Disclosures

• I have not received funds from any drug company for this lecture

• I *will* give each company credit by name for their innovative work throughout the talk
73 year-old man with 20 pack-years of smoking

18 months of dry cough and slowly progressive DOE
Natural Course of IPF

Median survival: 3 years from diagnosis \textbf{(probably higher now)}
Acute worsening: 5-10% annually
Treatment of IPF

If you don’t know where you’re going, any road will get you there...
Failed therapies prior to the current age of anti-fibrotic medications

<table>
<thead>
<tr>
<th>No Significant Benefit</th>
<th>Worse outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisone</td>
<td>Azathioprine + NAC + Prednisone</td>
</tr>
<tr>
<td>Imatinib</td>
<td>Ambrisentan</td>
</tr>
<tr>
<td>N-acetylcysteine</td>
<td>Coumadin</td>
</tr>
<tr>
<td>Bosentan</td>
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<tr>
<td>Macitentan</td>
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<tr>
<td>Sildenafil</td>
<td></td>
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<tr>
<td>IFN-gamma</td>
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</tbody>
</table>
Why were we failing to effectively treat this disease?
The progression of pulmonary fibrosis on CT imaging

Possible UIP/IPF

Moderate honeycomb

Severe honeycomb
“Spatial heterogeneity and fibroblastic foci” constitute a pattern of UIP on biopsy

Courtesy of Paul Vanderlaan, MD
Pathogenesis

- TNFα
- IL-1
- MCP-1
- TGFβ
- FGF-R
- PDGF
- VEGF-R

**Cells and Processes**
- Fibrocytes
- Fibroblasts
- Myofibroblasts
- Collagen

**Components**
- Alveolar epithelium
- Capillary endothelium
Pirfenidone—CAPACITY trials

Capacity 004 (72 weeks): 435 patients (174 high-dose; 87 low; 174 placebo)
FVC change: -8% vs -12.4% (p=0.001)
Change in 6MWT (m) -60.4 vs -76.8 (p=0.171)

Capacity 006 (72 weeks): 344 patients (171 high-dose; 173 placebo)
FVC change: -9% vs -9.6% (p=0.51)
Change in 6MWT (m) -45.1 vs -76.9 (p=0.0009)

Pooled data (72 weeks):
FVC change: -8.5% vs -11% (p=0.005)
Mortality
   All cause: 27 (8%) vs 34 (10%) p=0.315
   IPF-related: 18 (5%) vs 28 (8%) p=0.117
Pirfenidone (Esbriet)—ASCEND trial

555 patients followed 52 weeks (278 high-dose; 277 placebo)
FVC 10% decline or death: 46 [16.5%] vs. 88 patients [31.8%]) p<0.001
FVC no decline: 63 patients [22.7%] vs. 27 patients [9.7%]) p=0.001

Mortality:
Overall: 11 (4%) vs 20 (7.2%) P = 0.10
IPF-related: 3 patients (1.1%) vs 7 patients (2.5%) P = 0.23

Pooled mortality (ASCEND + CAPACITY high-dose cut off at 52 weeks)
Overall: 22 (3.5%) vs 42 (6.7%) p=0.01
IPF-related: 7 (1.1%) vs 22.5 (3.5%) p=0.006
Pirfenidone (Esbriet)

+ 

Airspace lining + ?

Capillary endothelium

TNFα 

IL-1 
MCP-1 

Fibrocytes

Fibroblasts

TGFβ 

VEGF-R 

PDGF 

Myofibroblasts

Collagen
Nintedanib (Ofev)—INPULSIS trials

INPULSIS-1 (52 weeks) 513 patients (309 drug; 204 placebo)
FVC decline (52 weeks): −114.7 ml vs −239.9 (p<0.001)
Time to first exacerbation: HR 1.15 (P = 0.67)

INPULSIS-2 (52 weeks) 548 patients (329 drug; 219 placebo)
FVC decline (52 weeks): −113.6 ml vs −207.3 (p<0.001)
Time to first exacerbation: HR 0.38 (P = 0.005)

Pooled mortality from any cause:
5.5% vs 7.8%; HR 0.70 (P = 0.14)
Nintedanib (Ofev)
Side Effects

Pirfenidone (Esbriet)
- Nausea (36%)
- Diarrhea (26%)
- Abdominal pain (24%)
- Photosensitivity (9%)

Nintedanib (Ofev)
- Nausea (24%)
- Diarrhea (62%)
- Vomiting (12%)

$110,000/yr
$124,000/yr

Why not try combination therapy?

IPF involves dysregulation of multiple, complex pathways.

Barriers:
- Cost
- GI side effects
- Hard to show efficacy
- ? Pirfenidone decreases nintedanib levels

No biomarker to predict which agent is better
Pirfenidone *and* Nintedanib in combination

-- Perhaps more nausea or vomiting in the combination group
-- Pirfenidone lowers nintedanib levels?
73 patients with nintedanib added to pirfenidone—combination was as well tolerated as each agent alone

| TABLE 2 Summary of common treatment-emergent adverse events (TEAEs) and TEAEs leading to discontinuation (safety population*) |
|---|---|---|---|---|
| **Patients with at least one TEAE** | **Patients with at least one TEAE related to pirfenidone only** | **Patients with at least one TEAE related to nintedanib only** | **Patients with at least one TEAE related to both pirfenidone and nintedanib** |
| **≥1 TEAE** | 88 (99) | 15 (17) | 67 (75) | 26 (29) |
| **≥1 treatment-related TEAE** | 74 (83) | 2 (2) | 38 (43) | 5 (6) |
| Dizziness | 44 (49) | 1 (1) | 21 (24) | 12 (14) |
| Nausea | 41 (46) | 3 (3) | 31 (35) | 16 (18) |
| Vomiting | 21 (24) | 1 (1) | 16 (18) | 7 (8) |
| Decreased appetite | 14 (16) | 2 (2) | 7 (8) | 5 (6) |
| Fatigue | 11 (12) | 0 | 8 (9) | 3 (3) |
| Dyspepsia | 8 (9) | 1 (1) | 6 (7) | 1 (1) |
| Headache | 8 (9) | 0 | 7 (8) | 1 (1) |
| Weight decreased | 6 (7) | 1 (1) | 3 (3) | 1 (1) |
| Photosensitivity or rash | 7 (8) | 4 (5) | 2 (2) | 1 (1) |
| **TEAEs occurring in ≥5% of patients** | | | | |
| Abdominal pain upper | 5 (6) | 1 (1) | 2 (2) | 2 (2) |
| Dizziness | 5 (6) | 0 | 4 (5) | 1 (1) |
| **TEAEs leading to discontinuation** | | | | |
| **≥1 TEAE** | 13 (15) | 0 | 10 (11) | 1 (1) |
| **≥1 treatment-related TEAE** | 11 (12) | 0 | 3 (3) | 1 (1) |
| Nausea | 4 (5) | 0 | 3 (3) | 1 (1) |
| Dizziness | 4 (5) | 0 | 3 (3) | 1 (1) |
| Fatigue | 2 (2) | 0 | 2 (2) | 0 |
| Weight decreased | 2 (2) | 0 | 2 (2) | 0 |
| Deep vein thrombosis | 1 (1) | 0 | 1 (1) | 0 |
| Epigastric discomfort | 1 (1) | 0 | 1 (1) | 0 |
| Malaise | 1 (1) | 0 | 1 (1) | 0 |
| Migraine | 1 (1) | 0 | 1 (1) | 0 |
| Vomiting | 1 (1) | 0 | 1 (1) | 0 |

Eur Respir J 2018; 52: 1800230
Nintedanib with Add-on Pirfenidone in Idiopathic Pulmonary Fibrosis
Results of the INJOURNEY Trial

Carlo Vancheri1, Michael Kreuter2, Luca Richeldi3, Christopher J. Ryerson4, Dominique Valeyre5, Jan C. Grutters6,7, Sabrina Wiebe8, Wibke Stansen9, Manuel Quaresma2,9, Susanne Stowasser9, and Wim A. Wuyts10; on behalf of the INJOURNEY Trial Investigators

51 Nintedanib alone; 53 combination

<table>
<thead>
<tr>
<th></th>
<th>Nintedanib 150 mg Twice Daily with Add-on Pirfenidone (n = 53)</th>
<th>Nintedanib 150 mg Twice Daily (n = 51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse events</td>
<td>47 (88.7)</td>
<td>45 (88.2)</td>
</tr>
<tr>
<td>Most frequent adverse</td>
<td></td>
<td></td>
</tr>
<tr>
<td>events*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>20 (37.7)</td>
<td>16 (31.4)</td>
</tr>
<tr>
<td>Nausea</td>
<td>22 (41.5)</td>
<td>6 (11.8)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>15 (28.3)</td>
<td>6 (11.8)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>10 (18.9)</td>
<td>6 (11.8)</td>
</tr>
<tr>
<td>Upper abdominal pain</td>
<td>7 (13.2)</td>
<td>4 (7.8)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>6 (11.3)</td>
<td>5 (9.8)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>2 (3.8)</td>
<td>8 (15.7)</td>
</tr>
<tr>
<td>Headache</td>
<td>7 (13.2)</td>
<td>1 (2.0)</td>
</tr>
<tr>
<td>Any serious adverse</td>
<td>2 (3.8)</td>
<td>5 (9.8)</td>
</tr>
<tr>
<td>events†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any fatal adverse</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>events</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The role of lysophosphatidic acid (LPA) and autotaxin in pulmonary fibrosis

**Bleomycin mouse model:**
- Increased LPA levels following lung injury
- Mice lacking the LPA1 receptor are protected from fibrosis and mortality
  --Less fibroblast recruitment and vascular leak
- Increased autotaxin expression following bleomycin injury
- Mice whose lung epithelium can’t produce autotaxin have fibrotic damage following bleomycin

**In humans with IPF:**
- Elevated levels of LPA in lung lavage fluid of IPF patients
- Inhibiting the LPA1 receptor in a test tube reduced fibroblast activity
- Increased expression of autotaxin in the lung tissue of patients with lung fibrosis

GLPG1690: selective autotaxin inhibitor
Safety, tolerability, pharmacokinetics, and pharmacodynamics of **GLPG1690**, a novel autotaxin inhibitor, to treat idiopathic pulmonary fibrosis (FLORA): a phase 2a randomized placebo-controlled trial
Results from FLORA, the phase 2 study of **GLPG1690**, an autotaxin inhibitor

**Change in blood LPA concentration**

**Change in blood LPA concentration**

**ISABELA2**: A Phase 3, Randomized, Double-blind, Parallel-group, Placebo-controlled, Multi-center Study to Evaluate the Efficacy and Safety of Two Doses of **GLPG1690** in Addition to Local Standard of Care for Minimum 52 Weeks in Subjects With Idiopathic Pulmonary Fibrosis. NCT03733444

Clinical Trials Number NCT03733444
132 locations
Target enrollment: 750 patients
Pentraxin 2 (serum amyloid P) inhibits fibrocytes
Pentraxin-2 inhibits TGFβ–induced fibrocyte activation in a mouse model
-Phase II study of 117 patients
-Placebo vs PRM-151
-Treated for 28 weeks
FVC decline: -2.5% vs -4.8% (p = .001)

6MWD change −0.5 m vs −31.8 m (p < .001)
The role of connective tissue growth factor (CTGF) in pulmonary fibrosis

CTGF

TGFβ

Myofibroblast Activation/differentiation

Extracellular Matrix Deposition

Tissue Remodeling

Fibrosis

**CTGF** messenger RNA expression is significantly enhanced in the lung lavage fluid from patients with IPF.

**TABLE 3**  
*Summary of IGFBP-rP2 gene expression*

<table>
<thead>
<tr>
<th>Subject Group (n)</th>
<th>mRNA Transcripts/10⁶ G3PDH Molecules*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (7)</td>
<td>512 (± 97)</td>
</tr>
<tr>
<td>IPF (18)</td>
<td>5,455 (± 2,560)</td>
</tr>
<tr>
<td>Sarcoid [I + II] (8)</td>
<td>20,932 (± 11,714)</td>
</tr>
<tr>
<td>Sarcoid [III + IV] (5)</td>
<td>47,910 (± 24,505)</td>
</tr>
</tbody>
</table>

*Mean (± standard error of the mean).*
Pamrevlumab—monoclonal antibody that inhibits connective tissue growth Factor (CTGF).

Phase 2 study

Richeldi et al. Lancet Respir Med 2020;8: 25–33
Pamrevlumab appears to slow the progression of IPF

*A Phase 3 study is now ongoing

Richeldi et al. Lancet Respir Med 2020;8: 25–33
Elevated Galectin-3 levels are associated with ILD

Q4 Gal-3 had an OR of 2.67 to have interstitial lung abnormalities (95% CI, 1.49–4.76; P=0.001).

Nishi et al. Allergology International. 2007;56:57-65
A Study to Test the Efficacy and Safety of Inhaled TD139 in Subjects With IPF (GALACTIC-1)

Clinical trials number NCT03832946

TD139
• Galectin-3 inhibitor (dry powder)
• 450 patients over 52 weeks
\( \alpha \nu \beta 6 \) expression is associated with fibrotic ILD

\( \alpha \nu \beta 6 \) expression in different disease states

Survival based on level of \( \alpha \nu \beta 6 \) expression in lung biopsy tissue

How does $\alpha v \beta 6$ contribute to pulmonary fibrosis?

- TGF-\(\beta\) is secreted in a latent form and coupled with latency-associated protein (LAP).

- $\alpha v \beta 6$ binds to LAP, releasing TGF-\(\beta\) so that it is activated and free to bind to its receptor.

- Mice lacking $\alpha v \beta 6$ are protected from lung fibrosis in a bleomycin model.

Figure adapted from Stockis et al. *Eur. J. Immunol.* 2009. 39: 3315–3322
How does αvβ6 contribute to pulmonary fibrosis?

- TGF-β is secreted in a latent form and coupled with latency-associated protein (LAP).
- αvβ6 binds to LAP, releasing TGF-β so that it is activated and free to bind to its receptor.
- Mice lacking αvβ6 are protected from lung fibrosis in a bleomycin model.
An Efficacy and Safety Study of \textit{BG00011} in Participants With Idiopathic Pulmonary Fibrosis (SPIRIT)

Clinical trials number NCT03573505

A Randomized, Double-Blind, Placebo-Controlled Study (phase 2) with 109 participants

\textit{BG00011} = humanized anti-\(\alpha\nu\beta6\) monoclonal antibody

Study was terminated due to safety concerns
A Phase 2a, multicenter, 3-part, randomized, double-blind, dose-ranging, placebo-controlled study to evaluate the safety, tolerability, and PK of once-daily treatment with PLN-74809 in participants with idiopathic pulmonary fibrosis.

Clinical trials number NCT04396756
84 patients

PLN-74809 is an inhibitor of αvβ1 / αvβ6
The role of Hsp47 in collagen synthesis

JUNIPER: A Phase 2 Study to Evaluate the Safety, Biological Activity, and PK of ND-L02-s0201 in Subjects With IPF
Clinical trials number NCT03538301

ND-L02-s0201 is a targeted siRNA therapy that is designed to inhibit Hsp47

120 participants
(MGH, BWH)
Do the bacteria in the lung play a role in IPF?

- 64 IPF
- 17 COPD
- 27 Healthy controls

Study of Clinical Efficacy of Antimicrobial Therapy Strategy Using Pragmatic Design in Idiopathic Pulmonary Fibrosis (CleanUp-IPF)

Clinical trials number NCT02759120

Comparing standard care with either trimethoprim/sulfamethoxazole or doxycycline for 36 months
Genetics and personalized medicine

• Polymorphisms on chromosome 11p15 are known risk factors for IPF:
  Mucin 5B (MUC5B)
  Toll-interacting protein (TOLLIP) locus

• Can genetic factors predict an individual response to IPF therapy?

• Should we revisit agents previously deemed ineffective in larger studies?
Post-hoc analysis of subjects enrolled in the PANTHER-IPF study (Prednisone, Azathioprine, NAC)

154 patients were analyzed

- 54 placebo
- 60 NAC
- 40 NAC, Azathioprine, prednisone
TOLLIP genotype is associated with outcomes in IPF patients treated with NAC

- Genotype CC—NAC is bad
- Genotype CT—NAC does nothing
- Genotype TT—NAC is good
96 Studies found for: Idiopathic pulmonary fibrosis | Recruiting Studies

Also searched for Lungs. See Search Details
## Active drug trials in IPF

<table>
<thead>
<tr>
<th>Company</th>
<th>Drug name</th>
<th>Mechanism of action</th>
<th>Phase of trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toray Industries</td>
<td>TRK-250</td>
<td>Inhibits TGF-β1 expression</td>
<td>Phase 1</td>
</tr>
<tr>
<td>Novartis</td>
<td>VAY736 (Ilanalumab)</td>
<td>Anti-B-cell activating factor receptor antibody</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Pliant Therapeutics</td>
<td>PLN-74809</td>
<td>Inhibitor of αvβ1 / αvβ6</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Algernon Pharmaceuticals</td>
<td>NP-120 (Ifenprodil)</td>
<td>NDMA glutamate Receptor antagonist</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Celgene</td>
<td>CC-90001</td>
<td>Jun N-Terminal Kinase (JNK) Inhibitor</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Nitto</td>
<td>ND-L02-s0201</td>
<td>siRNA that inhibits HSP47</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Galecto Biotech</td>
<td>TD139</td>
<td>Galectin-3 inhibitor</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Galapagos</td>
<td>GLPG1690</td>
<td>Autotaxin inhibitor</td>
<td>Phase 3</td>
</tr>
<tr>
<td>FibroGen</td>
<td>Pamrevlumab</td>
<td>Antibody against (CTGF)</td>
<td>Phase 3</td>
</tr>
</tbody>
</table>
Summary

Although we still don’t have a cure for IPF, we have gained a MUCH better understanding of its pathophysiology.

Nintedanib and pirfenidone, while a step in the right direction, will only be the tip of the iceberg when it comes to treating this disease.

There are numerous promising drug trials on the horizon.
Thank you for your courage and inspiration.

Stay safe!