NOVEL PHARMACEUTICAL COMPOSITION OF INTERFERON GAMMA OR PIRFENIDONE WITH MOLECULAR DIAGNOSTICS FOR THE IMPROVED TREATMENT OF INTERSTITIAL LUNG DISEASES

The present invention relates to a novel pharmaceutical composition of compounds having the biological activity of interferon gamma (IFN-γ) or pirfenidone in combination with a diagnostic array of candidate polynucleotides for the improved treatment of all forms of interstitial lung diseases, in particular of idiopathic pulmonary fibrosis (IPF).

BACKGROUND OF THE INVENTION

Interstitial lung diseases

Reliable diagnosis of is of critical importance for disease management, research, epidemiology and development of specific therapies.

Interstitial lung diseases (ILD) are a heterogeneic group of chronic inflammatory reactions of the lung. Different forms of ILD are known which comprise, for example, of idiopathic pulmonary fibrosis (IPF), hypersensivity pneumonitis, scleroderma, Systemic Lupus Erythematosus, Rheumatoid Arthritis, Churg-Strauss syndrome, Wegener's granulomatosis, and Goodpasture Syndrome. This process is characterized by a combination of injury and exaggerated but futile attempts of tissue repair that transforms the regular maintenance of cellular growth into progressive development of scars. Characteristic features of this reaction are: repeated damage; intensified proteolytic activity and change in the composition of extracellular matrix (ECM) components. This combination leads to a shifted cellular immune response and a relentless induction of mesenchymal growth.

Cytokines, such as tumor necrosis factor-α, and mediators of growth, such as transforming growth factor β_1 (TGFβ_1), have long been implicated in this process. Of these mediators, TGFβ_1 has probably become the most important one, due to its strong activity to stimulate mesenchymal growth and its abil-

ity to modulate cellular immune functions. TGF-β_1 is known to cause severe pulmonary fibrosis when overexpressed in animal models *(Sime PJ, Xing Z, Graham FL, Csaky KG, Gauldie J. Adenovector-mediated gene transfer of active transforming growth factor β1 induces prolonged severe fibrosis in rat lung. J Clin Invest 1997;100:768-76.)*, and a significant overexpression of this mediator is found in human pulmonary fibrosis *(Broekelmann TJ, Limper AH, Colby TV, McDonald JA. Transforming growth factor beta 1 is present at sites of extracellular matrix gene expression in human pulmonary fibrosis. Proc Natl Acad Sci USA 1991;88:6642-6.)*. The immunomodulatory action of TGF-β_1 is well-known *(Qin L, Ding Y, Bromberg JS. Gene transfer of transforming growth factor-beta 1 prolongs murine cardiac allograft survival by inhibiting cell-mediated immunity. Hum Gene Ther 1996;7:1981-8; Gilbert KM, Thoman M, Bauche K, Pham T, Weigle WO. Transforming growth factor-beta 1 induces antigen-specific unresponsiveness in naive T cells. Immunol Invest 1997;26:459-72; Lawrence DA. Transforming growth factor-beta: a general review. Eur Cytokine Netw 1996;7:363-74.)*. It includes the inhibition of interferon gamma release *(Naganuma H, Sasaki A, Satoh E, Nagasaka M, Nakano S, Isoe S, et al. Transforming growth factor-beta inhibits interferon gamma secretion by lymphokine-activated killer cells stimulated with tumor cells. Neurol Med Chir Tokyo 1996;36:789-95.)*, the suppression of interferon gamma-dependent immune reactions *(Lee YJ, Han Y, Lu HT, Nguyen V, Qin H, Howe PH, et al. TGF-beta suppresses interferon gamma induction of class II MHC gene expression by inhibiting class II transactivator messenger RNA expression. J Immunol 1997;158:2065-75.)*, and the induction of immunosuppressive CD8+ lymphocytes *(Gray JD, Hirokawa M, Horwitz DA, J Exp Med 180, 1937-1942, 1994.)*. Indeed, modulation of cellular immunity in patients with progressive fibrosis has been observed for years, even in forms, which clearly represent *different* mechanisms of initial damage. Recent investigations have demonstrated that progressive scarring in idiopathic pulmonary fibrosis is accompanied by a shift of the cytokine balance in T lymphocytes that favors the formation of the so-called T helper type 2 (Th2) reaction

(Prior C, Haslam PL. In vivo levels and in vitro production of interferon gamma in fibrosing interstitial lung diseases. Clin Exp Immunol 1992;88:280-7.; Ziesche R, Kink E, Herold C, Podolsky A, Block LH. Therapy of chronic interstitial lung disease with a combination of Interferon gamma and low-dose prednisolone. Chest 1996;110:25S.). This reaction is characterized by an increase of 'Th2' cytokines, such as interleukin (IL)-4, IL-10 and IL-13, and a reduction or even a complete loss of interferon gamma, the main mediator of the T helper type 1 reaction *(Majumdar S, Li D, Ansari T, et al. Tissue cytokine profiles of cryptogenic fibrosing alveolitis (CFA) and fibrosing alveolitis associated with systemic sclerosis (FASSc) are distinct: a quantitative in situ study of open lung biopsies. Eur Respir J 1999; 14: 251-7.)*. In bleomycin-induced lung fibrosis, transcription of the interferon gamma gene decreases from day 7 onwards and is no longer detectable on day 28. Reciprocally, transcription of IL-13, which also has fibrogenic activity, (*Romagnani S. Th1/Th2 cells. Inflamm Bowel Dis. 1999; 5: 285-94.; Fallon PG, Richardson EJ, McKenzie GJ, McKenzie AN. Schistosome infection of transgenic mice defines distinct and contrasting pathogenic roles for IL-4 and IL-13: IL-13 is a profibrotic agent. J Immunol. 2000; 164 :2585-91.)*, begins to increase on day 7.

In contrast to the chronic inflammatory reaction in fibrosis, acute inflammation of the pulmonary interstitium as a result of infection with *M. pneumoniae* is characterized by a simultaneous transcription of both Th1 and Th2 cytokine genes, i.e. IL-12 and interferon gamma, and IL-4. In addition, this reaction includes an increased transcription of TGF-β_1, probably as a sign of activated tissue repair.

Unfortunately, as a result of the usually late recognition of IPF, the early cellular events in this disease are virtually impossible to assess. However, analysis of mRNA accumulation for IL-4, interferon gamma, and TGF-β_1 in an individual with familial idiopathic pulmonary fibrosis, with symptoms of breathlessness on maximum exertion of less than a year, already demonstrates the shift of the immune balance and the

intense activation of transcription of TGF-β_1. In the group of individuals with idiopathic pulmonary fibrosis, we found that the amount of mRNA accumulation of the TGF-β_1 gene was seven fold higher than that in normal lungs. In conclusion, our observations clearly demonstrate features of pathologically intensified repair mechanisms.

The intensity of repair is directly influenced by mechanisms of inflammation causing intensified turnover of both ECM and cellular components. As a result, chronic inflammation, usually induced by various infective agents, aggravates pathologic tissue repair.

Even if the causative agents were known, at present organ fibrosis cannot be sufficiently treated with any medication. Millions of people are dying from slow destruction of vital organ systems owing to pathological restructuring of functional organ tissue. This relentless process is known as fibrosis or tissue remodeling that is primarily due to fibroproliferative mechanisms. The only remedy is organ transplantation, which is associated with numerous costly complications.

The fibroproliferative reaction concerns all organs of the body. In the gas-exchanging lung tissue it is known as lung fibrosis, in the bronchi it is known as bronchial asthma, in the liver as cirrhosis, in the kidney as glomerulosclerosis, in the general circulation as arteriosclerosis and coronary artery sclerosis, and in the pulmonary circulation as pulmonary hypertension.

These conditions are collectively known as fibroproliferative diseases. In fibrosis, healthy tissue is progressively replaced by components of the connective and supporting tissue of the human body. This process is based on the pathologically accelerated growth rate of tissue cells, which would normally accomplish regular wound healing. Thus, fibroproliferative diseases may be defined as uncontrollably accelerated wound healing. In fibrosis, the replacement of functional organ tissue continues until complete loss of organ function occurs. The currently available modes of diagnosis and treatment for all fibroproliferative diseases are inadequate.

Pirfenidone

Pirfenidone is an orally active small molecule drug that appears to inhibit collagen synthesis, down regulates production of multiple cytokines and blocks fibroblast proliferation and stimulation in response to cytokines. Pirfenidone, which has demonstrated activity in multiple fibrotic indications, is currently in Phase II clinical development for fibrotic diseases of the lung, kidney and liver.

Interferon gamma (IFN-γ)

IFN-γ is a naturally glycoprotein cytokine, acting synergistically with other cytokines to exert its wide ranging effects. IFN-γ is a naturally occurring glycoprotein having a molecular weight of about 17.000 which can be commercially produced today also by recombinant techniques.

For improvement of the pharmacokinetic features, IFN-γ can be modified by pegylation to obtain PEG-IFN-γ. In addition to injection techniques, IFN-γ can be administered by inhalation to the lungs to diminish undesirable side effects. IFN-γ exhibits antiviral activity and together with other cytokines it plays an pivotal immunoregulatory role within the human immune system (an immunostimulating or an immunosuppressive effect, dependent on cell activation and location). Effects of IFN-γ include the induction of MHC class II antigens, macrophage activation, increased immunoglobulin production from B lymphocytes and enhanced NK cell activity.

The general antifibrotic properties of IFN-γ are well-documented *(Lortat-Jacob H, Kleinman HK, Grimaud JA. High-affinity binding of interferon-gamma to a basement membrane complex (matrigel). J Clin Invest. 1991; 87: 878-83.; Narayanan AS, Whithey J, Souza A, Raghu G. Effect of gamma-interferon on collagen synthesis by normal and fibrotic human lung fibroblasts. Chest. 1992 May;101(5):1326-31; Hjelmeland LM, Li JW, Toth CA, Landers MB 3d. Antifibrotic and uveitogenic properties of gamma interferon in the rabbit eye. Grae-*

fes Arch Clin Exp Ophthalmol. 1992;230(1):84-90; Hyde DM, Henderson TS, Giri SN, Tyler NK, Stovall MY. Effect of murine gamma interferon on the cellular responses to bleomycin in mice. Exp Lung Res. 1988;14(5):687-704.). It has already been demonstrated that IFN-γ causes a reduced expression of TGF-β_1 together with a reduction in the amount of fibrosis *(Giri SN, Hyde DM, Marafino BJ Jr. Ameliorating effect of murine interferon gamma on bleomycin-induced lung collagen fibrosis in mice. Biochem Med Metab Biol. 1986 Oct;36(2):194-7.)*. When using IFN-γ under clinical conditions, the transcription of TGF-β_1 and that of CTGF are significantly diminished after six months of therapy *(Ulloa L, Doody J, Massague J. Inhibition of transforming growth factor-beta/SMAD signalling by the interferon-gamma/STAT pathway. Nature 1999; 397: 710-3.)*. The simultaneous improvement of lung function in individuals suffering from IPF receiving IFN-γ provides additional support for the hypothesis that the mesenchymal activation in individuals with lung fibrosis depends, at least in part, on the continuous overexpression of TGF-β_1 and CTGF *(Ziesche R, Hofbauer E, Wittmann K, Petkov V, Block LH. A preliminary study of long-term treatment with interferon gamma-1b and low-dose prednisolone in individuals with idiopathic pulmonary fibrosis. N Engl J Med. 1999; 341: 1264-9; EP0795332A2.)*. Moreover, these results suggest that an acquired deficiency of IFN-γ may be one reason for the exaggerated wound healing process characteristic of progressive organ fibrosis.

IFN-γ was shown to be the first clinically applicable anti-fibrotic drug. As any endogenous substance, IFN-γ has pleiotropic effects dependent on the existing conditions within the body. In case of an exaggerated, yet non- or low-inflammatory wound healing, such as in IPF, the drug exerts powerful highly beneficial anti-fibrotic properties. However, in the presence of accompanying infections, such as chronic bacterial, viral or fungal infections, the drug will add to the inflammatory process and even reinforce, by intensifying tissue repair, the fibrotic process.

Thus, for a safe and effective use of the drug, it is necessary to molecularly measure the state of tissue response prior to application of the drug. The absence of the mRNA transcription of the gene for IFN-γ in the presence of intensified transcription of factors of wound healing may serve as the first vague discriminator between fibrosis as a result of deregulated wound healing itself, versus fibrosis as a result of intensified inflammation. The first attempts to analyze gene expression patterns in pulmonary fibrosis in animal models demonstrate the power of this tool to discriminate between the fibrotic process itself and accompanying mechanisms *(Kaminski et al., Proc Natl Acad Sci U S A 2000 Feb 15;97(4):1778-83 Global analysis of gene expression in pulmonary fibrosis reveals distinct programs regulating lung inflammation and fibrosis; Katsuma et al., Biochem Biophys Res Commun 2001 Nov 9;288(4):747-51 Molecular monitoring of bleomycin-induced pulmonary fibrosis by cDNA microarray-based gene expression profiling)*. A medication which combines the molecular diagnosis (transcription analysis in diseased ILD patients compared to control populations - healthy individuals or patients suffering from different lung diseases - with a distinct quantitative, specific expression difference to those) with proven effectiveness of a antifibrotic drug like IFN-γ or pirfenidone under clinical conditions provides the essential step for the first bio-medical based treatment of these multifunctional diseases.

To sum up, the real effectiveness of IFN-γ therapy mainly depends on four conditions:

(a) the proof of IFN-γ deficiency in pulmonary tissue;

(b) the control of infections or other inflammatory conditions, either pre-existing or acquired during therapy;

(c) the gene expression profiling of the patients suspected to have an interstitial lung disease;

(d) the duration of disease-related symptoms, reflecting the extent of completed scarring.

Clinical experience suggests that repeated phases of increased inflammation due to a large variety of infectious agents are the most common reason for a failure of IFN-γ in the treatment of ILD. Thus, clinical and molecular control of inflammation and infections, especially in the peripheral bronchi is crucial for a success of an anti-fibrotic treatment with IFN-γ.

Thus it is goal of the work of the present invention to improve the treatment of lung diseases, especially ILD and its various subforms with novel pharmaceuticals using either pirfenidone or IFN-γ in pharmaceutical composition with a diagnostic array of candidate polynucleotides (genechip).

Disease-related gene expression profiles

With the completion of the Human Genome Project sequencing, biomedical research will be revolutionised by the ability to carry out investigations on a genome wide scale:

Arch Ophthalmol 2001 Nov;119(11):1629-34
Microarray analysis of gene expression in human **donor corneas**.

Jun AS et al.
Ann Surg 2001 Dec;234(6):769-78; discussion 778-9
Identification of disease-specific genes in **chronic pancreatitis** using DNA array technology.
Friess H et al.

DNA Cell Biol 2001 Nov;20(11):683-95
A gene expression profile of **Alzheimer's disease**.
Loring JF et al.

Pharmacogenomics J 2001;1(4):272-87
Molecular classification of **psoriasis** disease-associated genes through pharmacogenomic expression profiling.

Oestreicher JL et al.

Gene expression technology is gaining increasingly widespread use as a means to determine the expression of potentially all human genes at the level of messenger RNA. Gene specific sequences (oligo-, polynucleotides or cDNAs) are immobilised on arrays, hybridised with complex probes represented by a mixture of cDNAs of respective samples from human biopsies and other human materials (reversely transcribed from messenger RNA), and labelled with different dyes. Hybridised slides are analysed with sensitive scanning methodologies. Genechips containing gene sequences deliver fast and excellent overview of the expression pattern of the biological samples. Thus, the genome-wide gene expression analysis provides new insights into causes of disease, and elucidates the as yet unknown biological gene expression variations between seemingly similar diseases in defined detection ranges, leading to a new classification system valuable in accurate diagnosis.

Important applications include:

(a) development of a more global understanding of the qualitative and quantitative gene expression profiles that contribute to disease processes;

(b) discovery of new diagnostic and prognostic indicators and biomarkers of therapeutic response;

(c) identification and validation of new molecular targets for drug development;

(d) provision of an improved understanding of the molecular mode of action during lead identification and optimisation;

(e) designing more specific and efficient treatment strategies;

(f) prediction of potential side-effects during development and toxicology studies;

(g) confirmation of molecular modes of action during hypothesis-testing clinical trials;

(h) identification of genes involved in conferring drug sensitivity and resistance;

(i) prediction of patients most likely to benefit from the drug and use in general pharmacogenomic studies.

As a result of further technological improvements, array-based genechips will become essential part for clinical interventions in identifying and quantifiying individual gene-expression patterns for purposes of patient-oriented therapy, and in establishing a method for predicting efficacy of drugs for individual patients, given the functional complexity of most diseases, especially those involving fibroproliferative processes. Considering the fact that inflammatory diseases reflect qualitative and quantitative changes in the activity of certain genes and/or gene clusters, the molecular assessment will allow for a higher specificity and efficacy of medical treatments and will be considered integral part of the therapeutic composition.

To achieve this goal, new molecular markers and markers of progression are needed for improved staging and for better assessment of diagnosis and treatment of complex diseases. Gene expression profiling techniques in combination with therapeutics offer the opportunity to discover such pathophysiologically relevant markers of disease.

In the context of this disclosure, a number of terms shall be utilized.

The term "polynucleotide" refers to a polymer of RNA or DNA that is single-stranded, optionally containing synthetic, non-natural or altered nucleotide bases. A polynucleotide in the form of a polymer of DNA may be comprised of one or more segments of cDNA, genomic DNA or synthetic DNA.

The term "subsequence" refers to a sequence of nucleic acids that comprises a part of a longer sequence of nucleic acids.

The term "immobilized on a support" means bound directly or indirectly thereto including attachment by covalent binding,

hydrogen bonding, ionic interaction, hydrophobic interaction or otherwise.

An aspect of the invention relates to polynucleotide arrays, which allows to qualitatively and quantitatively study mRNA expression levels of selected candidate genes in human materials.

Polynucleotide or DNA arrays consist of large numbers of DNA molecules spotted in a systematic order on a solid support or substrate such as a nylon membrane, glass slide, glass beads or a silicon chip. Depending on the size of each DNA spot on the array, DNA arrays can be categorized as microarrays (each DNA spot has a diameter less than 250 microns) and macroarrays (spot diameter is grater than 300 microns). When the solid substrate used is small in size, arrays are also referred to as DNA chips. Depending on the spotting technique used, the number of spots on a glass microarray can range from hundreds to tens of thousands.

DNA microarrays serve a variety of purposes, including gene expression profiling, de novo gene sequencing, gene mutation analysis, gene mapping and genotyping. cDNA microarrays are printed with distinct cDNA clones isolated from cDNA libraries. Therefore, each spot represents an expressed gene, since it is derived from a distinct mRNA.
Typically, a method of monitoring gene expression involves providing

(1) a pool of sample polynucleotides comprising RNA transcripts of target genes or nucleic acids derived from the RNA transcripts;

(2) hybridizing the sample polynucleotides or nucleic acids derived from the RNA transcripts to an array of probes (for example, polynucleotides obtained from a polynucleotide library including control probes, and

(3) detecting the hybridized double-stranded polynucleotides/nucleic acids. The label used to mark polynucleotide samples is selected from the group consisting

of radioactive, colorimetric, enzymatic, molecular amplification, bioluminescent or fluorescent label.

The invention relates also to any polynucleotide library as previously described wherein said polynucleotides are immobilized on a solid support in order to form a polynucleotide array.

Preferably the support is selected from the group consisting of a nylon membrane, glass slide, glass beads, or a silicon chip.

The invention relates to a polynucleotide library useful in the molecular characterization of a fibrotic interstitial lung disease like Idiopathic Pulmonary Fibrosis (IPF), the library including a pool of polynucleotide sequences or subsequences thereof wherein the sequences or subsequences are either underexpressed or overexpressed in IPF diseased cells.

Preferably, a set of sequences is selected from oligo- or polynucleotide probes having a sequence defined by, or correlated to, or derived from the group of genes consisting of candidate genes indicated in the following list, representing increased gene expression levels of IPF cells versus cells from patients with a different lung disorder:

PTH-responsive osteosarcoma B1 protein, AF095771.1

matrix associated, actin dependent regulator of chromatin, subfamily f, member 1, AF231056.1

deleted in lung and esophageal cancer 1 (DLEC1), NM_007337.1

major histocompatibility complex, class II, DQ beta 1, AW276186

SB classII histocompatibility antigen alpha-chain, AI128225

mucin 4, tracheobronchial, AJ242547.1

forkhead box J1 (FOXJ1), U69537.1

hypothetical protein FLJ21616, NM_024567.1

neuronal specific transcription factor DAT1, AF258348.1

hematopoietic PBX-interacting protein, BF344265

proline oxidase homolog, AA074145

mucin 5, subtype B, tracheobronchial, AI697108

golgi membrane protein GP73, AF236056.1

ATP citrate lyase, U18197.1

NG22 protein, NM_025257.1

cDNA DKFZp434A2322, AL137706.1

hepatocyte nuclear factor 3, alpha, U39840.1

major histocompatibility complex, class II, DQ alpha 1, X00452.1

myosin regulatory light chain 2, smooth muscle isoform, J02854.1

plexin B1, AV693216

pyruvate kinase, muscle, BC000481.1

tetraspanin TM4-C, AF133425.1

insulin-like growth factor binding protein 2 (36kD), BC004312.1

FLJ13945 fis, clone Y79AA1000969, AU160041

hypothetical protein DKFZp586M1120, NM_031294.1

CD24 signal transducer, L33930

hypothetical protein FLJ23571, NM_025111.1

glutathione S-transferase M2 (muscle), M63509.1

cadherin 1, type 1, E-cadherin (epithelial), L08599.1

NTT5 protein, AF265578.1

lipocalin 2 (oncogene 24p3), NM_005564.1

myotonic dystrophy kinase (DM kinase), L08835

uncoupling protein 2 (mitochondrial, proton carrier), U76367.1

dynein intermediate chain 2, NM_023036.1

discoidin receptor tyrosine kinase isoform b, discoidin domain receptor family, member 1, NM_001954.2

sperm associated antigen 6, AF079363.1

hypothetical protein FLJ23049, NM_024687.1

nasopharyngeal epithelium specific protein 1, AF094758.1

nuclear receptor subfamily 4, group A, member 2, NM_006186.1

hypothetical protein FLJ22215, BC003543.1

non-specific cross reacting antigen, M18728.1

amylase, alpha 1A; salivary (AMY1A), NM_004038.1

carcinoembryonic antigen-related cell adhesion molecule 6 (non-specific cross reacting antigen), BC005008.1

glutathione S-transferase subunit 4 (EC 2.5.1.18), X08020.1

SH3-containing protein SH3GLB2, AF257319.1

KDEL (Lys-Asp-Glu-Leu) endoplasmic reticulum protein retention receptor 1, NM_006801.1

anterior gradient 2 (Xenepus laevis) homolog, AF038451.1

sv7-MUC4 apomucin, mucin 4, tracheobronchial, AJ242547.1

stratifin, BC000329.1

connective tissue growth factor, M92934.1

cytochrome P450-IIB (hIIB3), M29873.1

filamin A, alpha (actin-binding protein-280), AW051856

membrane glycoprotein LIG-1, AB050468.1

E74-like factor 3 (ets domain transcription factor, epithelial-specific), U73844.1

elastin (supravalvular aortic stenosis, Williams-Beuren syndrome), M36860.1

ephrin receptor EPHA3, AF213459.1

fibrillin 1 (Marfan syndrome), L13923.1

discs, large (Drosophila) homolog 1, U13896.1

lysyl oxidase-like 1 (LOXL1), L21186.1

calumenin, U67280.1

male germ cell-associated kinase, NM_005906.2

plectin 1, intermediate filament binding protein, 500kD, Z54367

peroxisome biogenesis factor 1, AF026086.1

mast cell tryptase beta III, AF099143

ataxia-telangiectasia group D-associated protein, AF230388.1

hypothetical protein FLJ10921, NM_018272.1

biglycan, BC002416.1

BLu protein, AC002481

CGI-92 protein, AF151850.1

adaptor-related protein complex 1, mu 2 subunit, BC003387.1

keratin 15, BC002641.1

B7 protein, U72508.1

S100 calcium-binding protein A2, BC002829.1

MUF1 protein, BC004953.1

cholesterol 25-hydroxylase, AF059214.1

cytidine monophosphate-N-acetylneuraminic acid hydroxylase (CMP-N-acetylneuraminate monooxygenase), AF074480.1

neuropilin 2, AF022859.1

Fas-interacting serinethreonine kinase 3, homeodomain-interacting protein kinase 3, AF305239.1

a disintegrin and metalloproteinase domain 28 (ADAM28), transcript variant 2, AF137334.1

cDNA DKFZp434A119 , AW663632

complement component 6, J05064.1

cytokeratin 17, Z19574

wingless-type MMTV integration site family, member 5A, AI968085

matrix metalloproteinase 7 (matrilysin, uterine), BC003635.1

leiomodin 1 (smooth muscle), NM_012134.1

Cip1-interacting zinc finger protein, AB030835.1

cyclin-dependent kinase inhibitor 1A (p21, Cip1), BC000275.1

integrin, alpha 7, AF032108.1

DKFZP586G011 protein, BG289527

fatty acid binding protein 6, ileal (gastrotropin), U19869.1

glutathione S-transferase M4, M96234.1

Ras-related associated with diabetes, L24564.1

claudin 3, AB000714.1

matrix metalloproteinase 10 (stromelysin 2), BC002591.1

fibulin 2, NM_001998.1

serine threonine kinase 11 (STK11), AF035625

eukaryotic translation initiation factor 1A: AF000987.1

DEADH (Asp-Glu-Ala-AspHis) box polypeptide: AF000985.1

ribosomal protein S4: AF116711.1

ubiquitin specific protease 9: AF000986.2

SMC (mouse) homolog: U52191.1

myelin basic protein: L18865.1

S100 calcium-binding protein: NM_005980.1

Jagged2 (JAG2): AF003521.1

latent transforming growth factor beta binding protein 4: NM_003573.1

microtubule-associated protein, RPEB family, member 3: AB025186.1

Unknown (protein for MGC:2854): BC003629.1

clone=IMAGE-2406340: AI830563

AQP3 gene for aquaporine 3 (water channel): AB001325

cDNA DKFZp434A119

fenestrated-endothelial linked structure protein (FELS), PV1 protein (PLVAP): AF326591.1

LUNX protein; PLUNC (palate lung and nasal epithelium clone); tracheal epithelium enriched protein (LOC51297): AB024937.1

RAB, member of RAS oncogene family-like 2A: AF095350.1

chromosome 11 open reading frame 16: NM_020643.1

hypothetical protein FLJ23049: NM_024687.1

hypothetical protein FLJ11767: NM_024593.1

dynein, axonemal, intermediate polypeptide: AF091619.1

brain specific protein (LOC51673): AF132972.1

MUC4 apomucin, mucin 4, tracheobronchial: AJ242547.1

myotonin protein kinase (DM): M87313.1

cytokeratin 4: X07695.1

KIAA0362 gene, MCF.2 cell line derived transforming sequence-like: AB002360.1

cytokeratin 17: Z19574

LIM domain protein: BC003096.1

E74-like factor 3 (ets domain transcription factor, epithelial-specific) : U73844.1

fatty acid binding protein 6, ileal (gastrotropin): U19869.1

sperm associated antigen 6: AF079363.1

eyes absent (Drosophila) homolog 2: U71207.1

phosphatidic acid phosphatase type 2C: BC002806.1

epoxide hydrolase 2, cytoplasmic: AF233334.1

tubulin, beta, 2: BC002783.1

heat shock 105kD: D86956.1

villin 2 (ezrin): J05021.1

a disintegrin and metalloproteinase domain 28 (ADAM28), transcript variant 3: AF137335.1

deleted in lung and esophageal cancer 1: NM_007337.1

arachidonate 15-lipoxygenase: NM_001140.1

UDP glycosyltransferase 1 family, polypeptide A1: M57899.1

hypothetical protein PRO2834: AF119903.1

lectin, galactoside-binding, soluble, 7 (galectin 7): L07769.1

B7 protein: U72508.1

ephrin receptor EPHA3: AF213459.1

forkhead box J1: U69537.1

BLu protein: U70824.1

aldehyde dehydrogenase 3 family, member A1: BC004370.1

NG22 protein: NM_025257.1

small inducible cytokine subfamily A (Cys-Cys), member 14: NM_004166.1

cysteine-rich protein 1 (intestinal): BC002738.1

putative GTP-binding protein similar to RAYRAB1C: BC000566.1

integrin, beta 4: NM_000213.1

serine (or cysteine) proteinase inhibitor, clade B (ovalbumin), member 5 (SERPINB5): U04313.1

Ras-related associated with diabetes: L24564.1

hepatic leukemia factor: M95585.1

keratin 15: BC002641.1

nuclear receptor subfamily 4, group A, member 2: NM_006186.1

sialyltransferase: U14550.1

glutathione S-transferase M2 (muscle): M63509.1

hypothetical protein FLJ13110: NM_022912.1

S100 calcium-binding protein A2: NM_005978.2

collagen, type VII, alpha 1 (epidermolysis bullosa, dystrophic, dominant and recessive) : L02870.1

claudin 3: AB000714.1

insulin-like growth factor binding protein 6: BC003507.1

fibroblast growth factor receptor 2 (bacteria-expressed kinase, keratinocyte growth factor receptor, craniofacial dys-

ostosis 1, Crouzon syndrome, Pfeiffer syndrome, Jackson-Weiss syndrome): M80634.1

insulin-like growth factor 1 receptor: NM_000875.2

insulin-like growth factor binding protein 2 (36kD): M35410.1

ataxia-telangiectasia group D-associated protein: AF230388.1

keratin 5 (epidermolysis bullosa simplex, Dowling-MearaKobnerWeber-Cockayne types): M21389.1

Duffy blood group: U01839.1

transforming growth factor β_1: NM_000660

wherein each oligo- or polynucleotide probe is obtainable on the basis of structural information mediated by the sequence data provided by the respective accession number set out for each candidate gene.

Yet another set of sequences is selected from oligo- or polynucleotide probes having a sequence defined by, or correlated to, or derived from the group of genes consisting of candidate genes indicated in the following list, representing decreased gene expression levels of IPF cells versus cells from patients with different lung disorder:

sorting nexin 10 (SNX10), AF121860.1

phospholipase A2, group IIA (platelets, synovial fluid), M22430.1

hemoglobin alpha-1 globin chain (HBA1), AF349571.1

macrophage scavenger receptor 1, AI299239

surfactant, pulmonary-associated protein C, BC005913.1

disintegrin protease (M12.219), NM_014479.1

retinol-binding protein 4, interstitial, AF119868.1

major histocompatibility complex, class II, DR beta 3, M27635.1

adipose differentiation-related protein, BC005127.1

hemoglobin, delta, NM_000519.2

beta-2-microglobulin, AW188940

hemoglobin, alpha 2, BC005931.1

protein C receptor, endothelial (EPCR), L35545.1

thymosin, beta 10, M92381.1

apolipoprotein C-I, W79394

hypothetical protein, AL133067.1

proteoglycan 4, (megakaryocyte stimulating factor, articular superficial zone protein), U70136.1

tetranectin (plasminogen-binding protein), NM_003278.1

platelet factor 4, M25897.1

tissue factor pathway inhibitor 2, BC005330.1

fatty acid binding protein 4, adipocyte, BC003672.1

cathepsin B (CTSB), M14221.1

transmembrane 4 superfamily member 1, M90657.1

MHC class I HLA-B51 major histocompatibility complex, class I, E, M31183.1

endothelial PAS domain protein 1, U51626.1

Apo-2 ligand tumor necrosis factor (ligand) superfamily, member 10, U37518.1

haptoglobin-related protein, NM_020995.1

Rho guanine exchange factor (GEF) 12, AF119898.1

major histocompatibility complex, class II, DR beta 5, M11867.1

interferon, gamma-inducible protein 30, AF097362.1

ferritin, light polypeptide, BG537190

prosaposin (variant Gaucher disease and variant metachromatic leukodystrophy), BC004275.1

calcium-binding protein A4 (calvasculin, metastasin,), NM_002961.2

hemoglobin, beta, M25079.1

CDW52 antigen (CAMPATH-1 antigen), BC000644.1

aldehyde dehydrogenase 1 family, member A2, AB015226.1

cathepsin Z, AF032906.1

MHC HLA-B39 major histocompatibility complex, class I, B, L37880.1

major histocompatibility complex, class II, DQ alpha 1, M33906.1

fibroblast growth factor 9 (glia-activating factor), D14838.1

hemoglobin, alpha 2, AF097635.1

transferrin receptor (p90, CD71), BC001188.1

complement component 3 (C3), K02765.1

cDNA DKFZp564D066, AL050025.1

complement component 1, q subcomponent, beta polypeptide, NM_000491.2

small inducible cytokine subfamily A (Cys-Cys), member 18, pulmonary and activation-regulated, AB000221.1

reticulon 1, L10333.1

major histocompatibility complex, class II, DR beta 1, M33600.1

haptoglobin, L29394.1

acid phosphatase 5, tartrate resistant, J04430.1

cytochrome P450, subfamily XXVIIA (steroid 27-hydroxylase, cerebrotendinous xanthomatosis), polypeptide 1, M62401.1

CD36 antigen (collagen type I receptor, thrombospondin receptor), M24795.1

calbindin 2, (29kD, calretinin), NM_001740.2

alpha-2-HS-glycoprotein, BG538564

cDNA DKFZp564A132, AL049963.1

fibronectin 1, AF130095.1

phosphodiesterase 4C, cAMP-specific, NM_000923.1

transcription factor 7 (T-cell specific, HMG-box), NM_003202.1

found in inflammatory zone 3 (FIZZ3), AF323081.1

claudin 15, NM_014343.1

carboxypeptidase B1 (tissue), M81057.1

hypothetical protein FLJ14054, NM_024563.1

bone marrow stromal cell antigen 1, D21878.1

interleukin 7 receptor, M29696.1

procollagen C-endopeptidase enhancer 2, AF098269.1

calcium-binding protein A8 (calgranulin A), AW238654

cDNA DKFZp564D193, AL049252.1

major histocompatibility complex, class II, DP beta 1, J03041.1

human leukocyte antigen C alpha chain, major histocompatibility complex, class I, C, AK024836.1

BCM-like membrane protein precursor, AF144235.1

CD14 antigen, M86511.1

pulmonary surfactant protein (SP5), J03553

signal transducer and activator of transcription 1, 91kD, BC002704.1

Wilms tumor 1 (WT1), transcript variant D, NM_024424.1

annexin A8, BC004376.1

macrophage receptor with collagenous structure, MARCO, AF035819.1

surfactant, pulmonary-associated protein A2, NM_006926.1

solute carrier family 6 (neurotransmitter transporter, serotonin), member 4, L05568.1

chitinase 1 (chitotriosidase), U29615.1

lung type-I cell membrane-associated glycoprotein, AU154455

fibronectin leucine rich transmembrane protein 2, AB007865.1

gamma-aminobutyric acid (GABA) A receptor, alpha 5, BF966183

hypothetical protein FLJ12983, NM_024856.1

sialophorin (gpL115, leukosialin, CD43), J04536.1

cerebellar degeneration-related protein (34kD), M16965.1

hydroxyacid oxidase 2 (long chain), hydroxy-delta-5-steroid dehydrogenase (3 beta-and steroid delta-isomerase 2), AL359553

CLONE=IMAGE:1032795=Hs.83623 nuclear receptor subfamily 1, group I, member 3

small inducible cytokine subfamily C, member 2: NM_003175.1

hypothetical protein similar to swine acylneuraminate lyase: NM_030769.1

fibrinogen, gamma polypeptide: AF118092.1

thrombospondin 1: NM_003246.1

SAM domain, SH3 domain and nuclear localisation signals, 1: AF222927.1

chitinase 3-like 1 (cartilage glycoprotein-39): M80927.1

cathepsin Z: AF032906.1

CLONE=IMAGE:3579023 collagen, type XIV, alpha 1 (undulin)

chloride intracellular channel 2: NM_001289.2

monokine induced by gamma interferon: NM_002416.1

KIAA0433 protein: NM_015216.1

tumor necrosis factor, alpha-induced protein 6: NM_007115.1

signal transducer and activator of transcription 1, 91kD: BC002704.1

thrombospondin 2: L12350.1

collagen, type IV, alpha 3 (Goodpasture antigen): NM_000091.1

integrin, beta-like 1 (with EGF-like repeat domains): AF072752.1

diubiquitin: NM_006398.1

protease, cysteine, 1 (legumain): D55696.1

cytochrome P450, subfamily I (dioxin-inducible), polypeptide 1 (glaucoma 3, primary infantile): U03688.1

integrin, alpha 1: X68742.1

GABA-B receptor, G protein-coupled receptor 51: AF056085.1

KIAA1199 protein: AB033025.1

collagen, type V, alpha 2: NM_000393.1

interleukin 13 receptor, alpha 2: U70981.1

translocase of inner mitochondrial membrane 8 (yeast) homolog A: BC005236.1

steroid sulfatase (microsomal), arylsulfatase C, isozyme S: M16505.1

CLONE=IMAGE:1982571 ATPase, H+ transporting, lysosomal (vacuolar proton pump) 9kD

proteoglycan 4, (megakaryocyte stimulating factor, articular superficial zone protein): U70136.1

nidogen (enactin): M30269.1

KIAA1598 protein: AU157109

vascular cell adhesion molecule 1: M60335.1

guanylate binding protein 1, interferon-inducible, 67kD: BC002666.1

cDNA DKFZp586E1124

apolipoprotein H (beta-2-glycoprotein I): M62839.1

ribosomal protein L37a: BE857772

cDNA DKFZp564A132

cathepsin S: M86553.1

a disintegrin and metalloproteinase domain 9 (meltrin gamma) (ADAM9): U41766.1

zinc finger protein 331: AF272148.1

lysosomal-associated membrane protein 2: J04183.1

carboxypeptidase M: NM_001874.1

collagen, type I, alpha 2: NM_000089.1

P311 protein: U36189.1

KIAA0372 gene product: AB002370.1

Human T cell-specific protein RANTES: M21121

interferon-gamma-inducible indoleamine 2,3-dioxygenase (IDO): M34455.1

hypothetical protein FLJ10430: NM_018092.1

transcription factor ISGF-3: M97935

interleukin 1 receptor-like 1 (IL1RL1): NM_003856.1

putative alpha chemokine (H174), small inducible cytokine subfamily B (Cys-X-Cys), member 11: AF002985.1

small inducible cytokine subfamily B (Cys-X-Cys), member 10: NM_001565.1

mesoderm specific transcript (mouse) homolog: BC002413.1

carboxypeptidase B-like protein: AB011969.1

CD2 antigen (p50), sheep red blood cell receptor: M16445.

interferon, alpha-inducible protein (clone IFI-6-16): NM_022872.1

RAS guanyl releasing protein 1 (calcium and DAG-regulated): AF081195.1

lipase, endothelial: AF118767.1

fatty-acid-Coenzyme A ligase, long-chain 4: NM_022977.1

klotho: AB005142.1

chondroitin sulfate proteoglycan 2 (versican): NM_004385.1

hypothetical protein, expressed in osteoblast: AB000115.1

CD14 antigen: M86511.1

CGI-83 protein: BC000878.1

leucine aminopeptidase: AF061738.1

UDP-Gal:betaGlcNAc beta 1,3-galactosyltransferase, polypeptide 3: AB050855.1

protocadherin alpha 12: AF152308.1

neuroglycan C: AF059274

neuroligin: AI338338

HSPC156 protein: AF161505.1

hypothetical protein FLJ13310: NM_025118.1

eosinophil chemotactic cytokine (TSA1902): AB025008.1

aminopeptidase: AF191545.1

semaphorin sem2: AB029496.1

protocadherin 12: AF231025.1

X transporter protein 3: NM_020208.1

transmembrane 4 superfamily member (tetraspan NET-2): AF124522.1

hypothetical protein FLJ10970: NM_018286.1

perforin 1 (pore forming protein): M28393.1

natural killer cell group 7 sequence: NM_005601.1

hypothetical protein DKFZp761N09121: BF435376

integrin, alpha 4 (antigen CD49D, alpha 4 subunit of VLA-4 receptor): BG532690

chitinase 3-like 2: U58515.1

FYN oncogene: N20923

relaxin 1 (H1): BC005956.1

hydroxyprostaglandin dehydrogenase 15-(NAD): U63296.1

sulfotransferase family, cytosolic, 1C, member 1: AF186254.1

TGF-b superfamily receptor type I: L17075.1

granzyme B (granzyme 2, cytotoxic T-lymphocyte-associated serine esterase 1): M36118.1

cystatin F (leukocystatin): AF031824.1

regulator of G protein signaling-Z (RGSZ1): AF060877.2

clone MGC:12387: M16942.1

zinc-alpha2-glycoprotein: D90427.1

BCG induced integral membrane protein BIGMo-103: AB040120.1

nectin-like protein 2 (NECL2): AF132811.1

CD209 antigen-like: AB015629.1

solute carrier family 6 (neurotransmitter transporter, serotonin), member 4: L05568.1

MAD (mothers against decapentaplegic, Drosophila) homolog 6: U59914.1

latrophilin: AF104939.1

platelet factor 4: M25897.1

calcitonin receptor-like: L76380.1

matrilin 3: NM_002381.2

solute carrier family 14 (urea transporter), member 1 (Kidd blood group): U35735.1

interleukin 7 receptor: M29696.1

MAP kinase kinase 6 (MKK6), mitogen-activated protein kinase kinase 6: U39656.1

protocadherin 17: AF029343.1

granulysin: NM_006433.2

interferon-stimulated protein, 15 kDa (ISG15): M13755.1

cadherin 5, type 2, VE-cadherin (vascularepithelium): U84722.1

thrombomodulin: M16552.1

interferon, alpha-inducible protein 27: NM_005532.1

interferon-gamma: X87308

wherein each oligo- or polynucleotide probe is obtainable on the basis of structural information mediated by the sequence data provided by the respective accession number set out for each candidate gene.

For example, suitable sequences which may be used for oligonucleotide design may be downloaded from the NCBI GenBank (http://www.ncbi.nlm.gov/GenBank/index.html) using the Accession number listed behind the gene name.

All accession numbers give access to mRNA sequences; since the cDNA of the patients is reverse transcribed, the oligonucleotide have to sense strand and are therefore identical with the mRNA sequence.

Preferably the pool of polynucleotide sequences or subsequences correspond substantially to the polynucleotide sequences useful in qualitative and quantitative differentiating a normal cell, or a cell from a patient suffering from non-fibrosing lung disease, from a cell of an patient with interstitial lung disease, most preferably with Idiopathic Pulmonary Fibrosis (IPF).

The invention concerns the part of pharmaceutical composition for detecting differentially expressed polynucleotide sequences which are correlated with IPF, said part comprising: a) obtaining a polynucleotide sample from a patient; and b) reacting the sample polynucleotide obtained in step (a) with a probe immobilized on a solid support wherein said probe comprises any of the polynucleotide sequences of the libraries previously described or an expression product encoded by any of the polynucleotide sequences of said libraries and c) detecting the reaction product of step (b) as a prerequisite for a subsequent administration of suitable drug.

The invention relates also to the part of pharmaceutical composition detecting differentially expressed polynucleotide sequences of the invention wherein the amount of reaction product of step (c) is compared to control samples.

The detection of differentially expressed polynucleotide sequences is used for detecting, diagnosing, staging, monitoring, prognosticating, preventing or treating conditions associated with ILD, and namelly idiopathic pulmonary fibrosis IPF, hypersensivity pneumonitis, scleroderma, Systemic Lupus Erythematosus, Rheumatoid Arthritis, Churg-Strauss syndrome, Wegener's granulomatosis, and Goodpasture Syndrome.

The detection of differentially expressed polynucleotide sequences is particular useful wherein the product encoded by any of the polynucleotide sequences or subsequences is involved in a receptor-ligand reaction on which detection is based.

The invention relates also to detecting differentially expressed polynucleotide sequences previously described wherein the sample has been treated with the anti-ILD drug to be screened.

The invention also relates to a library of polynucleotides comprising a population of polynucleotide sequences overexpressed or underexpressed in cells derived from ILD patients. A particular embodiment of the invention relates to a polynucleotide library of corresponding substantially to any combination of at least one polynucleotide sequence selected among those included in each one of predefined polynucleotide sequences sets mentioned above.

The invention relates to polynucleotide libraries comprising at least one polynucleotide selected among those included in at least 50%, preferably 75% and more preferably 100% of said predefined sets, allowing to obtain a discriminating gene pattern, namely to distinguish between normal individuals and patients suffering from ILD, particularly from IPF.

Polynucleotide sequences library useful for the realization of the invention can comprise also any sequence comprised between 3'-end and 5'-end of each polynucleotide sequence sets as defined above, allowing the complete detection of the implicated genes.

The invention relates also to a polynucleotide library useful to differentiate a normal cell from a cell of ILD patients wherein the pool of polynucleotide sequences or subsequences correspond substantially to any combination of at least one polynucleotide sequence selected among those included in each one of predefined polynucleotide sequences sets indicated above, useful in differentiating a normal cell from a cell from ILD patients.
Differences in gene expression are accepted as different when the signals from patient material are at least two fold lower or higher than those from comparative material, be it from

healthy volunteers material or from other diseased material. This threshold is commonly accepted for the evaluation of expression arrays.

The invention additionally provides a method for identifying gene expression or genomic DNA of infective agents including bacteria (Mycobacterium spec., Mycoplasma spec., Staphyllococcus aureus, treptococcus spec., Borrelia, Treponema pallidum, Leptospira interrogans, Campylobacter jejuni, fetus; Escherichia coli, EPEC, ETEC, EIEC, EHEC Salmonella enterica, Yersinia enterocolitica, Aeromonas spec., Campylobacter fetus, Moraxella catarrhalis, Moraxella catarrhalis, Brucella spec., Toxoplasma, Salmonella enterica, Shigella spec., Yersinia enterocolitica, Vibrio cholerae, Pseudomonas aeruginosa, Burkholderia cepacia, Stenotrophomonas maltophilia, Acinetobacter baumanii, Acitenobacter calcoaceticus, Klebsiella, Enterobacter, Citrobacter, Proteus, Serratia, Morganella, Providencia, Cardiobacterium hominis, Eikenella corrodens, Gardnerella vaginalis, Calymmatobacterium granulomatis, Bacteriodes, Porphyromonas, Prevotella, Fusobacterium, Rickettsia prowazekii, Bartonella bacilliformis, Bartonella henselae and Chlamydia spec.), yeasts, fungi, or viruses (retroviruses, adenoviruses, hepadnaviruses, herpesviruses, influenza viruses, paramyxoviruses) as cellular parasites in cells from patients with ILD.

SUMMARY OF THE INVENTION

It was surprisingly found that a pharmaceutical composition of interferon gamma together with a gene expression analysis of the patients with lung diseases results in a faster and more successful treatment of lung diseases, preferably ILD and ILD related lung diseases. Thus, the invention relates to

new pharmaceutical compositions and pharmaceutical kits comprising interferon gamma or pirfenidone and a disease-oriented gene expression analysis.

To sum up and in more detail, the invention relates to the following topics:

- A pharmaceutical composition comprising (i) interferon gamma (IFN-γ), pegylated (PEG) IFN-γ), or pirfenidone, optionally together with a pharmaceutically acceptable carrier, diluent or excipient, (ii) a gene expression analysis of patients with interstitial lung disease (genechip);
- a corresponding pharmaceutical composition, comprising additionally a glucocorticoid compound;
- a corresponding pharmaceutical composition, wherein the medication is selected from the following group:
- a pharmaceutical kit comprising

(i) a package comprising IFN-γ, PEG-IFN-γ, or pirfenidone,
(ii) a package comprising a gene expression analysis (genechip) of the patient with lung disease;

- a corresponding pharmaceutical kit further comprising a package comprising a glucocorticoid compound;
- a method or a use of a combination of a pharmaceutical composition or a pharmaceutical kit according as specified for the manufacture of a medicament for the treatment of interstitial lung diseases (ILD);
- a corresponding method or use, wherein IFN-γ is administered to the individual in a single dose amount varying from 2.0 to 3.0 µg / kg body weight;
- a corresponding method or use, wherein the glucocorticoid compound is administered to the individual in a

single dose amount varying from 100 to 150 µg / kg body weight;

- a corresponding method or use, wherein IFN-γ is administered to the individual by inhalation after a gene expression analysis.

DETAILED DESCRIPTION

Suitable compounds which have the therapeutic effect within the combination according to the invention, are, besides interferon gamma, pegylated interferon gamma, perfinidone, compounds which have the same, but also enhanced, biological activity of interferon gamma, pegylated interferon gamma, or pirfenidone in combination with the gene expression analysis of diseased patients.

The invention includes also derivatives, analogues, homologues, fusion proteins, stabilized forms, etc., of the disclosed drugs, as more specified above, which have the same biological activity as interferon gamma, or pirfenidone.

The term **"same biological activity"** means herein the same substantial biological, physiological or therapeutic activity or functionality, which however can be quantitatively enhanced or reduced compared with the relevant properties of said drugs.

The term **"stabilized form"** means a derivative or analogue wherein the parent drug was altered in order get more stability and increased half-life in blood and serum. Polypeptides and proteins may be protected against proteolysis by the attachment of chemical moieties. Such attachment may effectively block the proteolytic enzyme from physical contact with the protein backbone itself, and thus prevent degradation. Polyethylene glycol is one such chemical moiety which has been shown to protect against proteolysis (Sada, et al.,

J. Fermentation Bioengineering 71: 137-139, 1991). In addition to protection against proteolytic cleavage, chemical modification of biologically active proteins has been found to provide additional advantages under certain circumstances, such as increasing the stability and circulation time of the therapeutic protein and decreasing immunogenicity. (US. 4,179,337; Abuchowski et al., Enzymes as Drugs.; J.S. Holcerberg and J. Roberts, eds. pp. 367-383, 1981; Francis, *Focus on Growth Factors* 3: 4-10; EP 0 401 384). The addition of polyethylene glycol increases stability of the peptides and polypeptides of this invention at physiological pH as compared to non-pegylated compounds. The pegylated polypeptide /protein is also stabilized with regard to salts.

The term "**fusion protein**" means a compound, especially a stabilized form, consisting of a polypeptide according to the invention, preferably interferon gamma, which is fused to another peptide or protein.

The term "**pharmaceutical kit**" means a package comprising two or more packages or containers containing one or more, preferably one pharmaceutically active compound or agent and a gene expression analysis device, wherein the agent or compound in said packages or containers are administered to an individual after gene expression analysis is performed.

The pharmaceutical compositions according to the invention comprising interferon gamma or pirfenidone and a gene expression analysis as defined above and below can be used as medicament for the treatment of an individual.

The term "**individual**" preferably refers to mammals, especially humans.

The compound according to this invention, IFN-γ or pirfenidone, is used in a pharmaceutical formulations, comprising, as a rule, a pharmaceutically acceptable carrier, excipient or diluents. Techniques for the formulation and administra-

tion of the compounds of the present invention may be found in "Remington's Pharmaceutical Sciences" Mack Publishing Co., Easton PA.

As used herein, the term "**pharmaceutically acceptable carrier**" means an inert, non toxic solid or liquid filler, diluent or encapsulating material, not reacting adversely with the active compound or with the individual, or any other formulation such as tablets, pills, dragees, capsules, gels, syrups, slurries, suspensions and the like. Suitable, preferably liquid carriers are well known in the art such as sterile water, saline, aqueous dextrose, sugar solutions, ethanol, glycols and oils, including those of petroleum, animal, vegetable, or synthetic origin, for example, peanut oil, soybean oil and mineral oil. Tablets and capsules for oral administration contain conventional excipients such as binding agents, fillers, diluents, tableting agents, lubricants, disintegrants, and wetting agents. The tablets may be coated according to methods well known in the art.

The formulations according to the invention may be administered as unit doses containing conventional non-toxic pharmaceutically acceptable carriers, diluents, adjuvants and vehicles which are typical for parenteral administration.

The term "**parenteral**" includes herein subcutaneous, intravenous, intra-articular and intratracheal injection and infusion techniques. Parenteral compositions and combinations are most preferably administered intravenously either in a bolus form or as a constant fusion according to known procedures.

Also other administrations such as oral administration or administration by inhalation or nasal spray are also object of the invention. Inhalation of vapors containing interferon gamma as specified is also a preferred way of administration. For inhalations the compound according to the invention is preferably brought in an aerosol form. Aerosols and tech-

niques to make them are well known in the art. Aerosols applicable by inhalers containing a polypeptide of the invention, for example, interferon gamma are preferred if direct pulmonary symptoms have to be treated.

Unit doses according to the invention may contain daily required amounts of the compound according to the invention, or sub-multiples thereof to make up the desired dose. The optimum therapeutically acceptable dosage and dose rate for a given individual (mammals, including humans) depends on a variety of factors, such as the activity of the specific active material employed, the age, body weight, general health, sex, diet, time and route of administration, rate of clearance, enzyme activity, the object of the treatment, i. e., therapy or prophylaxis and the nature of the disease to be treated. Therefore, in the pharmaceutical compositions according to the invention for the therapy of an individual, a pharmaceutical effective daily dose of the respective compound in said composition is:

Interferon gamma (IFN-γ): It could be shown that interferon-γ is effective in the combination therapy according to the invention in a dose of 1.0 - 5.0 µg / kg body weight, preferably 2.0 - 3.0 µg / kg body weight, 1- 5 times per week. The above-indicated single dosages of interferon-γ are administered parenteral, preferably subcutaneously to the patient. The doses of glucocorticoids which can be administered optionally together with IFN-γ to an individual vary according to the invention from 10 - 100 mg / single dose and more preferably from 15 - 80 mg, which corresponds to approximately 100 - 350 µg /kg body weight, preferably 100-150 µg /kg body weight.

SHORT DESCRIPTION OF THE FIGURES

Fig. 1: Figure 1 depicts the total lung capacity (TLC), the partial pressure of arterial oxygen (PaO2), and the forced vital capacity (FVC) of a patient with histologically proven UIP (open lung biopsy) and failure of immunosuppressive treatment (f, 59 yr) treated with interferon gamma.

EXAMPLES

Biopsies were taken from patients suffering from severe interstitial lung disease (ILD), after informal consent was given, using the surgical method of bronchoscopy. Obtained tissue probes were stored and processed for isolation of total RNA in RNA*later*™ (patent pending), an aqueous, non-toxic tissue storage reagent that stabilizes and protects cellular RNA in intact, unfrozen tissue samples.

The dissected tissue (less than 0.5 cm in any one dimension) is submerged in approximately 5 volumes of RNA*later* (e.g., a 0.5 g sample requires about 2.5 ml of RNA*later*) at room temperature. The solution permeates the cells, stabilizing the RNA. Then, RNA is isolated using the one-step RNA isolation methods, such as TRIzol® Reagent (Life Technologies), following the instructions of the supplier and finally eluted in H_2O.

Preparation of Labeled cRNA and Hybridization to Microarrays.

Double-stranded cDNA was synthesized out of the isolated patients RNA samples using a cDNA synthesis kit (Superscript; Life Technologies) employing oligo(dT) priming. The resulting cDNA was used for *in vitro* transcription (Ambion T7 Megascript system) in the presence of biotin-11-CTP and biotin-16-UTP (Enzo Diagnostics). A total of 25-50 µg of the cRNA product in buffer [40 mM Tris·acetate (pH 8.1)/100 mM potassium acetate/30 mM magnesium acetate] was fragmented at 94°C for 35 min. It was then used as a hybridization probe from each

patient for hybridization as recommended (Affymetrix, Santa Clara, CA).

Aliquots of the hybridization patients cRNA mixtures (10 µg cRNA in 200 µl hybridization mix) were hybridized to a Human Genome U133A Array. Each array was washed and scanned (Hewlett Packard, GeneArray scanner G2500A) according to procedures developed by manufacturer (Affymetrix).

Analysis of GENECHIP Data. Scanned output files were visually inspected for hybridization artifacts and then analyzed with GENECHIP 3.1 software (Affymetrix).

The expression analysis files created by GENECHIP 3.1 software were transferred to a database (Microsoft Access) and linked to Internet genome databases (e.g., NHLBI, or Swiss Prot).

Analysis of Infectious agents in biopsies. As patients with ILD repeatedly suffer from inflammations, biopsied material was tested for the presence of infectious agents. Most dominant was the observation of underlying Herpes virus infections (treated with Ganciclovir) and various bacterial infections (treated with various antibiotics), or few fungal infections.

Therapy. Therapy with interferon gamma was only started after successful pretreatment of the underlying infections and the assessment of the gene expression of the endogenous disease signiture genes. Application of molecular gene expression analysis followed by interferon gamma, led to a surprising, statistically highly significant increase of total lung capacity that was accompanied by a substantial increase of physical exertion capacity, statistically significant increased partial pressure of arterial oxygen at rest and a strong decrease of disease symptoms. This indicates that the

pharmaceutical composition of gene expression analysis followed by interferon gamma is able to counterbalance fibrosing reactions in interstitial lung diseases and provides significant survival benefit to the patients with IPF.

Fig. 1a) depicts start data #1 of the treatment.

Levels of Gene transcription during long-term treatment

#	IFN g	IL-13	TGF-beta$_1$	CTGF
1	1.7	1.8	13.1	2.9
2				
3				
4				

t ↓

Immune response Wound healing

Fig. 1b) depicts the total lung capacity (TLC), the partial pressure of arterial oxygen (PaO2), and the forced vital capacity (FVC) of the same patient with histologically proven UIP (open lung biopsy) and failure of immunosuppressive treatment (f, 59 yr) between time #1 and time #2.

Levels of Gene transcription during long-term treatment

#	IFN g	IL-13	TGF-beta$_1$	CTGF
1	1.7	1.8	13.1	2.9
2	0	0	5.4	2.1
3				
4				

t ▼

Immune response Wound healing

Fig. 1c) depicts the same data for the same patient between time #1 and time #4.

Levels of Gene transcription during long-term treatment

#	IFN g	IL-13	TGF-beta$_1$	CTGF
1	1.7	1.8	13.1	2.9
2	0	0	5.4	2.1
3	0	0.2	3.1	1.3
4	0	0	1.2	0.4

t ▼

Immune response Wound healing

Pretreatment of CMV followed by selected gene transcription analysis and subsequent interferon gamma treatment lead to stabilization of the patient with a deadly disease.

Claims

1. A pharmaceutical composition comprising

2. (i) interferon gamma (IFN-γ), optionally together with a pharmaceutically acceptable carrier, diluent or excipient

(ii) a polynucleotide library for the molecular characterization of an interstitial lung disease (ILD), said library comprising a pool of polynucleotide sequences or subsequences thereof wherein said sequences or subsequences are either underexpressed or overexpressed in ILD cells

(iii) a polynucleotide library for the molecular characterization of infectious agents, said library comprising a pool of polynucleotide sequences or subsequences thereof wherein said sequences or subsequences are characteristic for bacteria, mycoplasma, viruses, fungi, or yeasts.

3. A pharmaceutical composition according to claim 1, comprising additionally a glucocorticoid compound.

4. A pharmaceutical composition comprising

(i) pegylated interferon gamma (PEG-IFN-γ), optionally together with a pharmaceutically acceptable carrier, diluent or excipient

(ii) a polynucleotide library for the molecular characterization of an interstitial lung disease (ILD), said library comprising a pool of polynucleotide sequences or subsequences thereof wherein said sequences or subsequences are either underexpressed or overexpressed in ILD cells

(iii) a polynucleotide library for the molecular characterization of infectious agents, said library com-

prising a pool of polynucleotide sequences or subsequences thereof wherein said sequences or subsequences are characteristic for bacteria, mycoplasma, viruses, fungi, or yeasts.

5. A pharmaceutical composition according to claim 3, comprising additionally a glucocorticoid compound.

6. A pharmaceutical composition comprising
(i) pirfenidone, optionally together with a pharmaceutically acceptable carrier, diluent or excipient
(ii) a polynucleotide library for the molecular characterization of an interstitial lung disease (ILD), said library comprising a pool of polynucleotide sequences or subsequences thereof wherein said sequences or subsequences are either underexpressed or overexpressed in ILD cells
(iii) a polynucleotide library for the molecular characterization of infectious agents, said library comprising a pool of polynucleotide sequences or subsequences thereof wherein said sequences or subsequences are characteristic for bacteria, mycoplasma, viruses, fungi, or yeasts.

7. A pharmaceutical composition according to claim 5, comprising additionally a glucocorticoid compound.

8. A pharmaceutical composition according to claims 1-6 for the treatment of idiopathic pulmonary fibrosis (IPF).

9. A pharmaceutical composition according to claims 1-6 for the treatment of hypersensivity pneumonitis.

10. A pharmaceutical composition according to claims 1-6 for the treatment of scleroderma.

11. A pharmaceutical composition according to claims 1-6 for the treatment of Systemic Lupus Erythematosus.

12. A pharmaceutical composition according to claims 1-6 for the treatment of Rheumatoid Arthritis.

13. A pharmaceutical composition according to claims 1-6 for the treatment of Churg-Strauss syndrome, Wegener's granulomatosis, and Goodpasture Syndrome.

14. A polynucleotide library according to claims 1-6 wherein said sequences are useful in classifying good and poor prognosis in ILD patients.

15. A polynucleotide library according to claims 1-6 wherein said polynucleotide sequences or subsequences correspond to any combination of at least one polynucleotide selected among those included in at least 50%, preferably 75% and more preferably 100% of the predefined sets.

16. A polynucleotide library according to claims 1-6 wherein said polynucleotides are immobilized on a solid support in order to form a polynucleotide array.

17. A polynucleotide library according to claims 1-6 wherein the support is selected from the group comprising a nylon membrane, nitrocellulose membrane, glass slide,

glass beads, membranes on glass support or a silicon chip.

18. A polynucleotide library according to claims 1-6 wherein the presence of or predisposition for ILD using expression profiling images comprises the steps of:
(a) isolation of material from an individual clinically diagnosed for a lung disease, or of familiar predisposition for an ILD,
(b) providing molecular probes as ligands selected from the group consisting of mRNA, polynucleotides, oligonucleotides, cDNAs, proteins or functional fragments thereof, isolated or generated from said individuals
(c) contacting said molecular probes as ligands with a set of immobilized receptors selected from the group consisting of polynucleotides, oligonucleotide or cDNA probes and antibodies or functional fragments thereof, specifically representing a respective set of genes involved with the presence of or predisposition for ILD, or an infection to be molecularly diagnosed, and qualitatively and quantitatively detecting the presence of bound ligand/receptor complexes to obtain an expression profiling image being representative for the current status of the individual to be diagnosed,
(d) comparing the expression profiling image obtained in step (c) with the expression profiling image(s) of normal individuals, expression profiling image(s) of individuals with clinically similar diseases, and/or with the expression profiling images(s) of individuals having a predisposition for or suffering from ILD to be diagnosed, and
(e) therefore on the basis of the results of the comparison obtained in step (d).

19. A pharmaceutical composition according to claims 1-6 wherein said polynucleotide library for the molecular characterization of an interstitial lung disease (ILD) comprises a pool of polynucleotide sequences or subsequences selected from a set of sequences defined by, or correlated to, or derived from the group of genes consisting of candidate genes indicated in the following list:

PTH-responsive osteosarcoma B1 protein, AF095771.1

matrix associated, actin dependent regulator of chromatin, subfamily f, member 1, AF231056.1

deleted in lung and esophageal cancer 1 (DLEC1), NM_007337.1

major histocompatibility complex, class II, DQ beta 1, AW276186

SB classII histocompatibility antigen alpha-chain, AI128225

mucin 4, tracheobronchial, AJ242547.1

forkhead box J1 (FOXJ1), U69537.1

hypothetical protein FLJ21616, NM_024567.1

neuronal specific transcription factor DAT1, AF258348.1

hematopoietic PBX-interacting protein, BF344265

proline oxidase homolog, AA074145

mucin 5, subtype B, tracheobronchial, AI697108

golgi membrane protein GP73, AF236056.1

ATP citrate lyase, U18197.1

NG22 protein, NM_025257.1

cDNA DKFZp434A2322, AL137706.1

hepatocyte nuclear factor 3, alpha, U39840.1

major histocompatibility complex, class II, DQ alpha 1, X00452.1

myosin regulatory light chain 2, smooth muscle isoform, J02854.1

plexin B1, AV693216

pyruvate kinase, muscle, BC000481.1

tetraspanin TM4-C, AF133425.1

insulin-like growth factor binding protein 2 (36kD), BC004312.1

FLJ13945 fis, clone Y79AA1000969, AU160041

hypothetical protein DKFZp586M1120, NM_031294.1

CD24 signal transducer, L33930

hypothetical protein FLJ23571, NM_025111.1

glutathione S-transferase M2 (muscle), M63509.1

cadherin 1, type 1, E-cadherin (epithelial), L08599.1

NTT5 protein, AF265578.1

lipocalin 2 (oncogene 24p3), NM_005564.1

myotonic dystrophy kinase (DM kinase), L08835

uncoupling protein 2 (mitochondrial, proton carrier), U76367.1

dynein intermediate chain 2, NM_023036.1

discoidin receptor tyrosine kinase isoform b, discoidin domain receptor family, member 1, NM_001954.2

sperm associated antigen 6, AF079363.1

hypothetical protein FLJ23049, NM_024687.1

nasopharyngeal epithelium specific protein 1, AF094758.1

nuclear receptor subfamily 4, group A, member 2, NM_006186.1

hypothetical protein FLJ22215, BC003543.1

non-specific cross reacting antigen, M18728.1

amylase, alpha 1A; salivary (AMY1A), NM_004038.1

carcinoembryonic antigen-related cell adhesion molecule 6 (non-specific cross reacting antigen), BC005008.1

glutathione S-transferase subunit 4 (EC 2.5.1.18), X08020.1

SH3-containing protein SH3GLB2, AF257319.1

KDEL (Lys-Asp-Glu-Leu) endoplasmic reticulum protein retention receptor 1, NM_006801.1

anterior gradient 2 (Xenepus laevis) homolog, AF038451.1

sv7-MUC4 apomucin, mucin 4, tracheobronchial, AJ242547.1

stratifin, BC000329.1

connective tissue growth factor, M92934.1

cytochrome P450-IIB (hIIB3), M29873.1

filamin A, alpha (actin-binding protein-280), AW051856

membrane glycoprotein LIG-1, AB050468.1

E74-like factor 3 (ets domain transcription factor, epithelial-specific), U73844.1

elastin (supravalvular aortic stenosis, Williams-Beuren syndrome), M36860.1

ephrin receptor EPHA3, AF213459.1

fibrillin 1 (Marfan syndrome), L13923.1

discs, large (Drosophila) homolog 1, U13896.1

lysyl oxidase-like 1 (LOXL1), L21186.1

calumenin, U67280.1

male germ cell-associated kinase, NM_005906.2

plectin 1, intermediate filament binding protein, 500kD, Z54367

peroxisome biogenesis factor 1, AF026086.1

mast cell tryptase beta III, AF099143

ataxia-telangiectasia group D-associated protein, AF230388.1

hypothetical protein FLJ10921, NM_018272.1

biglycan, BC002416.1

BLu protein, AC002481

CGI-92 protein, AF151850.1

adaptor-related protein complex 1, mu 2 subunit, BC003387.1

keratin 15, BC002641.1

B7 protein, U72508.1

S100 calcium-binding protein A2, BC002829.1

MUF1 protein, BC004953.1
cholesterol 25-hydroxylase, AF059214.1

cytidine monophosphate-N-acetylneuraminic acid hydroxylase (CMP-N-acetylneuraminate monooxygenase), AF074480.1

neuropilin 2, AF022859.1

Fas-interacting serinethreonine kinase 3, homeodomain-interacting protein kinase 3, AF305239.1

a disintegrin and metalloproteinase domain 28 (ADAM28), transcript variant 2, AF137334.1

cDNA DKFZp434A119 , AW663632

complement component 6, J05064.1

cytokeratin 17, Z19574

wingless-type MMTV integration site family, member 5A, AI968085

matrix metalloproteinase 7 (matrilysin, uterine), BC003635.1

leiomodin 1 (smooth muscle), NM_012134.1

Cip1-interacting zinc finger protein, AB030835.1

cyclin-dependent kinase inhibitor 1A (p21, Cip1), BC000275.1

integrin, alpha 7, AF032108.1

DKFZP586G011 protein, BG289527

fatty acid binding protein 6, ileal (gastrotropin), U19869.1

glutathione S-transferase M4, M96234.1

Ras-related associated with diabetes, L24564.1

claudin 3, AB000714.1

matrix metalloproteinase 10 (stromelysin 2), BC002591.1

fibulin 2, NM_001998.1

serine threonine kinase 11 (STK11), AF035625

eukaryotic translation initiation factor 1A: AF000987.1

DEADH (Asp-Glu-Ala-AspHis) box polypeptide: AF000985.1

ribosomal protein S4: AF116711.1

ubiquitin specific protease 9: AF000986.2

SMC (mouse) homolog: U52191.1

myelin basic protein: L18865.1

S100 calcium-binding protein: NM_005980.1

Jagged2 (JAG2): AF003521.1

latent transforming growth factor beta binding protein 4: NM_003573.1

microtubule-associated protein, RPEB family, member 3: AB025186.1

Unknown (protein for MGC:2854): BC003629.1

clone=IMAGE-2406340: AI830563

AQP3 gene for aquaporine 3 (water channel): AB001325

cDNA DKFZp434A119

fenestrated-endothelial linked structure protein (FELS), PV1 protein (PLVAP): AF326591.1

LUNX protein; PLUNC (palate lung and nasal epithelium clone); tracheal epithelium enriched protein (LOC51297): AB024937.1

RAB, member of RAS oncogene family-like 2A: AF095350.1

chromosome 11 open reading frame 16: NM_020643.1

hypothetical protein FLJ23049: NM_024687.1

hypothetical protein FLJ11767: NM_024593.1

dynein, axonemal, intermediate polypeptide: AF091619.1

brain specific protein (LOC51673): AF132972.1

MUC4 apomucin, mucin 4, tracheobronchial: AJ242547.1

myotonin protein kinase (DM): M87313.1

cytokeratin 4: X07695.1

KIAA0362 gene, MCF.2 cell line derived transforming sequence-like: AB002360.1

cytokeratin 17: Z19574

LIM domain protein: BC003096.1

E74-like factor 3 (ets domain transcription factor, epithelial-specific) : U73844.1

fatty acid binding protein 6, ileal (gastrotropin): U19869.1

sperm associated antigen 6: AF079363.1

eyes absent (Drosophila) homolog 2: U71207.1

phosphatidic acid phosphatase type 2C: BC002806.1

epoxide hydrolase 2, cytoplasmic: AF233334.1

tubulin, beta, 2: BC002783.1

heat shock 105kD: D86956.1

villin 2 (ezrin): J05021.1

a disintegrin and metalloproteinase domain 28 (ADAM28), transcript variant 3: AF137335.1

deleted in lung and esophageal cancer 1: NM_007337.1

arachidonate 15-lipoxygenase: NM_001140.1

UDP glycosyltransferase 1 family, polypeptide A1: M57899.1

hypothetical protein PRO2834: AF119903.1

lectin, galactoside-binding, soluble, 7 (galectin 7): L07769.1

B7 protein: U72508.1

ephrin receptor EPHA3: AF213459.1

forkhead box J1: U69537.1

BLu protein: U70824.1

aldehyde dehydrogenase 3 family, member A1: BC004370.1

NG22 protein: NM_025257.1

small inducible cytokine subfamily A (Cys-Cys), member 14: NM_004166.1

cysteine-rich protein 1 (intestinal): BC002738.1

putative GTP-binding protein similar to RAYRAB1C: BC000566.1

integrin, beta 4: NM_000213.1

serine (or cysteine) proteinase inhibitor, clade B (ovalbumin), member 5 (SERPINB5): U04313.1

Ras-related associated with diabetes: L24564.1

hepatic leukemia factor: M95585.1

keratin 15: BC002641.1

nuclear receptor subfamily 4, group A, member 2: NM_006186.1

sialyltransferase: U14550.1

glutathione S-transferase M2 (muscle): M63509.1

hypothetical protein FLJ13110: NM_022912.1

S100 calcium-binding protein A2: NM_005978.2

collagen, type VII, alpha 1 (epidermolysis bullosa, dystrophic, dominant and recessive) : L02870.1

claudin 3: AB000714.1

insulin-like growth factor binding protein 6: BC003507.1

fibroblast growth factor receptor 2 (bacteria-expressed kinase, keratinocyte growth factor receptor, craniofacial dysostosis 1, Crouzon syndrome, Pfeiffer syndrome, Jackson-Weiss syndrome): M80634.1

insulin-like growth factor 1 receptor: NM_000875.2

insulin-like growth factor binding protein 2 (36kD): M35410.1

ataxia-telangiectasia group D-associated protein: AF230388.1

keratin 5 (epidermolysis bullosa simplex, Dowling-MearaKobnerWeber-Cockayne types): M21389.1

Duffy blood group: U01839.1

transforming growth factor β_1, NM_000660

sorting nexin 10 (SNX10), AF121860.1

phospholipase A2, group IIA (platelets, synovial fluid), M22430.1

hemoglobin alpha-1 globin chain (HBA1), AF349571.1

macrophage scavenger receptor 1, AI299239

surfactant, pulmonary-associated protein C, BC005913.1

disintegrin protease (M12.219), NM_014479.1

retinol-binding protein 4, interstitial, AF119868.1

major histocompatibility complex, class II, DR beta 3, M27635.1

adipose differentiation-related protein, BC005127.1

hemoglobin, delta, NM_000519.2

beta-2-microglobulin, AW188940

hemoglobin, alpha 2, BC005931.1

protein C receptor, endothelial (EPCR), L35545.1

thymosin, beta 10, M92381.1

apolipoprotein C-I, W79394

hypothetical protein, AL133067.1

proteoglycan 4, (megakaryocyte stimulating factor, articular superficial zone protein), U70136.1

tetranectin (plasminogen-binding protein), NM_003278.1

platelet factor 4, M25897.1

tissue factor pathway inhibitor 2, BC005330.1

fatty acid binding protein 4, adipocyte, BC003672.1

cathepsin B (CTSB), M14221.1

transmembrane 4 superfamily member 1, M90657.1

MHC class I HLA-B51 major histocompatibility complex, class I, E, M31183.1

endothelial PAS domain protein 1, U51626.1

Apo-2 ligand tumor necrosis factor (ligand) superfamily, member 10, U37518.1

haptoglobin-related protein, NM_020995.1

Rho guanine exchange factor (GEF) 12, AF119898.1

major histocompatibility complex, class II, DR beta 5, M11867.1

interferon, gamma-inducible protein 30, AF097362.1

ferritin, light polypeptide, BG537190

prosaposin (variant Gaucher disease and variant metachromatic leukodystrophy), BC004275.1

calcium-binding protein A4 (calvasculin, metastasin,), NM_002961.2

hemoglobin, beta, M25079.1

CDW52 antigen (CAMPATH-1 antigen), BC000644.1

aldehyde dehydrogenase 1 family, member A2, AB015226.1

cathepsin Z, AF032906.1

MHC HLA-B39 major histocompatibility complex, class I, B, L37880.1

major histocompatibility complex, class II, DQ alpha 1, M33906.1

fibroblast growth factor 9 (glia-activating factor), D14838.1

hemoglobin, alpha 2, AF097635.1

transferrin receptor (p90, CD71), BC001188.1

complement component 3 (C3), K02765.1

cDNA DKFZp564D066, AL050025.1

complement component 1, q subcomponent, beta polypeptide, NM_000491.2

small inducible cytokine subfamily A (Cys-Cys), member 18, pulmonary and activation-regulated, AB000221.1

reticulon 1, L10333.1

major histocompatibility complex, class II, DR beta 1, M33600.1

haptoglobin, L29394.1

acid phosphatase 5, tartrate resistant, J04430.1

cytochrome P450, subfamily XXVIIA (steroid 27-hydroxylase, cerebrotendinous xanthomatosis), polypeptide 1, M62401.1

CD36 antigen (collagen type I receptor, thrombospondin receptor), M24795.1

calbindin 2, (29kD, calretinin), NM_001740.2

alpha-2-HS-glycoprotein, BG538564

cDNA DKFZp564A132, AL049963.1

fibronectin 1, AF130095.1

phosphodiesterase 4C, cAMP-specific, NM_000923.1

transcription factor 7 (T-cell specific, HMG-box), NM_003202.1

found in inflammatory zone 3 (FIZZ3), AF323081.1

claudin 15, NM_014343.1

carboxypeptidase B1 (tissue), M81057.1

hypothetical protein FLJ14054, NM_024563.1

bone marrow stromal cell antigen 1, D21878.1

interleukin 7 receptor, M29696.1

procollagen C-endopeptidase enhancer 2, AF098269.1

calcium-binding protein A8 (calgranulin A), AW238654

cDNA DKFZp564D193, AL049252.1

major histocompatibility complex, class II, DP beta 1, J03041.1

human leukocyte antigen C alpha chain, major histocompatibility complex, class I, C, AK024836.1

BCM-like membrane protein precursor, AF144235.1

CD14 antigen, M86511.1

pulmonary surfactant protein (SP5), J03553

signal transducer and activator of transcription 1, 91kD, BC002704.1

Wilms tumor 1 (WT1), transcript variant D, NM_024424.1

annexin A8, BC004376.1

macrophage receptor with collagenous structure, MARCO, AF035819.1

surfactant, pulmonary-associated protein A2, NM_006926.1

solute carrier family 6 (neurotransmitter transporter, serotonin), member 4, L05568.1

chitinase 1 (chitotriosidase), U29615.1

lung type-I cell membrane-associated glycoprotein, AU154455

fibronectin leucine rich transmembrane protein 2, AB007865.1

gamma-aminobutyric acid (GABA) A receptor, alpha 5, BF966183

hypothetical protein FLJ12983, NM_024856.1

sialophorin (gpL115, leukosialin, CD43), J04536.1

cerebellar degeneration-related protein (34kD), M16965.1

hydroxyacid oxidase 2 (long chain), hydroxy-delta-5-steroid dehydrogenase (3 beta-and steroid delta-isomerase 2), AL359553

CLONE=IMAGE:1032795=Hs.83623 nuclear receptor subfamily 1, group I, member 3

small inducible cytokine subfamily C, member 2: NM_003175.1

hypothetical protein similar to swine acylneuraminate lyase: NM_030769.1

fibrinogen, gamma polypeptide: AF118092.1

thrombospondin 1: NM_003246.1

SAM domain, SH3 domain and nuclear localisation signals, 1: AF222927.1

chitinase 3-like 1 (cartilage glycoprotein-39): M80927.1

cathepsin Z: AF032906.1

CLONE=IMAGE:3579023 collagen, type XIV, alpha 1 (undulin)

chloride intracellular channel 2: NM_001289.2

monokine induced by gamma interferon: NM_002416.1

KIAA0433 protein: NM_015216.1

tumor necrosis factor, alpha-induced protein 6: NM_007115.1

signal transducer and activator of transcription 1, 91kD: BC002704.1

thrombospondin 2: L12350.1

collagen, type IV, alpha 3 (Goodpasture antigen): NM_000091.1

integrin, beta-like 1 (with EGF-like repeat domains): AF072752.1

diubiquitin: NM_006398.1

protease, cysteine, 1 (legumain): D55696.1

cytochrome P450, subfamily I (dioxin-inducible), polypeptide 1 (glaucoma 3, primary infantile): U03688.1

integrin, alpha 1: X68742.1

GABA-B receptor, G protein-coupled receptor 51: AF056085.1

KIAA1199 protein: AB033025.1

collagen, type V, alpha 2: NM_000393.1

interleukin 13 receptor, alpha 2: U70981.1

translocase of inner mitochondrial membrane 8 (yeast) homolog A: BC005236.1

steroid sulfatase (microsomal), arylsulfatase C, isozyme S: M16505.1

CLONE=IMAGE:1982571 ATPase, H+ transporting, lysosomal (vacuolar proton pump) 9kD

proteoglycan 4, (megakaryocyte stimulating factor, articular superficial zone protein): U70136.1

nidogen (enactin): M30269.1

KIAA1598 protein: AU157109

vascular cell adhesion molecule 1: M60335.1

guanylate binding protein 1, interferon-inducible, 67kD: BC002666.1

cDNA DKFZp586E1124

apolipoprotein H (beta-2-glycoprotein I): M62839.1

ribosomal protein L37a: BE857772

cDNA DKFZp564A132

cathepsin S: M86553.1

a disintegrin and metalloproteinase domain 9 (meltrin gamma) (ADAM9): U41766.1

zinc finger protein 331: AF272148.1

lysosomal-associated membrane protein 2: J04183.1

carboxypeptidase M: NM_001874.1

collagen, type I, alpha 2: NM_000089.1

P311 protein: U36189.1

KIAA0372 gene product: AB002370.1

Human T cell-specific protein RANTES: M21121

interferon-gamma-inducible indoleamine 2,3-dioxygenase (IDO): M34455.1

hypothetical protein FLJ10430: NM_018092.1

transcription factor ISGF-3: M97935

interleukin 1 receptor-like 1 (IL1RL1): NM_003856.1

putative alpha chemokine (H174), small inducible cytokine subfamily B (Cys-X-Cys), member 11: AF002985.1

small inducible cytokine subfamily B (Cys-X-Cys), member 10: NM_001565.1

mesoderm specific transcript (mouse) homolog: BC002413.1

carboxypeptidase B-like protein: AB011969.1

CD2 antigen (p50), sheep red blood cell receptor: M16445.

interferon, alpha-inducible protein (clone IFI-6-16): NM_022872.1

RAS guanyl releasing protein 1 (calcium and DAG-regulated): AF081195.1

lipase, endothelial: AF118767.1

fatty-acid-Coenzyme A ligase, long-chain 4: NM_022977.1

klotho: AB005142.1

chondroitin sulfate proteoglycan 2 (versican): NM_004385.1

hypothetical protein, expressed in osteoblast: AB000115.1

CD14 antigen: M86511.1

CGI-83 protein: BC000878.1

leucine aminopeptidase: AF061738.1

UDP-Gal:betaGlcNAc beta 1,3-galactosyltransferase, poly-peptide 3: AB050855.1

protocadherin alpha 12: AF152308.1

neuroglycan C: AF059274

neuroligin: AI338338

HSPC156 protein: AF161505.1

hypothetical protein FLJ13310: NM_025118.1

eosinophil chemotactic cytokine (TSA1902): AB025008.1

aminopeptidase: AF191545.1

semaphorin sem2: AB029496.1

protocadherin 12: AF231025.1

X transporter protein 3: NM_020208.1

transmembrane 4 superfamily member (tetraspan NET-2): AF124522.1

hypothetical protein FLJ10970: NM_018286.1

perforin 1 (pore forming protein): M28393.1

natural killer cell group 7 sequence: NM_005601.1

hypothetical protein DKFZp761N09121: BF435376

integrin, alpha 4 (antigen CD49D, alpha 4 subunit of VLA-4 receptor): BG532690

chitinase 3-like 2: U58515.1

FYN oncogene: N20923

relaxin 1 (H1): BC005956.1

hydroxyprostaglandin dehydrogenase 15-(NAD): U63296.1

sulfotransferase family, cytosolic, 1C, member 1: AF186254.1

TGF-b superfamily receptor type I: L17075.1

granzyme B (granzyme 2, cytotoxic T-lymphocyte-associated serine esterase 1): M36118.1

cystatin F (leukocystatin): AF031824.1

regulator of G protein signaling-Z (RGSZ1): AF060877.2

clone MGC:12387: M16942.1

zinc-alpha2-glycoprotein: D90427.1

BCG induced integral membrane protein BIGMo-103: AB040120.1

nectin-like protein 2 (NECL2): AF132811.1

CD209 antigen-like: AB015629.1

solute carrier family 6 (neurotransmitter transporter, serotonin), member 4: L05568.1

MAD (mothers against decapentaplegic, Drosophila) homolog 6: U59914.1

latrophilin: AF104939.1

platelet factor 4: M25897.1

calcitonin receptor-like: L76380.1

matrilin 3: NM_002381.2

solute carrier family 14 (urea transporter), member 1 (Kidd blood group): U35735.1

interleukin 7 receptor: M29696.1

MAP kinase kinase 6 (MKK6), mitogen-activated protein kinase kinase 6: U39656.1

protocadherin 17: AF029343.1

granulysin: NM_006433.2

interferon-stimulated protein, 15 kDa (ISG15): M13755.1

cadherin 5, type 2, VE-cadherin (vascularepithelium): U84722.1

thrombomodulin: M16552.1

interferon, alpha-inducible protein 27: NM_005532.1

interferon-gamma, X87308

and allelic variants or mutants thereof

and sequences specific for infectious agents, comprising a pool of polynucleotide sequences or subsequences thereof wherein said sequences or subsequences are characteristic for Mycobacterium spec., Mycoplasma spec., Staphyllococcus aureus, Streptococcus spec., Borrelia, Treponema pallidum, Leptospira interrogans, Campylobacter jejuni, Escherichia coli, EPEC, ETEC, EIEC, EHEC Salmonella enterica, Yersinia enterocolitica, Aeromonas spec., Campylobacter fetus, Moraxella catarrhalis, Moraxella catarrhalis, Brucella spec., Toxoplasma, Salmonella enterica, Shigella spec., Yersinia enterocolitica, Vibrio cholerae, Pseudomonas aeruginosa, Burkholderia cepacia, Stenotrophomonas maltophilia, Acinetobacter baumanii, Acitenobacter calcoaceticus, Klebsiella, Enterobacter, Citrobacter, Proteus, Serratia, Morganella, Providencia, Cardiobacterium hominis, Eikenella corrodens, Gardnerella vaginalis, Calymmatobacterium granulomatis, Bacteriodes, Porphyromonas, Prevotella, Fusobacterium, Rickettsia prowazekii, Bartonella bacilliformis, Bartonella henselae, Chlamydia spec., yeasts, fungi, retroviruses, adenoviruses, hepadnaviruses, herpesviruses, influenza viruses, paramyxoviruses.

20. Use of a pharmaceutical kit comprising

(i) a package comprising IFN-γ,

(ii) a package comprising a polynucleotide library for the molecular characterization of an interstitial lung disease (ILD), said library comprising a pool of polynucleotide sequences or subsequences thereof wherein said sequences or subsequences are either underexpressed or overexpressed in ILD cells

(iii) a package comprising a polynucleotide library for the molecular characterization of infectious agents, said library comprising a pool of polynucleotide sequences or subsequences thereof wherein said sequences or subsequences are characteristic for bacteria, mycoplasma, viruses, fungi, or yeasts.

21. Use of pharmaceutical kit according to claim 19 further comprising a package comprising a glucocorticoid compound.

22. Use of a pharmaceutical kit comprising

(i) a package comprising pegylated IFN-γ,

(ii) a package comprising a polynucleotide library for the molecular characterization of an interstitial lung disease (ILD), said library comprising a pool of polynucleotide sequences or subsequences thereof wherein said sequences or subsequences are either underexpressed or overexpressed in ILD cells

(iii) a package comprising a polynucleotide library for the molecular characterization of infectious agents, said library comprising a pool of polynucleotide sequences or subsequences thereof wherein said sequences or subse-

quences are characteristic for bacteria, mycoplasma, viruses, fungi, or yeasts.

23. Use of pharmaceutical kit according to claim 21 further comprising a package comprising a glucocorticoid compound.

24. Use of a pharmaceutical kit comprising
(i) a package comprising pirfenidone,
(ii) a package comprising a polynucleotide library for the molecular characterization of an interstitial lung disease (ILD), said library comprising a pool of polynucleotide sequences or subsequences thereof wherein said sequences or subsequences are either underexpressed or overexpressed in ILD cells
(iii)a package comprising a polynucleotide library for the molecular characterization of infectious agents, said library comprising a pool of polynucleotide sequences or subsequences thereof wherein said sequences or subsequences are characteristic for bacteria, mycoplasma, viruses, fungi, or yeasts.

25. Use of pharmaceutical kit according to claim 23 further comprising a package comprising a glucocorticoid compound.

26. Use of pharmaceutical kit according to claims 19-24 for the manufacture of a medicament for the treatment of interstitial lung diseases (ILD).

27. Use of pharmaceutical kit according to claims 19-25, wherein IFN-γ is administered to the individual in a sin-

gle dose amount varying from 2.0 to 3.0 µg / kg body weight.

28. Use of pharmaceutical kit according to claims 19-26, wherein the glucocorticoid compound is administered to the individual in a single dose amount varying from 100 to 150 µg / kg body weight.

29. Use of pharmaceutical kit according to claims 19-27, wherein interferon gamma or pegylated interferon gamma is administered to the individual by inhalation.

30. Method for treatment of interstitial lung diseases (ILD) or related forms thereof comprising administering to a individual a pharmaceutical composition according to any of the claims 1 - 6 or a pharmaceutical kit according to any of the claims 19 - 28.

31. Method according to claim 29, wherein IFN-γ is administered to the individual in a single dose amount varying from 2.0 to 3.0 µg / kg body weight.

32. Method according to claims 29 or 30, wherein the glucocorticoid compound is administered to the individual in a single dose amount varying from 100 to 150 µg / kg body weight.