Molecular mechanism and non Steroidal treatment of Lung Fibrosis

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DM Seminar
Pathology of Pulmonary Fibrosis

- Histopathological lesion is UIP
- Normal lung alternates with fibroed portion
- Fibrosis: alveolar septal thickening with sub-pelural distribution
Observations

• Whorls of fibroblasts in ECM on the edge of dense scars
• Minimal interstitial inflammation
• Hyperplasia of type II pneumocytes is found in areas of fibrosis
• No alveolar exudates and hyaline membranes
Pathological categories of UIP

1. UIP pattern
2. Probable UIP
3. Possible UIP
4. Not UIP
UIP pattern

1. Fibrosis with architectural distortion
2. Patchy involvement of fibrosis
3. Fibroblastic foci
4. Absence of OP, Granuloma, Airway centered pathology, hyaline membranes
Probable UIP

1. Marked fibrosis with architectural distortion
2. Presence of patchy involvement or fibroblastic foci (one of these only)
3. Absence of other features
Possible UIP

1. Patchy or diffuse fibrosis within pulmonary parenchyma
2. In the absence of other UIP criteria
3. Absence of other patterns (4)
Seminar

Pathogenesis
- Basement membrane injury
- Alveolar epithelial cells
- Fibroblasts
- Others

Therapies
- Current
- Emerging
1. Basement membrane injury

• BM loss of integrity has been demonstrated
• Usual sites of breakdown are beneath type I pneumocytes
• Exposed BM provides a continuous signal for epithelial cell proliferation and fibroblast infiltration
• *Newer* type II cells are unable to send feedback sample to termination of epithelial cell proliferation
2. Alveolar Epithelium

• Currently the most accepted hypothesis: Low level *repeated* injury to a *vulnerable* epithelium

• Epithelial cell apoptosis: multiple agents have been implicated to cause increased loss of type I pneumocytes like TGF-β, Angiotensin, ROS, TNF-α

• Knockout of Individual genes for these agents have been shown to be protective against BILI Mice model.
• After loss of Type I pneumocytes there is chaotic hyperplasia of type II pneumocytes

• Once Injured there is downhill cascade: epithelial cells secrete cytokines and molecules to recruit fibrocytes and increase ECM
Role of ER stress in epithelial Cells

- Mutations of surfactant proteins A2 and C have been associated with IPF
- Protein misfolding in post translational process has been associated with increased ER stress causing Unfolded Protein Response
- UPR predisposes towards second hit like viruses, smoking or acid reflux to incite inflammations, apoptosis and fibrosis
3. Fibroblasts

• Main culprits of pulmonary fibrosis
• Source: *Fibrocytes* (released from bone marrow and recruited into lungs), *Epithelial cells* (via EMT), *Indigenous fibroblasts*
• Fibroblastic foci: areas intense fibrosis seen on histopathological examination
Fibrocytes

- CD45 and CD 34 positive
- Bone marrow derived cells which produce collagens at injured sites after recruitment
- Culprit cytokines: CXCL12, CCL2, CCL3, IL-10, TGFβ
EMT: epithelial to mesenchymal transition

- Transformation of epithelial cells into parenchymal cells is known and important step in wound healing process

- Three types
  - Type 1: Embryonic
  - Type 2: Fibrotic
  - Type 3: Malignant
Myofibroblast

• αSMA positive cells
• Produces new collagens
• Abundantly seen in fibroblastic foci
Fibroblast functions in pulmonary fibrosis

- TGF-β is the most profibrotic agent in Lung fibrosis
- Increases fibrocytes by recruitment, EMT and proliferation of resident fibroblasts
- Increases expression of myofibroblast via NOX4
- Integrins are critical to the activation of latent fibroblasts
- Through various inflammatory and non inflammatory cytokines procollagen and excessive ECM is secreted
Other mechanisms

1. Genes related to pulmonary fibrosis
2. Coagulation pathway
3. Reactive oxygen species
4. Role of Integrins
5. Fas-FasL
6. Inflammation
1. Genetic susceptibility for IPF

- FIP: most common genes involved are surfactant associate protein C (SFTPC) and less frequently SFTPA2
- These are the genes whose mutations are needed in EMT, apoptosis and protein misfolding
- Telomerase regulator genes mutations have also been implicated in development of FIP

Genes in Sporadic IPF

• Highest genetic risk factor is variant in promotor region of MUC5B
• MUC5B encodes mucin and is found in approximately one third patients in IPF
• Other genes which are commonly mutated in IPF are
  • DSP (Desmoplakin)
  • DPP6 (dipeptidyl peptidase 9),
  • Telomere specific genes like TERT, TERC, OBFC1, RTRL1, PARN
  • SNPs mutates like TOLLIP (Toll interacting protein)
2. Coagulation pathway

• Thrombin is a known mitogen for fibroblasts
• It also increases the production of procollagen
• Also binds with PAR (proteinase activated receptor)
• PAR are transmembrane protein which have a unique mechanism of activation when one of the part of the PAR protein gets cleaved off and acts as a Ligand for PAR
• Activation of PAR causes multiple downstream effects like inflammation, epithelial and mesenchymal cell function and TGF-β

• Thrombin also mediates differentiation into Myofibroblast phenotype from fibroblast
• Thrombin and PAR 1 also increased expression of PDGFβ1
• PAR2 is increased in expression by TGFβ1 and is activated by its ligand VIIa
• PAR2 has mitogenic effects on human fibroblasts
• Other coagulation factors also participate in profibrotic activities like factor Xa, Va, fibrin & VIIa

Bleomycin administration

1. FXa

2. Thrombin

3. PAR-2

4. Fibroblast proliferation
   Fibroblast differentiation
   ECM synthesis

5. TF expression

6. Fibrotic responses

PAR-1
3. Reactive Oxygen Species

• Superoxide Anions, Hydrogen Peroxide and Hydroxyl Radical
• NOX family of enzymes (NADPH oxidase)
• Protective entities: Superoxide dismutase, Glutathione, Catalase

IPF observations: ROS

- Fibroblasts from IPF patients have been found to generate high amount of ROS
- IPF lungs contain significantly lower level of GSH in biopsy specimen, BAL fluid and epithelial lining fluid
- Extracellular SOD was absent in fibroblastic foci of IPF patients
- NOX 4 expression is increased in fibroblastic foci
- Intraperitoneal instillation of MnTBP (metalloporphyrin) decreased Bleomycin induced lung fibrosis in Mouse models along with decrease in ROS

• ROS has been shown to activate latent TGF-β and TGF-β has been shown to increase NOX4 and ROS

• Similarly inhibiting the synthesis of GSH has been implicated in increased in TGF-β levels

• TGF-β and ROS have been implicated in the EMT

• TGF-β increased expression of NOX4, superoxide anion, αSMA, CTGF and fibronectin

The diagram illustrates the production and effects of reactive oxygen species (ROS) and reactive nitrogen species (RNS) within cells. The key components include:

- **Mitochondria**
- **Endoplasmic Reticulum**
- **NADPH oxidase**
- **Xanthine oxidase**
- **Additional oxygenases and oxidases**
- **Nitric synthase**

**Key ROS/RNS:**

- **O$_2^-$** (superoxide)
- **H$_2$O$_2$** (hydrogen peroxide)
- **OH** (hydroxyl radical)
- **OCI**
- **ONOO$^-$**

**Adaptive signaling molecules**

**Effects:**

- DNA damage
- Carbonylation of proteins and lipoproteins
- DNA damage
- Nitration and lipid peroxidation of proteins and lipoproteins

The diagram indicates the pathways through which these species can damage cellular structures and molecules.
4. Role of Integrins

• Integrins are transmembrane molecules that primarily mediate cell-cell and cell-ECM adhesion

- 18 α subunits and 8 β subunits to form 24 integrins

• Integrin αvβ6 has the ability to activate TGFβ

• Lack of the β6 subunit significantly reduces pulmonary fibrosis and β6 is upregulated in mice models of BILI

• αvβ6 is systemic sclerosis has been associated with UIP pattern as compared to NSIP pattern

Sheppard et al European Respiratory Review 2008 17: 157-162
• $\alpha_3\beta_1$ integrin acts as a laminin receptor and is protective against fibrosis

• Loss of $\alpha_3$ subunit expression is associated with inability to form $\beta$catenin/Smad 2 complexes which have been implicated in EMT

Sheppard et al European Respiratory Review 2008 17: 157-162
5. Fas-FasL

• Bronchiolar and alveolar epithelial cell apoptosis is consistent finding in BILI model
• Genes related to this pathway are upregulated
• Agonistic antibody use had been shown to increase apoptosis, inflammation, collagen deposition and upregulation of TGFβ
• Mice deficient in Fas or FasL have substantially reduced tissue inflammatory cells, apoptosis and fibrosis
6. Inflammation & immune mechanism

- Histologic analysis showed varied amount of lymphocytes, macrophages and neutrophils in SLB specimens
- Inflammation related cytokines are also increased
Against

- Anti-inflammatory therapies have been proved to be uniformly ineffective
- Upcoming hypothesis or injury and repair of epithelial cells
Role of cytokines

• TGF-β: major prothrombotic growth factor
  • Stimulates fibroblast ECM production
  • EMT differentiation
  • Production of reactive oxygen species
  • Myofibroblast differentiation
PDGF: fibroblast proliferation and chemotaxis

- Overexpression in vivo
- Inhibition reduces fibrosis
- Upregulated in human fibrotic diseases
• IFN-γ: proinflammatory cytokine
  • Enhances fibroblast apoptosis
  • Inhibits ECM production in vivo
  • In vivo models of Bleomycin induced lung fibrosis have shown to decrease fibrosis
• IL-1β and TNF-α: stimulate fibroblast proliferation and chemotaxis
  • Upregulated in Bleomycin model
  • Overexpression induces inflammation and subsequent fibrosis
• IL-17: proinflammatory cytokine
  • Upregulated in bleomycin model
  • Exogenous administration induces fibrosis
  • Fibrosis likely mediated through TGF-β
• Oncostatin M:
  • In fibroblasts stimulates proliferation and ECM production
  • Inhibits apoptosis
  • Overexpression and administration induces fibrosis
  • Works independent of TGF-β
• IL 10: anti-inflammatory cytokine
  • Inhibits fibroblast proliferation
  • Upregulation is protective in bleomycin model of fibrosis
Chemokines

- CCL 2: pro-inflammatory
  - Stimulates fibroblasts for ECM production
  - Inhibits apoptosis
  - Inhibition in animal models reduces fibrosis
  - Recruits BM derived Fibrocytes in lung
• CXCL 12:
  • Upregulated in bleomycin model
  • Recruits fibrocytes into the lung
  • Increased in BAL fluid of IPF patients
  • Inversely correlates with physiological parameters
Conclusion

• Multiple pathways
• Inter-correlation of cytokines
• Inhibition of single cytokines has not been proved to reduce fibrosis
• Small molecules like serotonin, endothelin, leptin and angiotensin have also been studied but their roles are still exploratory
Current therapies
Pirfenidone

- Pirfenidone is an antifibrotic agent that inhibits TGF-β stimulated collagen synthesis, decreases the extracellular matrix, and blocks fibroblast proliferation in vitro.
- Anti-inflammatory
- Decreases level of TGF-β by 33%
- Suppresses over expression of pro-collagen I and III genes
- Pirfenidone inhibits pulmonary fibroblast expression of heat shock protein 47, a collagen-specific molecular chaperone

<table>
<thead>
<tr>
<th>Name</th>
<th>N</th>
<th>Follow up</th>
<th>Primary end point</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAPACITY 004 (2:1:2)</td>
<td>435</td>
<td>52w</td>
<td>Change in FVC</td>
<td>Pirfenidone reduced decline in FVC (p=0·001)</td>
</tr>
<tr>
<td>CAPACITY 006 (1:1)</td>
<td>344</td>
<td>72w</td>
<td>Change in FVC</td>
<td>Difference between groups in FVC change at week 72 was not significant (p=0·501)</td>
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<tr>
<td>ASCEND</td>
<td>555</td>
<td>52w</td>
<td>Change in FVC</td>
<td>P&lt;0.001 for FVC change at week 52</td>
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<td>P&lt;0.001 for progression-free survival</td>
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<td></td>
<td>P=0.04 for 6-MWT distance change at week 52</td>
</tr>
<tr>
<td>Eur Respir J. 2010;35:821–829</td>
<td>275</td>
<td>52w</td>
<td>Change in FVC</td>
<td>Significant improvement in PFS and rate of decline of VC (in High dose group)</td>
</tr>
</tbody>
</table>
Inclusion criteria

- Diagnosis via HRCT or SLB
- Age 40–80 years
- FVC >50% but <90% pred
- DLCO >35% but <90% pred
- 6-MWT distance >150 m
Real world scenario (n=514)

Adverse effects

- Appetite loss: 17%
- Nausea + Vomiting: 15%
- Lethargy: 12%
- GOR: 7%
- Weight loss: 5%
- Diarrhoea: 3%
- Abdo discomfort: 4%
- Rash: 7%
- Chest infection: 10%
- Died: 6%
Caution

• Obtain liver function testing prior to initiation, monitor regularly
• Advise minimizing or avoiding sun exposure
• Kidney function impairment: use with caution; avoid with ESRD
Nintedanib
## Evidence

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<td>annual rate of decline in FVC</td>
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<td>52w</td>
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**INPUTSIS-1**

![Graph showing the mean observed change from baseline in FVC (ml) over weeks for Nintedanib, 150 mg twice daily and Placebo.](image)

- Nintedanib, 150 mg twice daily
- Placebo

Adjusted mean difference, 109.9 (95% CI, 71.3–148.6)
P < 0.001

**INPUTSIS-2**

![Graph showing the mean observed change from baseline in FVC (ml) over weeks for Nintedanib, 150 mg twice daily and Placebo.](image)

- Nintedanib, 150 mg twice daily
- Placebo

Adjusted mean difference, 109.8 (95% CI, 70.9–148.6)
P < 0.001
Adverse effects Nintedanib
N-acetylcysteine

• PANTHER IPF: Harmful effect of triple therapy were highlighted (Prednisolone, azathiprine and NAC)
• Increased rate of death (8 vs. 1, P=0.01) and hospitalization (23 vs. 7, P<0.001)
• Theoretically N-acetylcysteine increases the synthesis of glutathione, a potent antioxidant, and decreases the fibrotic response.
• A second hypothesis is that N-acetylcysteine-mediated downregulation of lysyl oxidase activity alleviates bleomycin-induced pulmonary fibrosis in rats

Evidence

• Double blind, placebo controlled, multicenter trial
• 3 groups, triple therapy vs NAC alone Vs Placebo
• First group removed in middle of trial due to safety concerns of triple regimen
• Results: No difference in FVC decline in two groups, death or AE
• Increased Walking distance, $D_{\text{LCO}}$ measurements and mental well-being associated with the use of NAC
• Favorable but insignificant benefits
• Similar results of PANORMA trial (Pirfenidone plus NAC)

But:

- *post hoc* studies suggested potential therapeutic effects with NAC monotherapy in a subgroup of patients with genotypes for TOLLIP,
- The potential benefit of NAC monotherapy was observed in IPF patients carrying a particular TOLLIP and not a MUC5B genotype

• In pt with a CC genotype, NAC is associated with worse survival than placebo ($P = 0.01$; [HR], 3.23; 95% [CI], 0.79–13.16; $P = 0.10$).

• In those with a CT genotype ($B$), survival is similar between groups ($P= 0.82$; HR 0.76; 95% CI 0.27–2.19; $P = 0.62$).

• In those with a TT genotype ($C$), NAC therapy is associated with improved survival compared with placebo ($P= 0.06$; HR 0.14 ; 95% CI 0.02–0.83; $P = 0.03$).
Warfarin in IPF: ACE-IPF trial

• Double-blind, Randomized, placebo-controlled trial
• Due to a low probability of benefit and an increase in mortality observed in the subjects randomized to warfarin (14 warfarin versus 3 placebo deaths; P = 0.005) an independent Board recommended stopping the study
• The mean follow-up was 28 weeks.

Ambrisentan in IPF

• Endothelin-1 is one of many profibrotic cytokines
• It acts in an autocrine and paracrine manner through endothelin A (ETA) and endothelin B (ETB) receptor subtypes.
• Contractile activity of activated lung fibroblasts and endothelin-1–induced lung fibroblast proliferation are blocked by ETA antagonism
• ETA receptor can also promote epithelial–mesenchymal transition via TGFβ
• Data from preclinical models suggest that antagonism of endothelin receptors may decrease the severity of pulmonary fibrosis
Evidence- ARTEMIS-IPF

• Eligible patients
  • Aged 40 to 80 years
  • Diagnosis of IPF for at least 3 months.
  • Patients with greater than 5% honeycombing on HRCT scans were excluded

Intervention

• Randomly assigned in a 2:1 ratio to receive Ambrisentan or placebo.
• Ambrisentan at 5 mg/d and titrated to 10 mg/d after 2 weeks
Placebo ($n = 163$)

Ambrisentan ($n = 329$)

Disease Progression Events, %

Week

Pulmonary Function Decline Events, %

Week

Antacids in IPF

• The incidence of GERD is higher in patients with IPF (8–87%) compared with the general population
• This may be due to shared risk factors, including age and smoking
• Current treatment guidelines give a conditional recommendation for AAT in patients with IPF, albeit with very low confidence in estimates of effect
Evidence

• *Post Hoc* analysis of CAPACITY and ASCEND trials
• A total of 623 patients were included in the study, of whom 273 (43.8%) received AAT and 350 (56.2%) received no AAT
• AAT users had similar mean changes in FVC from baseline to week 52 compared with non-AAT users
• Absolute and relative declines in FVC, a decrease in 6MWD of ≥50 m, and hospitalization rates after 52 weeks were similar between the two group

Adverse events

• Patients who received AAT had significantly more severe GI-related AEs than those who did not (3.7 vs. 0.9%; \( p = 0.015 \))

• Overall, the incidence of infections was similar between the AAT and the non-AAT group (67.4 vs. 67.7%; \( p = 0.934 \)).

• More severe pulmonary infections were observed in the AAT group than in the non-AAT group (3.7 vs. 1.1%; \( p = 0.035 \)).
Emerging therapies
Recombinant Human Pentraxin 2

• PTX-2 has been shown to accumulate at sites of fibrosis in animal models
• PTX-2 inhibits differentiation of monocytes into pro-inflammatory and pro-fibrotic macrophages and fibrocytes
• This in turn promotes epithelial healing and resolution of inflammation and scarring.
Phase II RCT: 21 patients

Anti- CTGF monoclonal antibody FG-3019

• FG-3019 is a fully human monoclonal antibody specific for CTGF.
• Pre-clinical studies suggest that FG-3019 penetrates into tissues to reduce effective tissue levels of CTGF resulting in reduction of pro-fibrotic factors
• In a mouse model of radiation-induced pulmonary fibrosis, administration of FG-3019 resulted in altered gene expression in the lungs, reversal of lung pathology, decrease in abnormal lung density, abrogation of fibrosis, improvement in lung function and prolonged survival
Evidence:

• Open-label, Single-arm, multicenter, phase IIa clinical trial
• 67 patients of IPF were randomized to receive either of the two doses of FG-3019.
  • 15 mg·kg\(^{-1}\) (cohort 1) or 30 mg·kg\(^{-1}\) (cohort 2)
• Result showed: no significant AE, well tolerated, improvement on fibrosis scores on HRCT
• Decline in pulmonary function were equal in the two groups

Raghu et al Eur Respir J. 2016 May;47(5):1481-91
Mesenchymal stem cell

• MSC produce soluble factors such as HGF, fibronectin, periostin, and insulin-like growth factor-binding protein 7 that are implicated in epithelial repair.

• Recently results of Phase Ib study were published to confirm the safety of MSC in IPF

• No adverse events were noted win 8 IPF patients with no significant benefit in lung functions on incremental doses

Mitochondrial dysfunction

• In IPF lungs, dysfunctional mitochondria have been found in AEC2 and lung fibroblasts.
• Mitochondrial dysfunction contributes to DNA damage, senescence, SASP, telomere attrition, stem cell exhaustion, inflammation and other key age-related cell processes
Evidence

• MitoQ, a ubiquinone conjugated molecule, attenuates the expression of TGFβ1 and NOX4 which are the two important mediators of myofibroblast differentiation

• Have found to decrease bleomycin induced lung fibrosis in rat models
Other mitochondrial agents

• Mice that are deficient in PINK1 are more susceptible for bleomycin induced lung fibrosis and increased secretion TGFβ1
• Kinetin almost completely restores the downstream pathways of PINK1 and have found to decrease fibrosis in mice models of BILI
• Similarly E3 ubiquitin ligase Prakin if knocked out in mice show enhanced myofibroblast trans-differentiation
• SRT3, NAD dependent deacetylase protects against ling fibrosis
• Hexaflurohonokiol induces expression of SRT3 and protect against lung fibrosis
• Similarly as a corollary Boosting NAD levels has been shown to be an effective approach to protect against BILI
Altered protein folding, trafficking

• Adaptive unfolded protein response has been found in AEC2 of IPF lungs secondary to alerted proteiostasis
• Multiple agents have been tried to overcome this particular mechanism
• mTOR inhibitors like Everolimus have been found to worsen the disease
• Trials to increase expression of chaperones by decreasing intracellular calcium are underway (Diltiazem and Verapamil)
• 4-PBA (4-phenyl butyric acid) has also been found to decrease ER stress, collagen synthesis, αSMA and myofibroblast differentiation

Malouf et al. Respirology 16, 776–783(2011)
Epigenetics and miRNA

• Epigenetic modifications occur during ageing and other age related diseases like IPF

• Varied genes commonly found modified in IPF have the mechanism of action of altered expression based upon epigenetic like histone aceylation and miRNA

• *Vorinostat*- a pan histone deacetylase inhibitor has been shown to protect against paraquat induced lung fibrosis and induce apoptosis of myofibroblast by preventing the deacetylation of SMAD4

• Anti-fibrotic properties of Valproic acid are also being evaluated for in pre-clinical trials.
SASP: Senescence associated secretory phenotype

- Dual action protein which increases wound healing process by releasing growth factors but if present chronically induces fibrosis
- *Dasatinib* and *Quercetin* have been found to decrease senescence and SASP markers in AEC2 of bleomycin exposed mice
- *Navitoclax* is potent inhibitor of BCL2 and BCL X1 which are anti-apoptotic proteins expressed by fibroblasts of IPF lungs. Mice models have demonstrated their efficacy against fibrosis
- GKT137831 is NOX1 and NOX 4 inhibitor which decreases reactive oxygen species and senescence markers in IPF fibroblasts
- Metformin, *Rapamycin, Omipalisib* and *Rupatadine* are being evaluated in pre-clinical trials for lung fibrosis through the mechanism of senescence prevention
Telomere attrition

- Telomere shortening has been associated with senescence and IPF.
- Estrogens and androgens have been long evaluated for lengthening of telomeres.
- Trials with primary outcome of lengthening of telomeres in IPF are underway with Danazol and Nandrolone Decanoate.
LPA/Autotaxin inhibitors

- Autotaxin enzyme converts LPC into LPA
- LPA acts through G Protein coupled receptors
- LPA control migration of Fibroblasts, contraction and proliferation
- LPA and autotaxins have been found to be increased BAL fluids of IPF patients
- LPAR\textsuperscript{1} inhibitors have been found to decrease Fibrosis in Mice models
- GLPG1690 (Galapagos): Inhibits Autotaxin and has been shown to have strong anti-fibrotic activity in BILI models
- FLORA trial in underway to assess its safety in humans
TGF $\beta$ 1

- Most potent pro-fibrotic agent
- Fresolimumab is human monoclonal antibody to neutralize TGF $\beta$1
- Study for its use in IPF is completed but results have yet not published
- Receptor for TGF$\beta$1 $\alpha \nu \beta$ 6 integrin has also been targeted
- CWHM 12 is an inhibitor which is found to decrease fibrosis in multiple organs including lungs
• GSK3008348 (inhaled) and BG00011 (IV) are inhibitors of integrin receptors of TGF which have tested in pre clinical setting of BILI and found to decrease lung fibrosis

• BC1485 targets fibrosis inducing E3 ligase- PIAS4 pathway which promotes TGFβ signaling and reduces the severity of fibrosis in BILI mice model
Growth factors

• FGF1 and KGF are potent anti fibrotic, mitogenic factors which if over expressed have been found to promote surfactant, AEC2 proliferation
Serum Amyloid P

- Serum Amyloid P (SAP) is a member of Pentraxin family of proteins
- SAP inhibits monocytes and macrophages
- It also decreases EMT and recruitment of Fibrocytes into lungs
- Anti-fibrotic activities of SAP has been shown to be mediated through Fcγ Receptors
- Therapeutic administration of SPA has been shown to have protective effects of fibrosis in murine models

Other agents with RCTs

• **No results**: IFN γ, Etanercept, Bosentan and Macitentana, Sildenafil, Imatinib

• **Worsened disease activity**: Ambrisentan, Warfarin, Everolimus

• **On going safety studies**: Lebrikizumab (anti IL13), Tipelukast (Anti Leukotriene)
Markers of IPF- Summarizing

- Expression markers of AEC1, AEC2, airway cell, TGFβ1, WNT, p53 and PI3K are increased in IPF
- PDGF, TGFβ1, TNFα, endothelin, CTGF, Osteopontin, CXC chemokine ligand-12 are all expressed by AEC2 and promote profibrotic response
- Activated AEC2 inhibit angiogenesis, reflected by paucity of capillaries, also they activate the coagulation pathway that is involved in wound healing
- FXa induces αSMA expression promoting differentiation of fibroblasts into myofibroblast