### 352. Idiopathic pulmonary fibrosis

### P3145

The functional MUC5B rs35705950 promoter polymorphism is associated with IPF but not with systemic sclerosis related interstitial lung disease <u>Raphael Borie</u><sup>1</sup>, Bruno Crestani<sup>1</sup>, Philippe Dieude<sup>4</sup>, Hilario Nunes<sup>2</sup>, Yannick Allanore<sup>3</sup>, Caroline Kannengiesser<sup>5</sup>, Paolo Airo<sup>6</sup>, Marco Matucci-Cerinic<sup>7</sup>, Benoit Wallaert<sup>10</sup>, Dominique Israel-Biet<sup>11</sup>, Jacques Cadranel<sup>8</sup>, Vincent Cottin<sup>9</sup>, Dominique Valeyre<sup>2</sup>, Bernard Grandchamp<sup>5</sup>. <sup>1</sup>Service de Pneumologie A, APHP, Hopital Bichat, Paris, France; <sup>2</sup>Service de Pneumologie, APHP, Hopital Avicenne, Bobigny, France; <sup>3</sup>Service de Rhumatologie, APHP, Hopital Avicenne, Bobigny, France; <sup>3</sup>Service de Rhumatologie, APHP, Hopital Avicenne, Bobigny, France; <sup>4</sup>Service de Rhumatologie, APHP, Hopital Cotini, Paris, France; <sup>4</sup>Service de Rhumatologie, APHP, Hopital Bichat, Paris, France; <sup>5</sup>Service de Génétique, APHP, Hopital Bichat, Paris, France; <sup>6</sup>Rheumatology and Clinical Immunology, Spedali Civili, Brescia, Italy; <sup>7</sup>Department of Biomedicine, Section of Rheumatology, University of Florence, Italy; <sup>8</sup>Service de Pneumologie, Hopital Tenon, Paris, France; <sup>9</sup>Service de Pneumologie, Hopital Louis Pradel, Lyon, France; <sup>10</sup>Service de Pneumologie, CHRU de Lille, Lille, France; <sup>11</sup>Service de Pneumologie, Hopital Européen Georges Pompidou, Paris, France

A MUC5B promoter polymorphism has been associated with IPF in the North American population (frequency of T risk allele 35% in IPF patients compared to 10% in controls. The polymorphism of MUC5B has not been investigated in the European population or in non-IPF pulmonary fibrosis.

MUC5B was genotyped in the first 168 patients of the French national prospective IPF cohort (COFI), in 870 French patients with systemic sclerosis (SSc) (346 with interstitial lung disease, ILD), in 598 Italian SSc patients (207 with ILD), 1383 French controls and 494 Italian controls. The diagnosis of IPF was based on the 2000 ATS/ERS criteria and centrally reviewed.

The T risk allele frequency was strongly increased in the IPF patients compared to the control population: 38.6% vs 10.8%, P = 2x10-44, OR 19 [9-36] for homozy-gotous patients. No statistical difference of frequency was observed in both SSc and SSc-ILD in the French population: 10% and 11.1%, respectively.

Polymorphism of MUC5B in the French populations

	TT (%)	GT (%)	GG (%)
IPF (n=168)	11.9	53.5	34.5
SSc (n=981)	1.2	17.5	81.2
SSc-ILD+ (n=346)	1.4	19.5	79.1
Controls (n=1383)	1.4	18.7	79.8

Similar results were observed in the Italian population regarding the T allele frequency in SSc and SSc-ILD when compared to controls: 12% and 13.5%, respectively vs 11.7%.

Our study provide for the first time i) an independent replication of an association between MUC5B rs35705950 T risk allele and IPF in the French population ii) a lack of association of MUC5B rs35705950 with SSc-related ILD suggesting a distinct pathogenesis.

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### P3146

## Cytokine profiles of bronchoalveolar lavage fluid in patients with combined pulmonary fibrosis and emphysema

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Background: Combined pulmonary fibrosis and emphysema (CPFE) is characterized by upper lobe emphysema associated with lower lobe fibrosis.

**Objectives:** We aimed to examine whether the cytokine levels in the alveolar space are associated with the development of emphysematous changes that were superimposed on pulmonary fibrosis.

**Methods:** We retrospectively evaluated 102 consecutive patients who were diagnosed with pulmonary fibrosis after bronchoalveolar lavage (BAL). Cytokine levels and differential cell counts in BAL fluid, pulmonary function, CT scores, and levels of serum markers were compared between patients with emphysema and those without.

**Results:** Among the 102 patients (14 females, mean age, 68 y/o), 38 showed upper lobe emphysema on CT. In BAL fluid, the levels of ENA-78/CXCL5 and IL-8/CXCL8 were significantly higher in patients with emphysema than in those without. The levels of MCP-1/CCL2, MIP-1 $\alpha$ /CCL3, TNF- $\alpha$ , TGF- $\beta$ 1, and neutrophil elastase did not differ between the two patient groups. In patients with emphysema, whereas %VC was greater, FEV1/FVC and %DL<sub>CO</sub>/V<sub>A</sub> were lower than in those without emphysema. The composite physiologic index and serum levels of KL-6 and SP-D, markers of interstitial lung disease, were not different between the groups. Levels of CXCL8 and CXCL5 were associated with the groups.

proportion or absolute number of neutrophils in BAL fluid. In addition, CXCL8 levels were correlated inversely with %VC and % $DL_{CO}/V_A$  and positively with the area of low attenuation on CT.

Conclusion: Elevated CXC chemokine levels in the airspace might contribute to the emphysematous change in patients with pulmonary fibrosis, which may be associated with the development of CPFE.

### P3147

Gene expression profiles of idiopathic interstitial pneumonias: Identification of disease-specific diagnostic markers and molecular therapeutic targets Nobuhisa Ishikawa, Noboru Hattori, Masaya Taniwaki, Yasushi Horimasu, Tomoyo Matsuda, Nobuoki Kohno. Department of Molecular and Internal Medicine, Graduate School of Biomedical Sciences, Hiroshima University, Hiroshima, Japan

Introduction: Idiopathic pulmonary fibrosis (IPF) and nonspecific interstitial pneumonia (NSIP) are characterized by alveolar epithelial damage and inflammatory responses that lead to fibroblast proliferation and, ultimately, to loss of normal pulmonary architecture and function. Differential diagnosis between IPF and NSIP may be difficult. The molecular mechanisms underlying idiopathic interstitial pneumonias (IIPs) remain unclear.

Aims: This study aimed to elucidate the mechanisms underlying IIPs and identify disease-specific diagnostic markers and molecular therapeutic targets

Methods: The study included 12 patients with IIPs (IPF, 7 patients; NSIP, 5 patients). RNA was extracted from frozen lung specimens from the study population and was profiled using Illumina Human WG-6 v3 BeadChips. Gene ontology functional annotations were investigated in the genes upregulated in IIPs.

Results: Evaluation of 48,000 transcripts in the expression profiles helped identify 1594 transcripts that were commonly upregulated in lung tissues from IIP patients compared to those from normal control subjects. The transcriptional profiles of IPF and NSIP were unexpectedly similar. Lungs with IIP were characterized by increased expression of transcripts associated with cell cycle, ABC transpoters and p53 signaling pathways, such as MDM2, RBL1, RAD21, CFTR and BAX.

Conclusion: The current data provide valuable information on the molecular mechanism underlying pulmonary fibrosis in IIP patients. Additionally, several potentially promising and novel diagnostic biomarkers as well as therapeutic targets have been identified for IIPs.

### P3148

### The JAK3 inhibitor CP-690550 is a potent anti-fibrosis agent in a murine model of pulmonary fibrosis induced by bleomycin

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Rationale: We previously suggested that JAK3, a cytoplasmic tyrosine kinase involved in receptor signaling for cytokines storm, is a molecular determinant in exacerbated innate immune inflammation. A selective JAK3 inhibitor can alleviate immunopathologic injury. Dose it has a potential for treating the lung fibrosis associated with autoimmunity? In the present study, CP-690550, a novel inhibitor of JAK3, was subjected to examination of its effects on lung fibrosis in a murine model of Bleomycin(BLM)-induced pulmonary inflammation.

Methods & results: Flow cytometry for typing bronchoalveolar lavage fluid (BAL) cells showed much higher level of T cells containing high frequencies of CD3+CD8+ and NKT+ cells in the BLM-challenged mice than control, but no significant changes were detected in the mice with CP-690550 treatment(15 mg/kg/d for two weeks) or JAK3-/- mice where pathology displayed attenuation of the lung fibrosis, corresponding to significantly increased survival rates(38.5% of BLM-challenged mice v.s.100% of the mice treated with CP-690550 or 84.6% of JAK3-/- mice following BLM challenge, P<0.01).Cytokines profiling by liquid-Chip demonstrated significantly elevated levels of IP-10, IFN-y and reduced TGF-\$1 secretion following BLM challenge in the lung homogenates and blood of the JAK3-/- or reduction of TGF-\$1 in the blood of JAK3+/+ mice with CP-690550 treatment, compared to the JAK3+/+ mice.

Conclusion: These results suggest that CP-690550 treatment has the capacity to counter immune inflammation-associated lung fibrosis through modulation of cytotoxic T cells-mediated autoimmune inflammation as well as inhibition of production of fibrostic cytokines.

### P3149

Hepatocyte growth factor (HGF) expression in bronchoveolar lower (BAL) does not confirm its anti-fibrotic activity in interstitial lung diseases (ILD) Piotr Kopinski<sup>1</sup>, Joanna Chorostowska-Wynimko<sup>2</sup>, Andrzej Dyczek<sup>3</sup>, Teresa Iwaniec<sup>3</sup>, Ada Rozy<sup>2</sup>, Paulina Jagus<sup>2</sup>, Karina Szablowska<sup>1</sup>, Tomasz Wandtke<sup>1</sup>, Barbara Balicka-Slusarczyk<sup>4</sup>. <sup>1</sup>Dept of Gene Therapy, Collegium Medicum, Nikolaus Copernicus University, Bydgoszcz, Poland; <sup>2</sup>Lab of Molecular Biology and Immunology, Institute of Tuberculosis and Lung Diseases, Warszawa, Poland; <sup>3</sup>Dept of Internal Medicine, Collegium Medicum, Jagiellonian University, Krakow, Poland; <sup>4</sup>Dept of Environmental Diseases and Toxicology, Collegium Medicum, Jagiellonian University, Krakow, Poland

Background: We have previously shown that BAL-derived T cells secrete HGF, regarded as a potent anti-fibrotic cytokine, antagonist of TGFB, and the promising tool for experimental therapies in lung fibrosis. However, our preliminary results concerning HGF expression in ILD lower airways were not convergent.

Methods: HGF concentration in BAL fluid from pulmonary sarcoidosis (PS), idiopathic pulmonary fibrosis (IPF), extrinsic allergic alveolitis, nonspecific interstitial pneumonia (NSIP), BOOP and eosinophilic pneumonia (n=48, 20, 7, 13, 7, 6 resp.) was assessed by ELISA method, BAL cells were analyzed for intracellular HGF by flow cytometry.

Results: HGF concentration was significantly increased in IPF nonsmokers (317±136 pg/ml vs 148±17 in controls, p<0,02, median±SEM), IPF smokers  $(215\pm12 \text{ vs } 141\pm10, \text{ p}<0.001)$  and in smokers with advanced PS. A trend towards increased HGF levels in NSIP and BOOP was observed. HGF concentrational towards increased HGF levels in NSIP and BOOP was observed. tion was strongly negatively correlated with pulmonary function ((VC% pred) and positively, inter alia, with BAL neutrophil and eosinophil relative count as well as with TGF $\beta$  levels. Systemic steroid therapy resulted in decline of HGF expression Conclusions: Our data seem to disagree with the previously suggested HGF strong

antifibrotic activity. Its high expression was paradoxally observed in ILD patients with severe lung fibrosis Still, our observations might reflect the up-regulated TGF enhanced expression aimed at sustaining lung homeostasis.

#### P3150

### Autoimmunity profile in patients with combined pulmonary fibrosis and emphysema (CPFE)

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Background: The combination of pulmonary fibrosis and emphysema (CPFE) is a recently defined syndrome, encompassing a distinct radiologic, revealing both upper lobe emphysema and lower lobe fibrosis, as well as lung function profile, with apparently preserved lung volumes contrasting with disproportionally impaired gas exchange. It has also been recently described in the context of connective tissue diseases. Our primary aim was to investigate the autoimmunity profile of patients with CPFE.

Patients and methods: Thirty nine patients, mean age of 66,5 years, 37 men, all smokers, with CPFE based on radiologic and functional criteria (mean FVC: 68,5% pred, FEV1/FVC:78,2, DLCO: 34,9% pred) were recruited on a retrospective and prospective basis. All patients underwent a thorough investigation of their immunologic profile.

Results: Fourteen patients (36%) had positive anti-nuclear antibodies (ANA). Patients with positive ANA presented with elevated CD20 levels in lung biopsy specimens suggestive of elevated B cell activity. In additon, 6 patients (15%) presented with positive antineutrophil cytoplasm antibodies (ANCAs) against myeloperoxidase (MPO) indicative of microscopic polyangiitis. Among the latters three developed respiratory and renal insufficiency and were succesfully treated with cyclophosphamide and methylprednisolone whereas the remaining three were switched to azathioprine maintenance treatment.

Conclusions: A significant proportion of patients with CPFE may present with underlying auto-immune disorders that may reside incospicuously. Early identification of these patients using a panel of auto-antibodies may lead to more targeted and potentially effective therapeutic applications.

### P3151

### Frequencies and dynamics of peripheral immune cell subsets in idiopathic pulmonary fibrosis: Preliminary results and clinical implications Marialuisa Bocchino<sup>1</sup>, Domenico Galati<sup>2</sup>, Marina De Martino<sup>1</sup>,

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Involvement of the immune response in the pathogenesis of idiopathic pulmonary fibrosis (IPF) is not well clarified. Emerging T cell subsets including IL-17 secreting T helper cells (TH17) and regulatory T lymphocytes (Treg) expressing TGF-beta may exert antithetical actions. Distribution and phenotype characteristics of peripheral immune cells along with TH17/Treg dynamics were investigated by multi-parametric flow cytometry in 15 IPF patients (mean age 63 yrs; 13 men) and 10 age- and sex-matched healthy subjects. Proportions of CD4<sup>+</sup> and CD8<sup>+</sup> T cells and of B (CD20<sup>+</sup>) lymphocytes were similar in the two groups. Frequencies of NKT (CD3+CD56+) and NK cells (CD3-CD56+CD16+) were reduced in IPF (p<0.0001 for NK cells), the 24% of the latter co-expressing CD161 and CD152a (versus 4.2±3.3; p=0.001). IPF patients displayed higher Treg proportions (CD4+CD25<sup>high</sup>FoxP3+) (0.71±0.4 vs 0.3±0.13; p<0.05). No differences in the distribution of highly suppressive Treg (CD13<sup>+</sup>) cells were found. Upon stimulation, Treg expression of TGF-beta was similar in the two groups. Conversely, frequencies of IL-17-espressing CD4+ cells were significantly lower in IPF  $(0.92\pm0.56 \text{ vs } 0.21\pm0.11; \text{ p} < 0.001)$ . This finding was associated with an increased TGF-beta/IL-17 ratio in IPF (2.18±1.15 vs 0.38±0.2; p=0.001). This study first provides evidence in IPF of a peripheral Treg/TH17 functional imbalance along

with a depletion of NK cells which display an inhibitory phenotype. Dynamics of Treg/TH17 cells may represent a non invasive tool for disease severity assessment and treatment monitoring. Efforts are requested to thoroughly delineate these observations at the lung level.

### P3152

## Silent microaspiration in idiopathic pulmonary fibrosis: The role of videolaryngoscopy

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A strong association between gastroesophageal reflux (GER) and idiopathic pulmonary fibrosis (IPF) has been reported. A significant proportion of patients may have signs of microaspiration and still remain asymptomatic. Videolaringoscopy can be a useful tool to detect silent microaspiration, which to date has never been investigated in IPF. The aim of the study was to assess signs of micro-aspiration by videolaryngoscopy in patients with IPF and to relate them with clinical findings. We recruited 20 IPF patients (mean age 52 + 7 yrs). We investigated the presence/absence of GER symptoms and performed videolaryngoscopy to evaluate abnormal laryngeal findings considered indirect signs of micro-aspiration. Three out of twenty patients (15%) had classic GER symptoms, while 17 (85%) did not report any kind of GER symptoms. Among asymptomatic patients, 5 (29%) had indirect signs of microaspiration at videolaryngoscopy while the remaining twelve had no such signs. Of interest, IPF patients with laryngeal abnormalities at videolaryngoscopy showed a lower FVC% at the diagnosis compared to patients without such abnormalities [46%(45-82) vs 75%(72-87) p=0,03]. Conversely, no differences in age, smoking history and BMI were found between the two groups of patients. In conclusion our study suggests that videolaryngoscopy may be a useful diagnostic tool to detect silent microaspiration in patients with IPF even in the absence of GER symptoms. These findings may have important therapeutic implications

### P3153

## Elevated serum LOXL2 levels are associated with rapid disease progression in idiopathic pulmonary fibrosis (IPF)

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**Background:** LOXL2, expressed in fibrotic lung, plays a crucial role in matrix remodeling and fibrogenesis. We hypothesized that elevated serum LOXL2 levels are associated with rapid IPF disease progression.

Methods: Baseline serum samples were collected prior to treatment randomization at selected U.S. clinical trial sites for ARTEMIS-IPF. LOXL2 levels were measured using proprietary anti-human-LOXL2 antibodies. Progression free survival ([PFS] lung function decline, respiratory hospitalizations [RH] and death) served as the primary endpoint.

**Results:** Subjects with (n=69) and without (n=423) serum samples had similar baseline IPF severity. Among subjects with detectable LOXL2 (n=67), the median LOXL2 level was 315.4pg/ml (IQR 144.5-752.4 pg/ml). Although subjects randomized to receive ambrisentan (n=49) had more severe IPF and higher LOXL2 levels than placebo treated subjects (mean 902.8pg/ml $\pm$ 1172 vs 294pg/ml $\pm$ 288, p=0.026), LOXL2 levels and IPF severity did not correlate. In multivariate analyses that included treatment assignment, 6-minute walk distance and composite physiologic index, high LOXL2 levels (>800pg/ml), in comparison to low LOXL2 levels ( $\leq$ 800pg/ml), were associated with increased risk for disease progression (hazard ratio [HR] 4.95, 95% confidence interval [CI] 1.52-16.18, p=0.008), lung function decline (HR 7.36, 95% CI 1.16-46.74, p=0.034, and RHs (HR 4.85, 95% CI 1.09-21.68, p=0.039).

**Conclusion:** High baseline serum LOXL2 levels are associated with rapid IPF progression and may reflect disease activity, not severity. Due to potential confounding effects of ambrisentan, these results need to be replicated in other IPF populations.

### P3154

### Hyaluroman syntchase-2 over expression has impact in the evolution and on the prognosis of idiopathic pulmonary fibrosis patients

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**Background:** The idiopathic pulmonary fibrosis (IPF) is a terminal illness characterized by unremitting extracellular matrix (ECM) deposition. In this regard, the myofibroblasts and the ECM components such as hyaluronan (HA) have an important role in the fibrosis. We analyzed the expression of HAS1 (HA synthase 1), HAS2, HAS3 and hyaluronic acid receptor (CD44) by epithelial and myofibroblasts cells in patients with IPF and we correlated with a survival. **Methods:** HAS-1, HAS2, HAS3 and CD44 epithelial and myofibroblast expression were evaluated in 27 surgical lung biopsies from patients with IPF in minimal and severe fibrosis by the point-counting technique. Impact of these markers was tested on pulmonary functional tests and follow-up until death from IPF. **Results:** HAS2 and CD44 expression were significantly increased and directly associated with severe fibrosis. Myofibroblast HAS2 activity was indirectly associated to DLO/VA (r=-0.584; p=0.05). Kaplan Maier curves determined a higher risk of death for patient with high HA2 (>6.83%) expression than in low expression (Log Rank p=0.05).



**Conclusion:** The increased HAS-2 activity in epithelial and myofibroblast cells have impact in the remodeling process and the survival evolution, suggesting that strategies aimed at preventing the effect of this ECM component may have a greater impact in patient's outcome. Financial support: FAPESP.

P3155

# Perceptions, experiences and information needs of patients with idiopathic pulmonary fibrosis (IPF): A qualitative study

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**Background:** Idiopathic Pulmonary Fibrosis (IPF) is a rapidly progressive lung disease, with median survival of 2-4 years from diagnosis with symptoms that impact on quality of life. There has been little work to date which explores the experiences of these patients, or their family carers, in-depth.

Aim: To understand the experiences, perceptions and information needs of patients with IPF.

**Methods:** Qualitative study, involving in-depth, audio-recorded, semi-structured interviews, supported by a topic guide (developed from review of the literature and input from patients and clinicians). Seventeen patients with moderate to advanced IPF referred to a tertiary respiratory centre in north-west England, and six of their family carers, were interviewed. Data were analysed using Framework Analysis (Ritchie and Spencer 1994).

**Results:** Patients' diagnostic pathway was often complex and several had initially been misdiagnosed. All patients and carers had unmet information needs throughout the disease trajectory, regarding disease causation, prognosis, treatments and side effects. Patients and carers reported a loss of the life they had, with IPF impacting markedly on independence, spontaneity and roles within relationships. Patients reported struggling to live with increasing breathlessness, cough, lethargy and fatigue. Learning to live with increasing disability and dependency on oxygen, whilst facing an uncertain future, was a struggle for all.

**Conclusions:** Patients with IPF have many unmet information and support needs. There is an urgent need for improved recognition of these needs, as well as increased availability and accessibility of services.

### P3156

### The correlation of pulmonary function tests and exercise testing with high resolution computed tomography in patients with idiopathic interstitial pneumonia in a tertiary care hospital in south India

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**Background:** Idiopathic interstitial pneumonias (IIP) are a heterogeneous group of diffuse parenchymal lung diseases (DPLD). Although open lung biopsy is the gold standard for its diagnosis, HRCT(High Resolution Computed Tomography) is gradually replacing the former. Repeating HRCT for follow up is costly and involves radiation exposure. Among pulmonary function tests(PFT) and exercise testing, it is unclear which parameter would correlate best with HRCT.

Aim: To find out the correlation of pulmonary function tests and exercise testing with HRCT in patients with IIP.

Methods: Consecutive patients who were diagnosed as IIP were included. PFT and exercise testing parameters were noted. HRCT was scored based on an alveolar

score, an interstitial score and a total score. Correlation of each of the parameters with HRCT scores were analyzed.

**Results:** A total of 94 patients [85 had Idiopathic Pulmonary Fibrosis(IPF)] were included to obtain a sample size of 105. Forced Vital Capacity, Total Lung Capacity and Diffusion Capacity of the Lung for Carbon Monoxide (DLCO) among PFT parameters and Distance Saturation Product and lowest saturation among exercise testing parameters had significant correlation with the total HRCT score. Among these DLCO corrected was the most correlating with a negative r value of 0.565. **Conclusion:** In patients with idiopathic interstitial pneumonia, pulmonary function tests and exercise testing parameter.

### P3157

## Osteoporosis treatment effectiveness in patient with idiopathic pulmonary fibrosis (IPF)

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Aim: To assess effectiveness of osteoporosis treatment by Calcium, Vitamin D3 (VD3), Bisphosphonates (BPN), Calcitonin (CTN) in patients with IPF.

Subjects: 95 Caucasian patients with IPF, 18 male, 77 female,  $55.4\pm10.9$  y.o., treated with glucocorticoids.

**Materials, methods:** Bone Mineral Density was measured by DEXA. Patients were categorized according to T-criterion value. 19 patients (1st group) had T-criterion > -1.5 SD. In this group only Calcium and VD3 were recommended. 24 patients (2nd group) had T-criterion value from -1.5 SD to -2.0 SD. In this group Calcium, VD3 and BPN were prescribed. 20 patients (3rd group) had T-criterion value from -2.0 SD to -2.5 SD. In these cases Calcium, VD3 and CTN were prescribed. 32 persons (4th group) had T-criterion lower than -2.5 SD. These patients received Calcium, VD3, CTN, BPN.

**Results:** Results were assessed in a year. The main criteria were: T-criterion change ( $\Delta$ T), fractures incidence, presence of bone pain (BP). In the 1st group  $\Delta$ T was -0.07 SD, 10.5% patients had manifestation of BP. In the 2nd group  $\Delta$ T was -0.25 SD; one hip fracture occurred; the number of patients with BP decreased from 66.7% to 25.0% (p<0.001). In the 3rd group  $\Delta$ T was +0,04 SD, no fractures were registered, the number of patients with BP increased from 20.0%. In the 4th group  $\Delta$ T was +0.11 SD; no fractures were registered, the number of patients with BP decreased from 25.0% to 6.3% (p<0.01).

**Conclusion:** Combination of Calcium and VD3 with antiresorptive agents (both CTN and BPN) is an essential way to prevent and treat osteoporosis in patients with IPF. CTN has an advantage due to its analgesic effect in osteoporotic patients with bone pain.

### P3158

### Post-marketing surveillance of pirfenidone for idiopathic pulmonary fibrosis in Japan: Interim analysis of 973 patients

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**Background:** Pirfenidone (Pirespa®), anti-fibrotic agent, was approved for the treatment of idiopathic pulmonary fibrosis (IPF) in Japan in 2008. We conducted a post-marketing surveillance enrolling all patients with IPF who were administered pirfenidone from Dec 2008 to Oct 2009 to gain understanding, in the clinical setting, of the safety and efficacy of pirfenidone in the treatment of IPF.

**Methods:** The safety was evaluated by comparing the incidence of adverse drug reactions with that reported in Phase II and III trials. The efficacy was evaluated on the change in vital capacity (VC).

**Results:** For this interim analysis, 973 cases were evaluable for safety (male 78.2%, age 69.5 $\pm$ 8.4 yrs). At baseline, 407 cases (41.8%) were ranked as severity grade IV in Japan ((PaO2 at rest <60 Torr) or (PaO2 at rest <70 Torr and 6MWT SpO2 <90%)). The incidence of adverse drug reactions was 67.01%. The major adverse drug reactions were decreased appetite (28.6%) and photosensitivity reaction (15.0%). The data on VC were available from 453 cases and the analyses are ongoing.

**Conclusions:** This analysis from a large surveillance study confirmed the safety of pirfenidone in the Japanese IPF patients treated in the clinical setting. This study included many patients with greater IPF progression compared with Phase II and III trials. Considering this situation, we are now in the process of analyzing the efficacy of pirfenidone.

Pirespa Advisory Board: Toshihiro Nukiwa, Shoji Kudo, Yukihiko Sugiyama, Arata Azuma, Moritaka Suga, Kingo Chida, Yoshikazu Inoue, Hiroyuki Taniguchi, and Takashi Ogura.

### P3159

## The long-term safety of pirfenidone (PFD) in patients with idiopathic pulmonary fibrosis (IPF)

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Introduction: PFD is an oral molecule that is approved in Europe and Japan for the treatment of IPF. Long-term safety is being assessed in two open-label (OL) studies in patients with IPF.

**Objective:** Further examine the long-term safety of PFD in patients with IPF. **Methods:** All patients receiving PFD 2403 mg/d in the CAPACITY studies or one of two ongoing OL studies of PFD in patients with IPF (Studies 002 and 012) were included in the analysis. Study 002 is a compassionate use study in the U.S.; Study 012 is an OL extension study evaluating PFD in patients who completed CAPACITY.

**Results:** A total of 789 patients were included in the analysis. The median duration of exposure to PFD was 2.6 years (range, 1 week–7.7 years); the median daily dose was 2257 mg (range 25–3600). The cumulative total exposure was 2,052 person exposure years (PEY). Consistent with previous studies, almost all patients (99.7%) reported at least one treatment emergent adverse event (AE). Gastrointestinal and skin-related events were the most commonly reported AE's; these were generally mild to moderate and rarely led to treatment discontinuation. AST/ALT elevations (>3 x ULN) occurred in 21/789 (2.7%) patients; the adjusted incidence of AST/ALT elevations was 1.7 per 100 PEY.

# Table 1. TEAEs in the integrated patient population over a median duration of 2.6 years compared with pirfenidone and placebo-treated patients in CAPACITY (median duration of 1.5 years).\*

Patients (%)	Integrated Open-label Population (N=789)	CAPACITY PFD 2403 (N=345)	CAPACITY Placebo (N=347)		
TEAEs with greater frequency than placebo in CAPACITY					
Nausea	40%	36%	17%		
Dizziness	38%	18%	10%		
Rash	26%	32%	12%		
Dyspepsia	21%	19%	7%		
Vomiting	18%	14%	4%		
Insomnia	17%	10%	7%		
TEAEs with frequency < 1.5 X p	lacebo in CAPA	CITY			
Cough	37%	30%	29%		
Upper respiratory infection	35%	31%	29%		
Fatigue	34%	30%	20%		
Dyspnea	32%	19%	22%		
Diarrhea	29%	29%	19%		
Idiopathic pulmonary fibrosis	29%	16%	21%		
Nasopharyngitis	27%	21%	24%		
Bronchitis	26%	14%	17%		
Headache	22%	19%	16%		
Back pain	17%	10%	8%		
Sinusitis	16%	14%	12%		

TEAE=treatment emergent adverse event

\*Occurring in ≥15% of patients in the cumulative clinical database

 $\dagger Occurring in at least 5\% of patients treated with pirfenidone 2403 mg/d and an incidence <math display="inline">{\geq}1.5$  times placebo

**Conclusions:** Analysis of safety data from IPF patients receiving PFD for up to 7.7 years demonstrates that long-term treatment with PFD is safe and generally well tolerated.

### P3160

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Introduction: Idiopathic pulmonary fibrosis (IPF) is a poor prognostic fibrotic lung disease with unknown etiologies. Pirfenidone (PFD) was recently reported to decrease the rate of decline in vital capacity and it is anticipated that PFD improves prognosis of IPF patients.

Aim: We prospectively examined clinical findings of IPF to predict the effects and adverse effects of PFD.

**Subjects:** PFD was administered to 41 cases of IPF between January 2009 and December 2010. Severity stage (I/II/III/IV) of IPF defined by Japanese Respiratory Society (JRS) were 9/6/9/17, respectively. PFD was discontinued within 3 months because of adverse effects or death in 11 cases. Effects of PFD were evaluated by definition by JRS in 30 cases treated with PFD for more than 3 months. Adverse effects were evaluated in all cases.

Method: Chi square test for univariate analysis and multivariate logistic regression analysis was performed using various clinical findings to clarify the predictor of short-term effects of PFD and its adverse effects, especially appetite loss and/or nausea.

**Results:** Improvement after PFD therapy was observed in 6 cases (20%). Severity stage I/II and diagnosis of IPF based on surgical biopsy specimens were significant predictors of improvement by chi square test and multivariate analysis. Appetite loss and/or nausea occurred more in IPF patients with older age (>68 yrs) and without intake of proton-pomp inhibitor (PPI) by multivariate logistic regression analysis.

**Conclusions:** Effects of PFD is better in IPF patients with severity stage I/II and/or diagnosed by histologically. Appetite loss and/or nausea significantly associated with older age and no PPI intake.

### P3161

Anti-fibrotic effects of nintedanib (BIBF 1120) in primary human lung fibroblasts derived from idiopathic pulmonary fibrosis

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Introduction: Idiopathic pulmonary fibrosis (IPF) is a progressive lung disease with poor prognosis. One year treatment with the receptor tyrosine kinase inhibitor nintedanib (BIBF 1120) specific for vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR) and fibroblast growth factor receptor (FGFR) was associated with a 68.4% reduction in the rate of decline of forced vital capacity in patients with IPF versus placebo, which approached statistical significance.

Aim: To determine the *in vitro* effect of nintedanib on primary human lung fibroblasts.

**Methods:** Primary human lung fibroblasts were isolated and propagated from lung parenchyma derived from patients with IPF (n=4). After treatment with nintedanib (0.001 – 1  $\mu$ M) enzymatic activity for matrix metalloproteinases (MMP) was assessed in aliquots of the culture medium by gelatin zymography. Gene expression of MMP was measured by quantitative real time PCR. Collagen secretion and deposition was quantitated by the Sircol assay, and cell proliferation was assessed by mechanical cell counting.

**Results:** Nintedanib significantly inhibited secretion and deposition of collagen by IPF fibroblasts in a dose-dependent manner. Nintedanib significantly increased MMP-2 gene expression and dose dependently stimulated MMP-2 enzymatic activity. The pro-proliferative effect induced by PDGF (10 ng/ml) was completely reversed by nintedanib.

**Conclusion:** Our data demonstrate a significant anti-fibrotic effect of nintedanib in primary human lung IPF fibroblasts.

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### P3162

## Management of idiopathic pulmonary fibrosis in France: A survey of 1,456 pulmonologists

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**Background:** Management of rare diseases including idiopathic pulmonary fibrosis (IPF) has been organised in France by the National plan for rare diseases. Clinical care in the community is coordinated by one national reference centre and nine regional competence centres.

**Objective:** To evaluate current diagnostic and treatment practice for IPF in the context of recent international guidelines.

**Methods:** A questionnaire (26 questions) has been submitted over the phone and on-line between December 7, 2011 and February 18, 2012, to 1,456 pulmonologists (out of 2,682 in France).

Results: 509 pulmonologists (35%) were involved in the management of IPF

patients. Of those, 36% discussed the cases with radiologists and pathologists. Out of 406 community pulmonologists practicing outside of reference or competence centres, 141 (35%) indicated referring patients to those centres. The 2011 ATS/ERS/JRS/ALAT guidelines were known by 67% of pulmonologists involved in IPF, 84% of whom considered them appropriate for practice. An estimate of 58% of patients were diagnosed with mild to moderate IPF as defined by % predicted FVC  $\geq$ 50% and % predicted DLCO  $\geq$ 35%.

**Conclusion:** Despite correct awareness of international IPF guidelines, modalities of multidisciplinary discussion and of early diagnosis need to be improved through the network of expert centres.

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