of patients ("Compendium of Pharmaceuticals and Specialties. Blenoxane®. Canadian Pharmacists Association." 2006).

The bleomycin animal model

Bleomycin as an agent to induce experimental lung fibrosis was first described in dogs (Fleischman et al., 1971), later in mice (Adamson & Bowden, 1974), hamsters (Snider, Celli, Goldstein, O'Brien, & Lucey, 1978), and rats (Thrall, McCormick, Jack, McReynolds, & Ward, 1979). It causes inflammatory and fibrotic reactions within a short period of time, even more so after intratracheal instillation. The initial elevation of pro-inflammatory cytokines (interleukin-1, tumor necrosis factor-α, interleukin-6, interferon-γ) is followed by increased expression of pro-fibrotic markers (transforming growth factor-β1, fibronectin, procollagen-1), with a peak around day 14. The "switch" between inflammation and fibrosis appears to occur around day 9 after bleomycin (Chaudhary, Schnapp, & Park, 2006). Notable in the murine model are remarkable strain differences in susceptibility to develop fibrosis following bleomycin, with CBA and C57Bl/6 mice being strong responders and Balb/c mice relatively fibrosis-resistant. These differences are likely due to different expression patterns of cytokines and proteases/ anti-proteases (Phan & Kunkel, 1992).

It has been reported that histological hallmarks, such as intra-alveolar buds, mural incorporation of collagen and obliteration of the alveolar space, are present in bleomycin-treated animals similar to IPF patients (Usuki K, 1995). This observation has led to the assumption, that bleomycin reproduces typical features of the human disease and hence, the use of this model has become very popular. Further, the bleomycin model has the advantage that it is quite easy to perform, widely accessible and reproducible, and therefore fulfills important criteria expected from a good animal model. Fairly consistent dosages have been established for each species to achieve a fibrotic response, and, dependent on the route of administration, different fibrotic patterns develop. Intratracheal instillation of bleomycin, the standard route of administration, results in bronchiocentric accentuated fibrosis, whereas intravenous or intraperitoneal administration induces subpleural scarring similar to human disease (Chua, Gauldie, & Laurent, 2005). The bleomycin model has contributed tremendously to elucidate the roles of cytokines, growth factors and signaling pathways involved in pulmonary fibrosis. For instance, it has helped to determine transforming growth factor (TGF) β as one of the key factors in the development of pulmonary fibrosis (J. Zhao et al., 2002). A number of novel (e.g. TGFβ antagonists) and not so novel (e.g. ACE-inhibitors) drugs interfering with TGFβ have been investigated in the bleomycin model, some of them quite promising. One of them is decorin, an endogenous proteoglycan and known TGFβ inhibitor. It has been shown that intratracheal administration of Decorin using an adenovirus vector leads to a substantial reduction of the fibrotic response to bleomycin (Kolb et al., 2001).

However, despite undisputed qualities and some similarities in histological alterations, the bleomycin model has significant limitations in regard to understanding the progressive nature of human IPF. As mentioned, bleomycin causes an inflammatory response, triggered by overproduction of free radicals, with induction of pro-inflammatory cytokines and activation of macrophages and neutrophils, thus resembling acute lung injury in some way. The subsequent development of fibrosis, however, is at least partially reversible, independent from any intervention (Izbicki, Segel, Christensen, Conner, & Breuer, 2002). The aspect of slow and irreversible progression of IPF in patients is not reproduced in the bleomycin model (Chua, Gauldie, & Laurent, 2005). One of the most critical hallmarks of human IPF is therefore not present in animals, which has to be considered when this model is used for drug intervention studies.

Drug intervention studies in the bleomycin model

The bleomycin animal model is widely used in the assessment of potential antifibrotic agents. A large number of compounds have been shown to prevent fibrotic progression in this model and have been suggested to qualify for clinical use. We performed a Pub Med search and identified 232 papers published between 1980 and 2006 which discuss antifibrotic compounds in the bleomycin model. All these compounds were reported to be successful and antifibrotic, either as “preventive treatment” (that means given early, ≤ day 7 after last bleomycin application), and/or therapeutically (> 7 days after last bleomycin application) (figure 1). Some authors compared the effects of several compounds, increasing the total number to 246 experimental attempts (table 1).

In most of the studies bleomycin was given by a single intratracheal instillation in weight adjusted dosages. We defined the day of bleomycin administration as day 0, allowing the association of this time point with the schedule of compound administration. This is important in order to distinguish between anti-inflammatory and antifibrotic drug effects, as the interpretation of drug effects is crucially dependent on timing of compound administration. Compounds administered during the early phase may predominantly act as anti-inflammatory agents and should be considered as “preventive treatment”, whereas “true” antifibrotic agents might be effective irrespective of timing, particularly if administered during the “fibrotic” phase of the model (Chaudhary, Schnapp, & Park, 2006). In the vast majority of the reviewed studies, the compound was given as preventive treatment, thus confounding the designation as anti-inflammatory or anti-fibrotic.

Different routes of drug administration were applied, including oral, subcutaneous, intraperitoneal, or intravenous injections. Further, gene modifying techniques were used, such as adenoviral or HVJ (hemagglutinating virus of Japan) envelope vector mediated gene transfer, intramuscular gene transfection, or gene knock out. Mice and rats were by far the most common species, followed by hamsters, rabbits and dogs. The endpoints were variable, ranging from day 1 to day 80 after bleomycin, most frequently between day 14 and day 28. Choosing the correct endpoint in the bleomycin model is critical, especially as it has been shown that the standard outcome parameters are highly variably after day 21 and may even return back to baseline (histomorphomerty and hydroxyproline lung content) (Izbicki, Segel, Christensen, Conner, & Breuer, 2002).

For the assessment of fibrosis several common methods were used, including semi-quantitative histological analysis, sometimes based on the scoring system by Ashcroft (Ashcroft, Simpson, & Timbrell, 1988), and quantification of hydroxyproline and/or collagen content. Broncho-alveolar lavage fluid (BALF) was often analyzed for changes in total cell count, differential count of leucocytes, and measurement of tumor necrosis factor alpha (TNF) α or TGFβ levels. The expression of other pro-inflammatory mediators, e.g. monocyte chemoattractant protein-1 (MCP-1) and macrophage inflammatory protein-2 (MIP-2) was quantified in some cases. Additional parameters such as weight, lung index (lung wet weight in mg versus body weight in g) and survival time were not always, but frequently assessed. Measurement of enzyme activities was performed, including superoxide dismutase (SOD) and catalase (CAT), as indicators of the generation of free radicals, myeloperoxidase (MPO), as a marker of neutrophil influx and malondialdehyde (MDA), as an index of oxidative stress. Occasionally the TUNEL (terminal deoxynucleotidyl transferase mediated dUTP nick end labeling) assay was applied to identify apoptotic cells in situ.

A great variety of compound classes showing apparent antifibrotic effects in the bleomycin model have been identified. Those that appear to have a major effect include: Antioxidants (Ambroxol (Pozzi et al., 1989; Pozzi et al., 1987), Niacin (A. Nagai et al., 1994; O'Neill & Giri, 1994; Q. J. Wang, Giri, Hyde, Nakashima, & Javadi, 1990), Taurin (Blaisdell & Giri, 1995; Giri & Wang, 1992; Gurujeyalakshmi, Hollinger, & Giri, 1998; Gurujeyalakshmi, Iyer, Hollinger, & Giri, 1996; Gurujeyalakshmi, Wang, & Giri, 2000; Q. Wang, Hyde, & Giri, 1992; Q. J. Wang, Giri, Hyde, & Nakashima, 1989), N-Acetylcysteine (Cortijo et al., 2001; Hagiwara, Ishii, & Kitamura, 2000; Mata et al., 2003; Serrano-Mollar et al., 2003; Shahzeidi, Sarnstrand, Jeffery, McAnulty, & Laurent, 1991; Yildirim et al., 2005), Vitamin E (Kilinc et al., 1993), Curcumin (Punithavathi, Venkatesan, & Babu, 2000), Aminoguanidine (X. L. Chen, Huang, Li, Wang, & Wang, 2001; X. L. Chen, Li, Zhou, Ai, & Huang, 2003; de Rezende, Martinez, Capelozzi, Simoes, & Beppu, 2000; Giri, Biring, Nguyen, Wang, & Hyde, 2002; Hu, Xu, & Li, 1999; Yildirim et al., 2004), Melatonin (Arslan, Zerin, Vural, & Coskun, 2002; Genovese, Di Paola et al., 2005; Yildirim et al., 2006), Bilirubin (H. D. Wang et al., 2002), CAPE = caffeic acid phenethyl ester (Ozyurt et al., 2004), Erdosteine (Boyaci et al., 2006; Sogut et al., 2004; Yildirim et al., 2005; Yildirim et al., 2004) etc.), Angiotensin converting enzyme inhibitors (Captopril (R. Wang, Ibarra-Sunga, Verlinski, Pick, & Uhal, 2000), Ramipril (Marshall et al., 2004) etc.), Angiotensin receptor blockers (Losartan (Fang, Zhu, Hu, & Liu, 2002; Marshall et al., 2004; Yao, Zhu, Zhao, & Lu, 2006), Candesartan (Otsuka, Takahashi, Shiratori, Chiba, & Abe, 2004), Valsartan (F. Liu, Xu, & Ye, 2005; Mancini & Khalil, 2005) etc.), Anticoagulants (TFPI = tissue factor pathway inhibitor (Kijiyama et al., 2006), Urokinase (Hart, Whidden, Green, Henkin, & Woods, 1994; Hattori et al., 2004; Howell et al., 2001; Howell, Laurent, & Chambers, 2002; Ikeda, Hirose, Koto, Hirano, & Shigematsu, 1989), Heparin (Gunther et al., 2003; Piguet, Van, & Guo, 1996), APC = anticoagulant protein C (S. Shimizu et al., 2003; H. Yasui et al., 2001), Thromboxane synthetase inhibitor (Sato et al., 2004) etc.), Macrolide antibiotics (Erythromycin (Azuma et al., 1998; B. Chen, Jiang, Zhao, Yu, & Hou, 1997; Y. Li, He, & Wang, 1999; Tan, Liu, He, & Xu, 1999), Azithromycin (J. Chen, He, Li, Wang, & Zhang, 1999; Ma, He, Li, & Zhang, 2002), Clarithromycin (Azuma et al., 2001; Kawashima et al., 2002; Y. Li, Azuma, Takahashi et al., 2002), Roxithromycin (Azuma et al., 2001; Kawashima et al., 2002; Y. Li, Azuma, Takahashi et al., 2002) etc.), Cytokines (Interferon-β (Azuma, Li et al., 2005), Interferon-γ (Gurujeyalakshmi & Giri, 1995; Hyde, Henderson, Giri, Tyler, & Stovall, 1988; Okada, Sugie, & Aisaka, 1993), Interleukin (IL)-1beta (M. Yasui et al., 1991), IL-10 (Arai et al., 2000), IL-18 (Nakatani-Okuda et al., 2005), Keratinocyte growth factor (Deterding et al., 1997; Sugahara, Iyama, Kuroda, & Sano, 1998; Yi et al., 1996), Hepatocyte growth factor (Dohi, Hasegawa, Yamamoto, & Marshall, 2000; Mizuno, Matsumoto, Li, & Nakamura, 2005; Umeda et al., 2004; Yaekashiwa et al., 1997), Chemokine ligand (CXCL)-10 (Tager et al., 2004),CXCL11 (Burdick et al., 2005), CD (cluster of differentiation)-36 (Yehualaeshet et al., 2000) etc.), Cytokine antibodies (Transforming growth factor-β (Giri, Hyde, & Hollinger, 1993), Tumor necrosis factor-α (Fichtner-Feigl, Strober, Kawakami, Puri, & Kitani, 2006; Fujita et al., 2003; Piguet & Vesin, 1994), Connective tissue growth factor (Matsuoka et al., 2002), IL-12 (Maeyama et al., 2001), IL-13 (Fichtner-Feigl, Strober, Kawakami, Puri, & Kitani, 2006), Platelet derived growth factor (Aono et al., 2005; Chaudhary, Schnapp, & Park, 2006; Daniels et al., 2004; Yoshida et al., 1999), Vascular endothelial growth factor (Hamada et al., 2005), CCR-1 (Tokuda et al., 2000), CCR-3 (Huaux et al., 2005), CCL-11 (Huaux et al., 2005), CD-11 (Piguet, Rosen, Vesin, & Grau, 1993), MCP-1 (Inoshima, Kuwano, Hamada, Hagimoto et al., 2004) etc.), Chinese herbs (Feitai (Gong et al., 2004; Gong et al., 2005; Shen et al., 2005), Salviae miltiorrhizae (Hua, Cui, & Liu, 1994; J. Liu, 1992; J. Liu et al., 1993), Ginkgo biloba (Daba et al., 2002; Iraz et al., 2006), Moxibustion (R. Li et al., 2005), Fufang (Kong et al., 2005) etc.), Immunosuppressants (Cyclosporin-A (Lossos, Or, Goldstein, Conner, & Breuer, 1996), Rapamycin analogue SDZ RAD (Simler et al., 2002)), Corticosteroids (Dexamethasone (F. Chen et al., 2006; Dik et al., 2003; H. P. Li, Li, He, Yi, & Kaplan, 2004), Methylprednisolone (Phan, Thrall, & Williams, 1981), Prednisolone (Chaudhary, Schnapp, & Park, 2006; Entzian et al., 1998) etc.), Chelating agents (D-Penicillamine (Geismar, Hennessey, Reiser, & Last, 1986) etc.), and Pirfenidone (Ammar et al., 2006; Gurujeyalakshmi, Hollinger, & Giri, 1999; Iyer, Gurujeyalakshmi, & Giri, 1999; Iyer, Hyde, & Giri, 2000; Iyer, Margolin, Hyde, & Giri, 1998; Iyer et al., 1995; Kakugawa et al., 2004; Mansoor, Chen, Schelegle, & Giri, 1999; Schelegle, Mansoor, & Giri, 1997). Considering the extensive number of compounds we will discuss only a few representative examples in greater detail. The full list is provided in table 1.

Selected examples of preventive compounds

Ginkgo biloba

is a flavonoid-rich antioxidant, containing ginkgolides extracted from Ginkgo leaves. Clinically, this substrate is used as a memory enhancer, anti-vertigo agent and for intermittent claudication. Evidence exists that Gingko biloba improves blood flow, protects from free radicals and blocks platelet aggregation and blood clotting (Dubey, Shankar, Upadhyaya, & Deshpande, 2004; Ernst, 2002; Mahady, 2002). These properties appear to be potentially antifibrotic, and for that reason Gingko biloba has been examined in the bleomycin model. Investigators administered Ginkgo biloba orally from day −1 to day 14, which led to a lower degree of fibrosis in treated animals compared to bleomycin controls. Fibrosis was assessed by using Ashcroft score, hydroxyproline content, BALF total cell count, nitrite levels, and enzyme activities (Iraz et al., 2006).

Losartan

is an angiotensin II receptor antagonist, clinically used for the treatment of systemic hypertension, diabetic nephropathy and for prevention of cardiovascular events. Several reports have promoted Losartan as inhibitor of fibrotic progression in the bleomycin model (Fang, Zhu, Hu, & Liu, 2002; Marshall et al., 2004; Molina-Molina et al., 2006), and a recent report confirmed these findings (Yao, Zhu, Zhao, & Lu, 2006). Losartan was given by daily gavage from day 0 to day 14 or to day 21. Alveolitis and fibrosis scores were significantly lower, hydroxyproline content reduced and TGF-β1 levels lower compared to untreated control rats, which had received bleomycin only. The drug treated animals also lost less weight and had lower indices of lung fibrosis. The antifibrotic effect of Losartan in the context of pulmonary fibrosis might be associated with antioxidant activity and reduction in TGF-β1 levels (Yao, Zhu, Zhao, & Lu, 2006).

EM703

is a derivate of erythromycin, a macrolide antibiotic, which is first line therapy for community-acquired pneumonia. Erythromycin is produced from a strain of actinomyces and contains a 14-membered lactone ring. It prevents growth of typical and atypical bacteria by interfering with their protein synthesis. EM703 is a derivate of erythromycin and has been reported to exhibit anti-inflammatory activity independent from anti-bacterial activity by suppressing nuclear factor-κ B and inhibiting interleukin-8 expression (Y. Li et al., 2006). Previously, 14-membered macrolides have been shown to attenuate leukocyte migration in the early inflammatory phase and thereby prevent bleomycin induced lung fibrosis (Y. Li, Azuma, Takahashi et al., 2002). A recent study confirms the preventive effect of EM703 when orally administered starting three days prior to bleomycin. The degree of fibrosis was assessed by Ashcroft score, hydroxyproline content, and BALF cell counts. The authors concluded that EM703 improves bleomycin-induced pulmonary fibrosis in mice by acting as an anti-inflammatory agent and regulating TGF-β signaling (Y. Li et al., 2006).

Selected examples of therapeutic compounds

Pirfenidone

is an orally active small molecule drug with anti-inflammatory, antioxidant and antifibrotic effects. It is known that Pirfenidone modifies the regulation of cytokines, including PDGF, and thereby inhibits fibroblast proliferation and extracellular matrix synthesis. It has also been shown to reduce the increase in TGF-β levels after bleomycin administration. The exact mechanism for the antifibrotic effect is not yet fully understood (Gurujeyalakshmi, Hollinger, & Giri, 1999). Therapeutic antifibrotic effects have been observed in the bleomycin model, when animals received Pirfenidone starting 14 days after bleomycin administration. The authors concluded that this drug may have antifibrotic potential, since it had been administered after the inflammatory phase had subsided. They speculated that this might be based on inhibition of heat shock protein 47 positive cells and α−smooth muscle actin positive myofibroblasts (Kakugawa et al., 2004). Pirfenidone has recently been tested in multiple clinical trials, showing some promising results such as improvement of vital capacity and reduction of acute exacerbations (Azuma, Li et al., 2005). To further clarify the safety of this drug, a large phase III clinical trial (CAPACITY) has been initiated in 2006.

Hepatocyte growth factor (HGF)

is a multifunctional growth factor produced by mesenchymal cells such as fibroblasts, macrophages and endothelial cells. HGF acts on epithelial cells as a mitogen, stimulating migration and morphogenesis (Dohi, Hasegawa, Yamamoto, & Marshall, 2000; Yaekashiwa et al., 1997). It is described as potent inducer of matrix metalloproteinases (MMPs), which degrade extracellular matrix and are overexpressed during progression of myofibroblast apoptosis (Mizuno, Matsumoto, Li, & Nakamura, 2005). HGF levels are increased in the BALF of IPF patients (Dohi, Hasegawa, Yamamoto, & Marshall, 2000) and evidence exists that its function is protective against lung damage, preventing subsequent fibrogenesis (Mizuno, Matsumoto, Li, & Nakamura, 2005). Similar antifibrotic properties were demonstrated in an animal study, where bleomycin was administered by intraperitoneal infusion from day 0 to day 7, followed by infusion of recombinant HGF from day 7 to day 14, day 14 to day 21, or day 21 to day 28. Fibrosis scores as well as hydroxyproline levels were markedly reduced in the different treatment times, even in the later time points where hydroxyproline levels fell to normal after one week of therapy, implying that recombinant HGF is effective in diminishing fibrotic changes even in established fibrosis (Yaekashiwa et al., 1997) (Mizuno, Matsumoto, Li, & Nakamura, 2005)

Most recently **BIBF 1000**, a selective inhibitor of the group of vascular endothelial growth factor (VEGF), platelet derived growth factor (PDGF) and fibroblast growth factor (FGF) receptor tyrosine kinases, has been tested as an anti-fibrotic agent. These growth factors are known as fibrogenic mediators promoting fibroblast proliferation and matrix contraction. BIBF has been applied orally from day 10 to day 21 in the bleomycin treated rat model leading to reduced gene expression of transforming growth factor (TGF)-β1, procollagen-1, fibronectin and connective tissue growth factor (CTGF), as well as less collagen staining in treated animals compared to bleomycin controls (Chaudary NI, 2007). This compound is currently entering clinical trials in IPF.

Clinical trials

Only a relatively small number of compounds considered as having “promising antifibrotic properties” in the bleomycin model were or currently are tested in clinical trials (Walter, Collard, & King, 2006). Some of them were retrospective analyses or case series only. Among the drugs tried or on trial are Etanercept, Imatinib, Prednisone (Daniil et al., 1999; Douglas et al., 1997; Douglas, Ryu, & Schroeder, 2000; Douglas et al., 1998; Nicholson AG, 2000; Riha et al., 2002; Ziesche, Hofbauer, Wittmann, Petkov, & Block, 1999), N-Acetylcysteine (Demedts et al., 2005), TGF-β antibody (Genzyme, 2007), Interferon-γ (Antoniou et al., 2006; Raghu et al., 2004; Raghu R, 2001), Interferon-β (Raghu, Bozic, & Brown, 2001), Pirfenidone (Azuma, Nukiwa et al., 2005; S. Nagai et al., 2002; Raghu, Johnson, Lockhart, & Mageto, 1999), Colchicine (Douglas, Ryu, & Schroeder, 2000; Douglas et al., 1998; Selman et al., 1998), Bosentan, Cyclosporin-A (Alton, Johnson, & Turner-Warwick, 1989; Moolman, Bardin, Rossouw, & Joubert, 1991), D-Penicillamin (Chapela, Zuniga, & Selman, 1986; Selman et al., 1998), Heparin (Kubo et al., 2005), Relaxin (ATS, 2002), Angiotensin converting enzyme (ACE) inhibitors (Nadrous, Ryu, Douglas, Decker, & Olson, 2004), and CTGF antibodies (Mageto Y, 2004). Interestingly, azathioprine and cyclophosphamide, two drugs that are still in the current ATS/ERS guidelines for IPF treatment (ATS, 2002), have never been evaluated in the bleomycin model as far as we know. However, to date none of these drugs have shown comparable success in patients as seen in the bleomycin model. One major issue is the fact that most agents were given to the animals in a preventive regimen, prior to or simultaneous with bleomycin. As discussed earlier, effectiveness in this setting may reflect more anti-inflammatory action by blocking the early response without influencing the subsequent events causing progressive fibrosis. This type of activity can hardly be considered as novel or sufficient, since other potent anti-inflammatory drugs, such as corticosteroids, have failed to improve the course of IPF in patients. Theoretically, compounds which are successfully administered as “therapeutic treatments” in animal models should be much more promising candidates for clinical use.

Selected examples of compounds in clinical trials

N-Acetylcysteine (NAC)

is a precursor in the formation of the antioxidant glutathione and possesses the ability of reducing free radicals. This drug has been in clinical use as mucolytic therapy in a variety of respiratory diseases, in the management of acetaminophen overdose, and in the prevention of radiocontrast-induced nephropathy by augmenting glutathione reserves for binding of toxic metabolites. In the context of pulmonary fibrosis, is has shown effectiveness as preventive medication in the bleomycin animal model (Yildirim et al., 2005). The IFIGENIA study, a double-blind, randomized, placebo-controlled trial enrolling 182 IPF patients, tested NAC in combination with prednisone and azathioprine. Treatment with NAC compared to placebo resulted in a small, but significant delay of functional deterioration over one year (forced vital capacity and diffusion capacity for CO), but there was no improvement in survival. The interpretation of this trial is difficult, because NAC was used in a triple therapy and may have helped to tolerate the cytotoxic drugs better without having an impact on fibrogenesis. The NIH-IPF network has announced the intention to perform a trial of monotherapy with NAC versus placebo to clarify this issue.

Bosentan (Tracleer®)

is an endothelin (ET) receptor antagonist, which blocks ET_A and ET_B receptors in endothelium and vascular smooth muscle and thereby prevents the hormone endothelin-1 (ET-1) from binding to these receptors. ET-1 causes vasoconstriction of pulmonary blood vessels leading to pulmonary artery hypertension. Currently, Bosentan is in clinical use for treatment of pulmonary hypertension, given orally in increasing dosages. Bosentan has been investigated in the bleomycin animal model as a preventive drug showing increased volumes of total air and decreased volumes of connective tissue. This led to the assumption that Bosentan might be a useful medication for IPF patients, even more so for those with superimposed pulmonary hypertension (Park, Saleh, Giaid, & Michel, 1997). A series of clinical trials has already been carried out. The outcomes of BUILD-1, a double-blind randomized, placebo-controlled study enrolling 158 patients with IPF showed no effect on functional parameters but positive trends on survival at 12 months. BUILD-2 showed similar effects in scleroderma patients with secondary interstitial lung disease. Currently, BUILD-3 is underway, expecting the enrollment of ~400 IPF patients with time to disease worsening or death as primary outcomes.

Etanercept (Enbrel®)

is an antagonist of tumor necrosis factor alpha (TNF-α) receptor. TNF-α is a cytokine, produced by monocytes and macrophages, which acts as inflammatory mediator by stimulation of leukocytes. Etanercept is a soluble TNF-α receptor, which inhibits TNF-α and thereby inhibits the inflammatory response. Clinically, Etanercept is classified as immunosuppressant and plays a role in the treatment of inflammatory immune diseases such as rheumatoid arthritis, psoriasis or psoriatic arthritis, and ankylosing spondylitis. Anti-fibrotic properties have been found in a recent bleomycin animal study (Fichtner-Feigl, Strober, Kawakami, Puri, & Kitani, 2006). Despite TNF-α being a prototype inflammatory molecule, the benefits in the bleomycin model have been interpreted as result of preventing IL-13-R-α2 expression by TNF-α blockage, leading to reduction of TGF-β expression and consequently to less inflammation and fibrosis (Fichtner-Feigl, Strober, Kawakami, Puri, & Kitani, 2006). Antagonism of TNF-α has previously been described as a method to prevent fibrosis (Piguet, Collart, Grau, Kapanci, & Vassalli, 1989) and showed some effects on established fibrosis in the bleomycin model (Piguet & Vesin, 1994). Recently, a double-blind, placebo-controlled, randomized, phase II study in IPF patients has been initiated. The outcomes will be analyzed regarding safety and efficacy, quality of life and pharmacokinetics comparing Etanercept treatment vs. no treatment (Wyeth, 2007).

None of the other drugs mentioned above in the experimental animal model have been able to qualify for clinical use, due to lack of beneficial outcome, adverse drug effects or deficits in study design. Other clinical trials, for instance a phase II study, enrolling 120 IPF patients treated with the tyrosine kinase inhibitor Imatinib (Gleevec®), are yet to be analyzed. Further trials in progress are CAPACITY, investigating the clinical usefulness of Pirfenidone in ~600 patients, as well as a recently initiated TGF-β antibody (GC1008®) study. Unfortunately, the largest trial in IPF to date, a study investigating the effect of interferon-1β (Actimmune®) treatment in more than 800 patients (INSPIRE), was terminated in early 2007 because of inefficacy in an interim analysis.

Summary

Major discrepancies between drug effects in animal models and in human trials have recently been pointed out, which may be due to design of the models, assessment tools for determination of drug efficacy, and timing of drug application (Perel et al., 2007). These facts have to be taken into consideration, especially for long term drug intervention studies. In the context of pulmonary fibrosis and the bleomycin model it means that experimental findings have to be interpreted carefully, with the knowledge that bleomycin fibrosis in the animal lacks important features of the human disease. Further, the assessment tools used to determine drug efficacy may need to be re-evaluated. Finally, drug intervention studies in the bleomycin model employing a preventive strategy appear to be difficult to translate to human disease. Using a therapeutic strategy will likely have more validity in determining “real” antifibrotic drug effects.

In conclusion, this review suggests that the bleomycin model of pulmonary fibrosis is very helpful to illustrate pathobiology *in vivo* and to identify new targets for medication, and it is a good tool to assess efficacy of potential compounds in general as proof of principle. However, the bleomycin model may be of limited valid to detailed assess and evaluate these novel drugs for clinical use.

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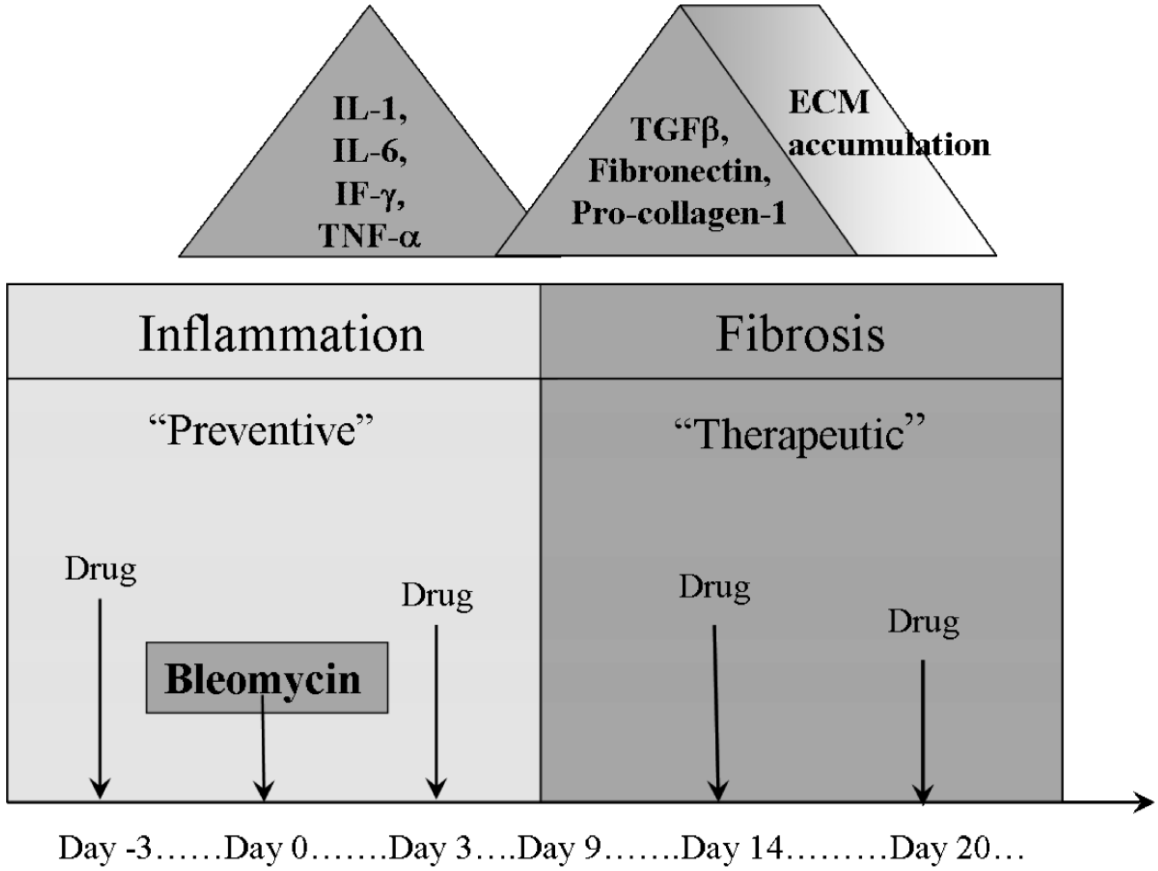

Figure 1. Sequence of events in Bleomycin-induced pulmonary fibrosis

After administration of bleomycin, there is the onset of an acute inflammatory response lasting up to 8 days, followed by fibrogenic changes resulting in deposition of matrix and distortion of lung structure out to 28 or 35 days. Treatments during the first seven days would be considered "preventive" while treatments during the later stages after day 7−10 would be considered "therapeutic".

Table 1

Preventive and therapeutic agents showing beneficial antifibrotic effects in the bleomycin model of pulmonary fibrosis

"Early" application means ≤ day 7 after last bleomycin application, "late" application > 7 days after bleomycin; "unclear" means that the exact information about the application schedule was not easily available and/or not specified in the article.

ID	Compound Name	Application	Reference
1	Pirfenidone analogues	early	(Ammar et al., 2006)
2	Imatinib mesylate	early	(Aono et al., 2005)
3	IL-10	early	(Arai et al., 2000)
4	Melatonin	early	(Arslan, Zerin, Vural, & Coskun, 2002)
5	Zndtp	early	(Atzori et al., 2004)
6	DDR1 KO	early	(Avivi-Green, Singal, & Vogel, 2006)
7	Erythromycin	early	(Azuma et al., 1998)
8	14-MRMLs	early	(Azuma et al., 2001)
9	IFN-beta	early	(Azuma, Li et al., 2005)
10	Taurine and Niacin	early	(Blaisdell & Giri, 1995)
11	EC-SOD	early	(Bowler, Nicks, Warnick, & Crapo, 2002)
12	Erdosteine	early	(Boyaci et al., 2006)
13	CME	early	(Breuer et al., 1995)
14	Tetrathiomolybdate	early	(Brewer, Ullenbruch, Dick, Olivarez, & Phan, 2003)
15	Tetrathiomolybdate	early	(Brewer, Dick, Ullenbruch, Jin, & Phan, 2004)
16	CXCL11	early	(Burdick et al., 2005)
17	Deferoxamine	early	(Chandler & Fulmer, 1985)
18	Diclofenac	early	(Chandler & Young, 1989)
19	Prednisolone	early	(Chaudhary, Schnapp, & Park, 2006)
20	Aminoguanidine	early	(X. L. Chen, Huang, Li, Wang, & Wang, 2001)
21	Aminoguanidine	early	(X. L. Chen, Li, Zhou, Ai, & Huang, 2003)
22	Dexamethasone	early	(F. Chen et al., 2006)
23	Batimastat	early	(Corbel et al., 2001)
24	N-Acetylcysteine	early	(Cortijo et al., 2001)
25	L-carnitine	early	(Daba et al., 2002)
26	Ginkgo biloba extract (EGb 761)	early	(Daba et al., 2002)
27	Ligustrazini and angelica sinensis	early	(Dai, Hou, & Cai, 1996)
28	Imatinib mesylate	early	(Daniels et al., 2004)
29	Aminoguanidine	early	(de Rezende, Martinez, Capelozzi, Simoes, & Beppu, 2000)
30	KGF	early	(Deterding et al., 1997)
31	Dexamethasone	early	(Dik et al., 2003)
32	HGF	early	(Dohi, Hasegawa, Yamamoto, & Marshall, 2000)
33	Air containing 75% O2	early	(Ekimoto et al., 1984)
34	Mesna	early	(El-Medany et al., 2005)
35	Colchicine	early	(Entzian et al., 1998)
36	Prednisolone	early	(Entzian et al., 1998)
37	Pentoxifylline	early	(Entzian et al., 1998)
38	IL13-receptor-α2-specific siRNA	early	(Fichtner-Feigl, Strober, Kawakami, Puri, & Kitani, 2006)
39	DFMO	early	(Frost, Rakieten, & Raisfeld-Danse, 1983)
40	Ethanol	early	(Frost, Rakieten, & Raisfeld-Danse, 1983)
41	TAFI knockout	early	(Fujimoto et al., 2006)
42	rTNFalpha	early	(Fujita et al., 2003)
43	TNFalpha overexpression	early	(Fujita et al., 2003)
44	Doxycycline	early	(Fujita et al., 2006)
45	Deuterium	early	(Gaeng et al., 1995)
46	CXCR3 −/−	early	(Gao & Lu, 2005)
47	Rosiglitazone	early	(Genovese, Cuzzocrea et al., 2005)
48	15d-PGJ2	early	(Genovese, Cuzzocrea et al., 2005)
49	Melatonin	early	(Genovese, Di Paola et al., 2005)
50	Poly I:C	early	(Giri & Hyde, 1988)
51	Taurine and Niacin	early	(Giri & Wang, 1992)
52	TGF-beta2 antibody	early	(Giri, Hyde, & Hollinger, 1993)
53	WEB 2086	early	(Giri, Sharma, Hyde, & Wild, 1995)
54	Decorin	early	(Giri et al., 1997)
55	Aminoguanidine	early	(Giri, Biring, Nguyen, Wang, & Hyde, 2002)
56	Feitai	early	(Gong et al., 2004)
57	Feitai	early	(Gong et al., 2005)
58	cHyp polymer	early	(Greco et al., 1997)
59	Heparin	early	(Gunther et al., 2003)
60	Taurine and Niacin	early	(Gurujeyalakshmi, Iyer, Hollinger, & Giri, 1996)
61	Taurine and Niacin	early	(Gurujeyalakshmi, Hollinger, & Giri, 1998)

ID	Compound Name	Application	Reference
62	*Pirfenidone*	*early*	(Gurujeyalakshmi, Hollinger, & Giri, 1999)
63	*Taurine and Niacin*	*early*	(Gurujeyalakshmi, Wang, & Giri, 2000)
64	*N-Acetylcysteine*	*early*	(Hagiwara, Ishii, & Kitamura, 2000)
65	*Anti-VEGF*	*early*	(Hamada et al., 2005)
66	*Urokinase*	*early*	(Hattori et al., 2004)
67	*ICRF-187*	*early*	(Herman et al., 1995)
68	*EPI-hNE-4*	*early*	(Honore et al., 2004)
69	*rThioredoxin*	*early*	(Hoshino et al., 2003)
70	*Thioredoxin overexpression*	*early*	(Hoshino et al., 2003)
71	*UK-156406*	*early*	(Howell et al., 2001)
72	*PAR-1 −/−*	*early*	(Howell et al., 2005)
73	*Aminoguanidine*	*early*	(Hu, Xu, & Li, 1999)
74	*CCR3 antibody*	*early*	(Huaux et al., 2005)
75	*CCL11 −/−*	*early*	(Huaux et al., 2005)
76	*Z2196*	*early*	(Hyde, Giri, Schiedt, & Krishna, 1990)
77	*Poly IC*	*early*	(Hyde & Giri, 1990)
78	*BHA, BHT*	*early*	(Ikezaki et al., 1996)
79	*IMD-0354*	*early*	(Inayama et al., 2006)
80	*mutant MCP-1*	*early*	(Inoshima, Kuwano, Hamada, Hagimoto et al., 2004)
81	*p21*	*early*	(Inoshima, Kuwano, Hamada, Yoshimi et al., 2004)
82	*Ginkgo biloba*	*early*	(Iraz et al., 2006)
83	*Gefitinib*	*early*	(Ishii, Fujimoto, & Fukuda, 2006)
84	*AG1478*	*early*	(Ishii, Fujimoto, & Fukuda, 2006)
85	*surfactant-TA*	*early*	(Ito, Suwabe, Suzuki, Tominaga, & Takahashi, 1997)
86	*Pirfenidone*	*early*	(Iyer et al., 1995)
87	*Pirfenidone*	*early*	(Iyer, Margolin, Hyde, & Giri, 1998)
88	*Pirfenidone*	*early*	(Iyer, Gurujeyalakshmi, & Giri, 1999)
89	*Pirfenidone*	*early*	(Iyer, Hyde, & Giri, 2000)
90	*Hepoxilin analogues*	*early*	(Jankov et al., 2002)
91	*14-/15-/16-MRMLs*	*early*	(Kawashima et al., 2002)
92	*rIL-12*	*early*	(Keane, Belperio, Burdick, & Strieter, 2001)
93	*Menhaden oil*	*early*	(Kennedy, Chandler, Fulmer, Wert, & Grizzle, 1989)
94	*TFPI*	*early*	(Kijiyama et al., 2006)
95	*Vitamin E*	*early*	(Kilinc et al., 1993)
96	*anti-TGFbeta-antibody*	*early*	(J. H. Kim et al., 2005)
97	*Alpha-galactosyl-ceramide*	*early*	(Kimura et al., 2004)
98	*Decorin*	*early*	(Kolb et al., 2001)
99	*Fufang Biejiafang*	*early*	(Kong et al., 2005)
100	*PG490−88*	*early*	(Krishna et al., 2001)
101	*Colchicine*	*early*	(Ledwozyw, 1994)
102	*Vinblastine*	*early*	(Ledwozyw, 1994)
103	*Erythromycin*	*early*	(Y. Li, He, & Wang, 1999)
104	*14-MRMLs*	*early*	(Y. Li, Azuma, Takahashi et al., 2002)
105	*14-MRMLs*	*early*	(Y. Li, Azuma, Usuki et al., 2002)
106	*Dexamethasone*	*early*	(H. P. Li, Li, He, Yi, & Kaplan, 2004)
107	*Moxibustion*	*early*	(R. Li et al., 2005)
108	*EM703*	*early*	(Y. Li et al., 2006)
109	*Aminophylline*	*early*	(Lindenschmidt & Witschi, 1985)
110	*Cyclosporin-A*	*early*	(Lossos, Or, Goldstein, Conner, & Breuer, 1996)
111	*IL-12-ab*	*early*	(Maeyama et al., 2001)
112	*Indomethacin*	*early*	(Mall, Zimmermann, Siemens, Burkhardt, & Otto, 1991)
113	*Valsartan*	*early*	(Mancini & Khalil, 2005)
114	*p47phox −/−*	*early*	(Manoury et al., 2005)
115	*Losartan*	*early*	(Marshall et al., 2004)

ID	Compound Name	Application	Reference
116	*Ramipril*	*early*	(Marshall et al., 2004)
117	*N-Acetylcysteine*	*early*	(Mata et al., 2003)
118	*FR-167653*	*early*	(Matsuoka et al., 2002)
119	*DDR-TKI-siRNA*	*early*	(Matsuyama et al., 2006)
120	*U74389F*	*early*	(McLaughlin & Frank, 1994)
121	*SLPI*	*early*	(Mitsuhashi et al., 1996)
122	*rh-HGF*	*early*	(Mizuno, Matsumoto, Li, & Nakamura, 2005)
123	*Losartan*	*early*	(Molina-Molina et al., 2006)
124	*Tranilast*	*early*	(Mori, Tanaka, Kawada, Nagai, & Koda, 1995)
125	*C-type natriuretic peptide*	*early*	(Murakami et al., 2004)
126	*ONO-1301*	*early*	(Murakami et al., 2006)
127	*Alpha 1-proteinase inhibitor*	*early*	(A. Nagai et al., 1992)
128	*Nicotinamide*	*early*	(A. Nagai et al., 1994)
129	*Niacin*	*early*	(A. Nagai et al., 1994)
130	*Halofuginone*	*early*	(Nagler et al., 1996)
131	*IL-18*	*early*	(Nakatani-Okuda et al., 2005)
132	*Amifostine*	*early*	(Nici, Santos-Moore, Kuhn, & Calabresi, 1998)
133	*IF gamma*	*early*	(Okada, Sugie, & Aisaka, 1993)
134	*Bt2cAMP*	*early*	(O'Neill, Giri, Wang, Perricone, & Hyde, 1992)
135	*Niacin*	*early*	(O'Neill & Giri, 1994)
136	*Cigarette smoke*	*early*	(Osanai et al., 1988)
137	*Candesartan*	*early*	(Otsuka, Takahashi, Shiratori, Chiba, & Abe, 2004)
138	*MnTBAP*	*early*	(Oury et al., 2001)
139	*Caffeic Acid Phenethyl Ester*	*early*	(Ozyurt et al., 2004)
140	*Bosentan*	*early*	(Park, Saleh, Giaid, & Michel, 1997)
141	*Methylprednisolone*	*early*	(Phan, Thrall, & Williams, 1981)
142	*Cobra venom factor*	*early*	(Phan & Thrall, 1982)
143	*LPS*	*early*	(Phan & Fantone, 1984)
144	*NDGA*	*early*	(Phan & Kunkel, 1986)
145	*anti-CXCL12 antibody*	*early*	(Phillips et al., 2004)
146	*anti-TNF antibody*	*early*	(Piguet, Collart, Grau, Kapanci, & Vassalli, 1989)
147	*GM-CSF*	*early*	(Piguet, Grau, & de Kossodo, 1993)
148	*Bombesin*	*early*	(Piguet, Vesin, & Thomas, 1995)
149	*cHyp*	*early*	(Poiani, Greco, Choe, Fox, & Riley, 1994)
150	*Ambroxol*	*early*	(Pozzi et al., 1987)
151	*Ambroxol*	*early*	(Pozzi et al., 1989)

ID	Compound Name	Application	Reference
152	*Curcumin*	*early*	(Punithavathi, Venkatesan, & Babu, 2000)
153	*cis-hydroxyproline*	*early*	(Riley et al., 1981)
154	*beta APN*	*early*	(Riley et al., 1982)
155	*BMD MSC*	*early*	(Rojas et al., 2005)
156	*NK3201*	*early*	(Sakaguchi et al., 2004)
157	*DP-1904*	*early*	(Sato et al., 2004)
158	*Acetyl-L-carnitine*	*early*	(Sayed-Ahmed, Mansour, Gharib, & Hafez, 2004)
159	*Pirfenidone*	*early*	(Schelegle, Mansoor, & Giri, 1997)
160	*N-Acetylcysteine*	*early*	(Serrano-Mollar et al., 2003)
161	*N-Acetylcysteine*	*early*	(Shahzeidi, Sarnstrand, Jeffery, McAnulty, & Laurent, 1991)
162	*YCD3*	*early*	(Sharma, MacLean, Pinto, & Kradin, 1996)
163	*Feitai*	*early*	(Shen et al., 2005)
164	*Y-27632*	*early*	(Y. Shimizu et al., 2001)
165	*APC*	*early*	(S. Shimizu et al., 2003)
166	*Decorin*	*early*	(Shimizukawa et al., 2003)
167	*SDZ RAD*	*early*	(Simler et al., 2002)
168	*Erdosteine*	*early*	(Sogut et al., 2004)
169	*KGF*	*early*	(Sugahara, Iyama, Kuroda, & Sano, 1998)
170	*Alpha-tocopherol*	*early*	(Suntres & Shek, 1997)
171	*IP-10*	*early*	(Tager et al., 2004)
172	*Superoxide dismutase*	*early*	(Tamagawa et al., 2000)
173	*anti-CCR1 antibody*	*early*	(Tokuda et al., 2000)
174	*SUN C8077*	*early*	(Tomimori et al., 2003)
175	*Heme oxygenase 1*	*early*	(Tsuburai et al., 2002)
176	*HGF*	*early*	(Umeda et al., 2004)
177	*SB 239063*	*early*	(Underwood et al., 2000)
178	*Relaxin*	*early*	(Unemori et al., 1996)
179	*AG1879*	*early*	(Vittal et al., 2005)
180	*Taurine*	*early*	(Q. J. Wang, Giri, Hyde, & Nakashima, 1989)
181	*Niacin*	*early*	(Q. J. Wang, Giri, Hyde, Nakashima, & Javadi, 1990)
182	*Taurin and Niacin*	*early*	(Q. Wang, Hyde, & Giri, 1992)
183	*Sodium tanshionone IIA sulfonate*	*early*	(C. M. Wang, He, & Zhang, 1994)
184	*TR*	*early*	(Q. Wang et al., 1999)
185	*PS2*	*early*	(Q. Wang et al., 2000)
186	*Captopril*	*early*	(R. Wang, Ibarra-Sunga, Verlinski, Pick, & Uhal, 2000)
187	*ZVAD-fmk*	*early*	(R. Wang, Ibarra-Sunga, Verlinski, Pick, & Uhal, 2000)

ID	Compound Name	Application	Reference
188	Bilirubin	early	(H. D. Wang et al., 2002)
189	TR	early	(Q. Wang, Hyde, Gotwals, & Giri, 2002)
190	Isoliensinine	early	(Xiao, Zhang, Chen, Feng, & Wang, 2005)
191	rHGF	early	(Yaekashiwa et al., 1997)
192	PC-SOD	early	(Yamazaki et al., 1997)
193	Losartan	early	(Yao, Zhu, Zhao, & Lu, 2006)
194	Facteur thymique serique	early	(Yara et al., 2001)
195	rhIL-1 beta	early	(M. Yasui et al., 1991)
196	APC	early	(H. Yasui et al., 2001)
197	CD36	early	(Yehualaeshet et al., 2000)
198	KGF	early	(Yi et al., 1996)
199	Aminoguanidine	early	(Yildirim et al., 2004)
200	Erdosteine	early	(Yildirim et al., 2004)
201	Erdosteine	early	(Yildirim et al., 2005)
202	N-Acetylcysteine	early	(Yildirim et al., 2005)
203	Melatonin	early	(Yildirim et al., 2006)
204	Azeptin	early	(Yoneda, Yamamoto, Ueta, & Osaki, 1997)
205	XR	early	(Yoshida et al., 1999)
206	R36	early	(Zaman et al., 2005)
207	p65 antisense oligonucleotides	early	(X. Y. Zhang, Shimura, Masuda, Saitoh, & Shirato, 2000)
208	Spironolactone	early	(L. Zhao, Zhao, & Fang, 1998)
209	Carbon monoxide	early	(Zhou et al., 2005)
210	Bropirimine	early	(Zia, Hyde, & Giri, 1992)
211	Gamma-linolenic acid	early	(Ziboh, Yun, Hyde, & Giri, 1997)
212	Follistatin	late	(Aoki, Kurabayashi, Hasegawa, & Kojima, 2005)
213	Imatinib	late	(Chaudhary, Schnapp, & Park, 2006)
214	Urokinase	late	(Gunther et al., 2003)
215	Urokinase	late	(Hart, Whidden, Green, Henkin, & Woods, 1994)
216	Pirfenidone	late	(Kakugawa et al., 2004)
217	DHP	late	(Kelley, Newman, & Evans, 1980)
218	anti CD-11a antibody	late	(Piguet, Rosen, Vesin, & Grau, 1993)
219	IL-1 receptor antagonist	late	(Piguet, Vesin, Grau, & Thompson, 1993)
220	TNFalpha antagonist	late	(Piguet & Vesin, 1994)
221	ONO-5046 Na	late	(Taooka, Maeda, Hiyama, Ishioka, & Yamakido, 1997)
222	Erythromycin	unclear	(B. Chen, Jiang, Zhao, Yu, & Hou, 1997)
223	Azithromycin	unclear	(J. Chen, He, Li, Wang, & Zhang, 1999)

ID	Compound Name	Application	Reference
224	*Pentoxifylline*	*unclear*	(Entzian, Gerlach, Gerdes, Schlaak, & Zabel, 1997)
225	*Losartan*	*unclear*	(Fang, Zhu, Hu, & Liu, 2002)
226	*Etanercept*	*unclear*	(Fichtner-Feigl, Strober, Kawakami, Puri, & Kitani, 2006)
227	*Activator Protein-1 decoy ODN*	*unclear*	(Fichtner-Feigl, Strober, Kawakami, Puri, & Kitani, 2006)
228	*Interferone gamma*	*unclear*	(Gurujeyalakshmi & Giri, 1995)
229	*UK-156406*	*unclear*	(Howell, Laurent, & Chambers, 2002)
230	*IH764−3*	*unclear*	(Hua, Cui, & Liu, 1994)
231	*IF gamma*	*unclear*	(Hyde, Henderson, Giri, Tyler, & Stovall, 1988)
232	*Urokinase*	*unclear*	(Ikeda, Hirose, Koto, Hirano, & Shigematsu, 1989)
233	*Colchicine*	*unclear*	(Jiang, Chen, & Li, 1998)
234	*N-benzyl-oxycarbonyl-Val-Ala-Asp-fluoro-methylketone*	*unclear*	(Kuwano et al., 2001)
235	*Proline*	*unclear*	(Ledwozyw, 1995)
236	*Panax notoginside*	*unclear*	(X. Li & Cui, 2002)
237	*IH764−3*	*unclear*	(J. Liu, 1992)
238	*IH764−3*	*unclear*	(J. Liu et al., 1993)
239	*Valsartan*	*unclear*	(F. Liu, Xu, & Ye, 2005)
240	*Azithromycin*	*unclear*	(Ma, He, Li, & Zhang, 2002)
241	*Pirfenidone*	*unclear*	(Mansoor, Chen, Schelegle, & Giri, 1999)
242	*Heparin*	*unclear*	(Piguet, Van, & Guo, 1996)
243	*Erythromycin*	*unclear*	(Tan, Liu, He, & Xu, 1999)
244	*Ampligen*	*unclear*	(Wild, Hyde, Hubbell, & Giri, 1996)
245	*Colchicine*	*unclear*	(L. Zhang, Zhu, Luo, Xi, & Yan, 1992)
246	*Biejia Ruangan Prescription*	*unclear*	(D. W. Zhang et al., 2004)