New Directions for IPF Treatments:

Understanding the Basis for Current Clinical Trials

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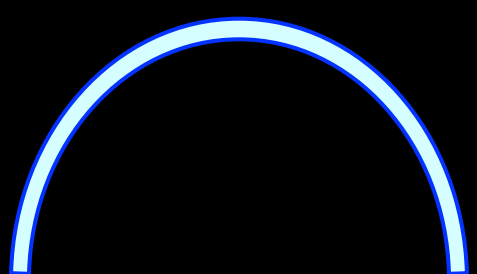
Overview

- Advances in understanding what drives IPF progression
- Clinical trials of new therapies based on new understanding

What is Fibrosis?

Fibrosis = Scarring

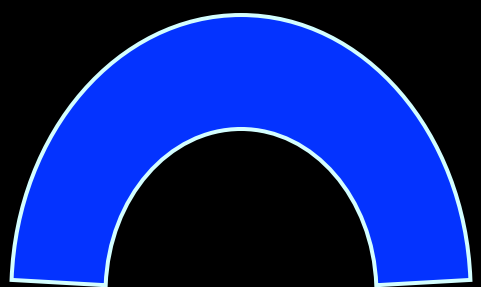
Normal tissue layers



Thin

Flexible

Scarred tissue layers



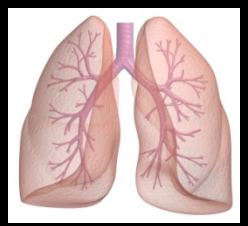
Thick

Stiff

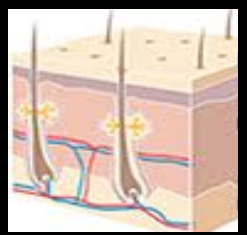
“Fibrosis Across Organs”

Many different diseases are characterized by fibrosis

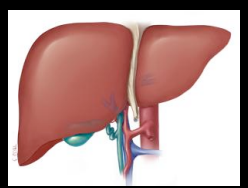
Scarring is a common disease process that can affect any organ



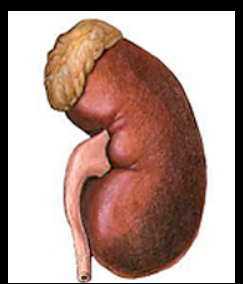
Lung → Idiopathic Pulmonary Fibrosis



Skin → Scleroderma

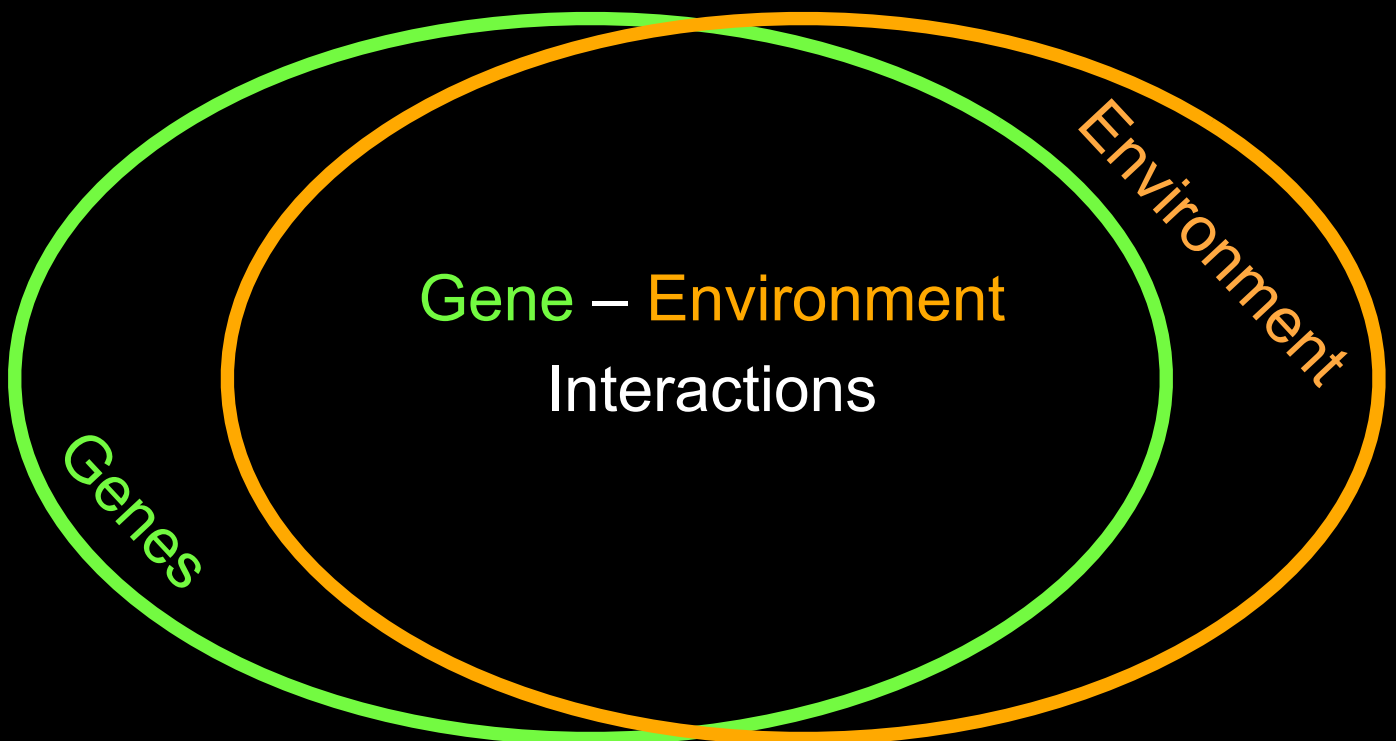


Liver → Cirrhosis



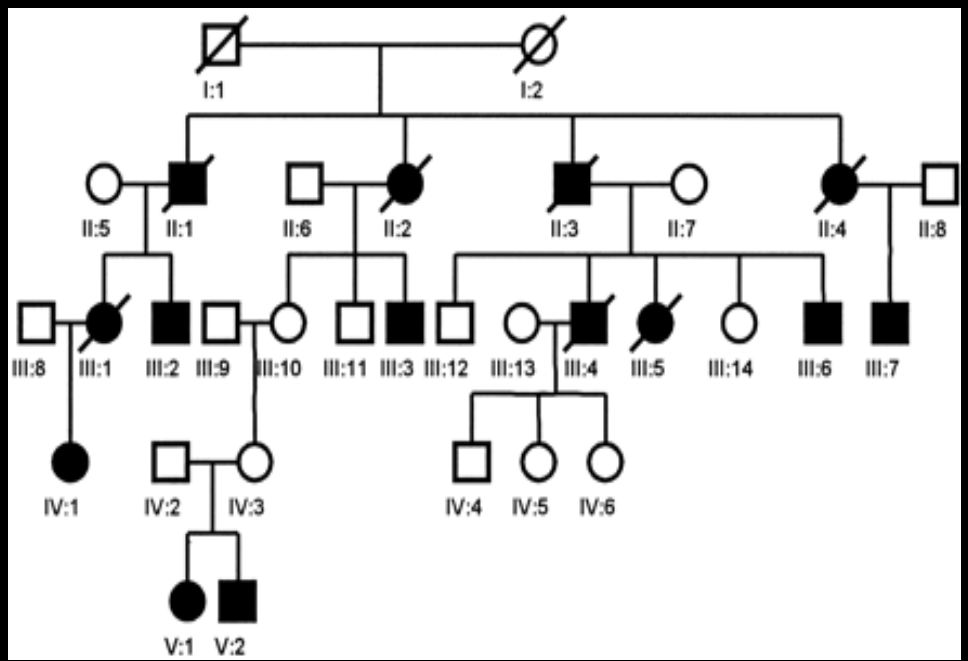
Kidney → End Stage Renal Disease

What Causes Fibrosis: Genes or Environment?



Genetic Causes of Pulmonary Fibrosis

- Familial Interstitial Pneumonia
  - Families with ≥ 2 cases among first-degree family members



- Due to gene mutations that can cause fibrosis by themselves
  - Telomerase mutations
  - Surfactant protein C gene mutations

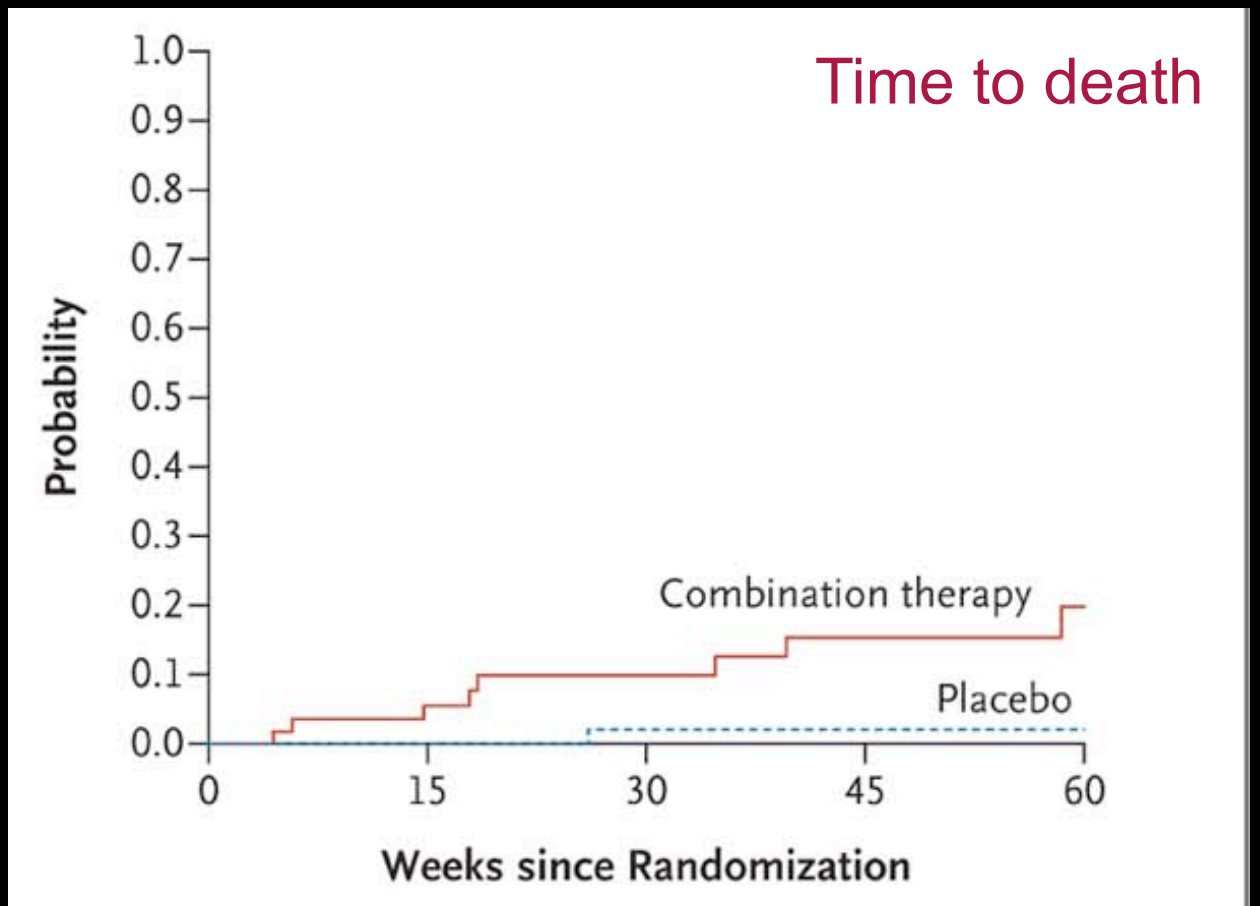
Environmental Exposures and Risk of IPF

Exposure	OR (95% CI)	Population Attributable Risk, %
Smoking	1.58 (1.3, 2.0)	49
Agriculture	1.65 (1.2, 2.3)	21
Livestock	2.17 (1.3, 3.7)	4.1
Wood Dust	1.94 (1.3, 2.8)	5.0
Metal Dust	2.44 (1.7, 3.4)	3.4
Stone/sand/silica	1.97 (1.1, 3.6)	3.5

How Do Environmental Exposures Trigger Pulmonary Fibrosis?

- Original Theory: Chronic Inflammation ➡ fibrosis
- Chronic Inflammation = responses of the body's immune cells / antibodies to exposures they recognize as foreign
- Treatment based on this theory: anti-inflammatory

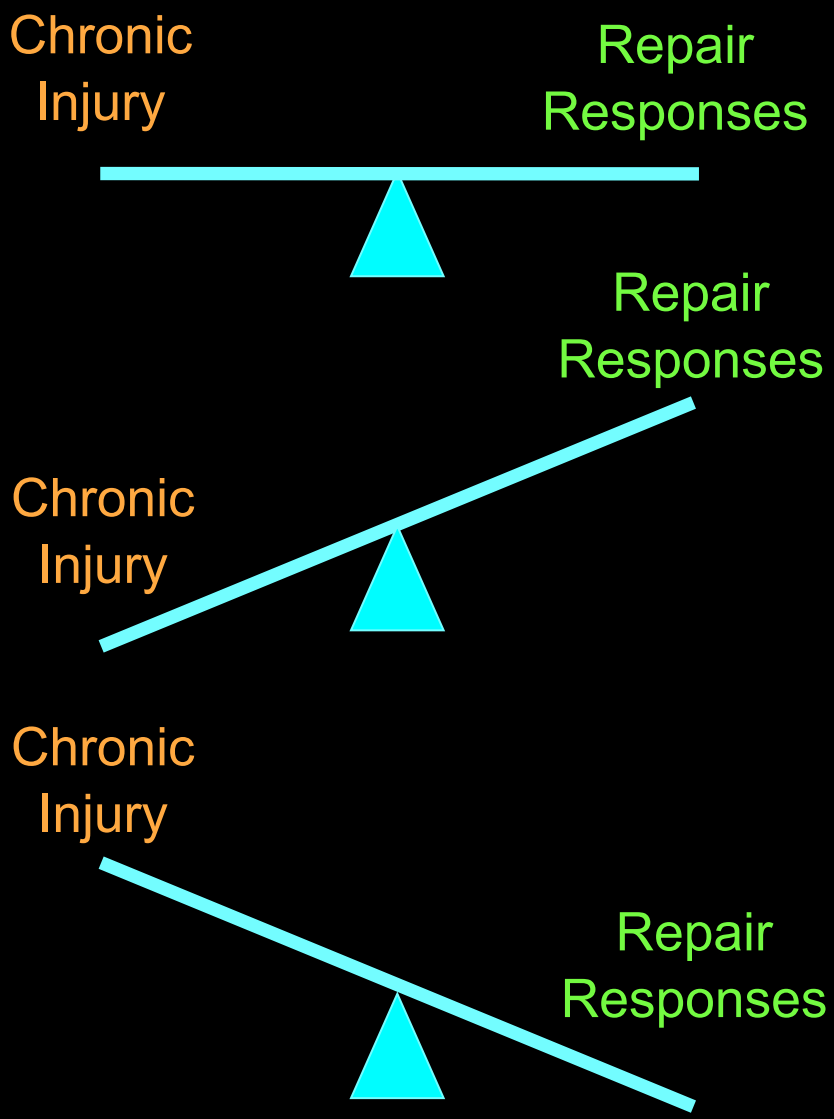
Increased Risk of Death with Anti-Inflammatory Therapy in PANTHER-IPF Trial



How Do Environmental Exposures Trigger Pulmonary Fibrosis?

- Current Theory: Chronic Injury → fibrosis
- Chronic injury = repetitive toxic exposures causing damage to lung tissues
- Treatment strategies based on this theory
  - Prevent injury
  - Improve “repair responses” of the lung

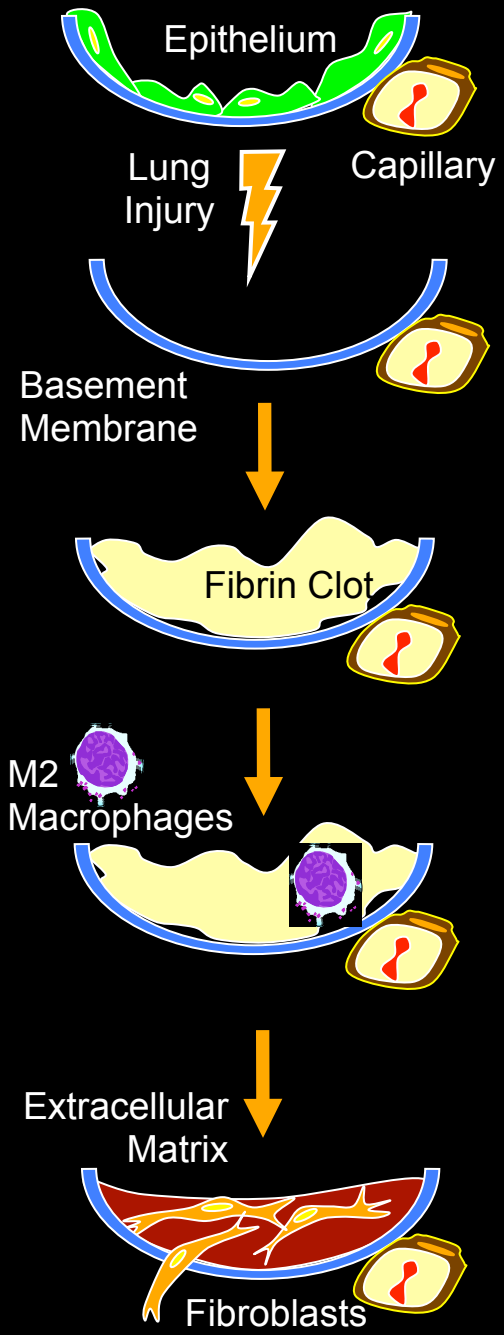
Focusing on the Lung's Repair Responses



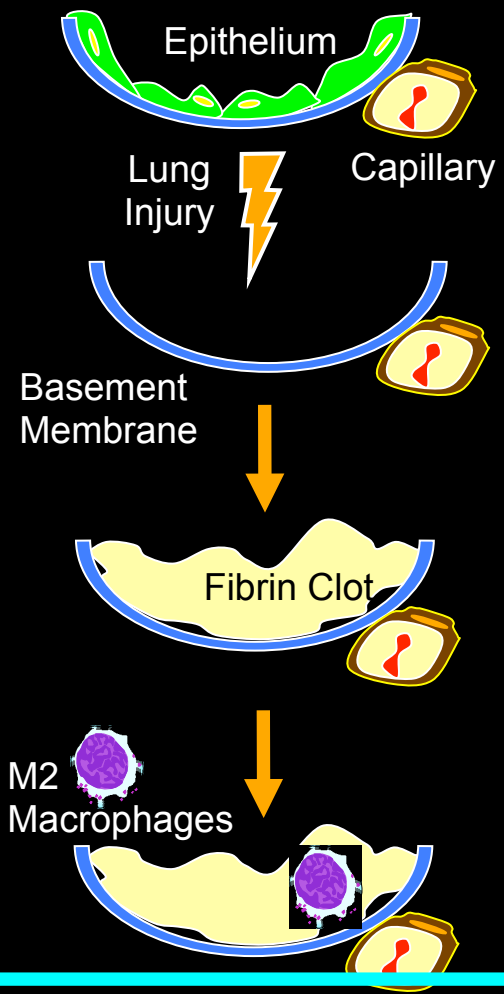
Appropriate Repair → Restoration of Normal Lung

Exaggerated Repair → Pulmonary Fibrosis

Inadequate Repair → Pulmonary Fibrosis



Injury Responses	Therapeutic Targets	IPF Trials
Epithelial Cell Death	Reactive O_2 Species	N-Acetyl Cysteine
Vascular leak and Extravascular Coagulation	Coagulation Cascade	
Innate Immune Activation	Alternatively activated (M2) macrophages	PRM-151 QAX576
Fibroblast Accumulation, Matrix Deposition and Stiffening	TGF-β	Pirfenidone STX-100
	PDGF FGF-2 VEGF	BIBF 1120
	CTGF	FG-3019
	LPA	AM152
	LOXL2	GS-6624



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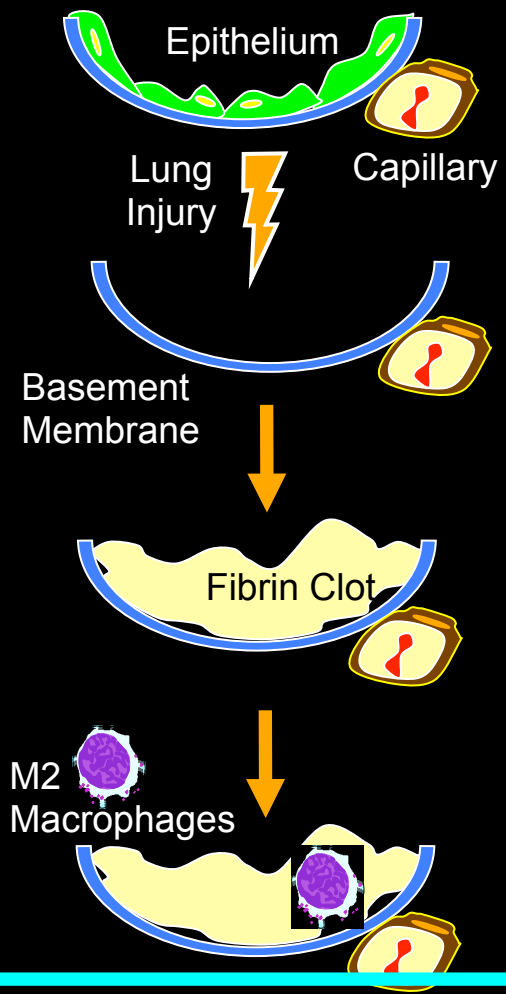

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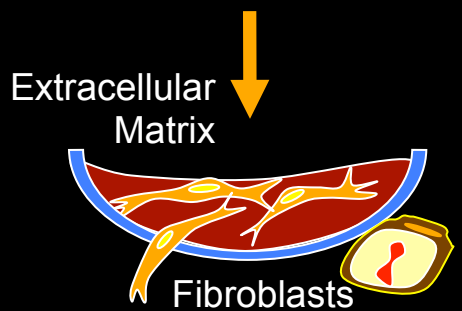

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Targeting Fibroblast Accumulation and Matrix Deposition: Pirfenidone

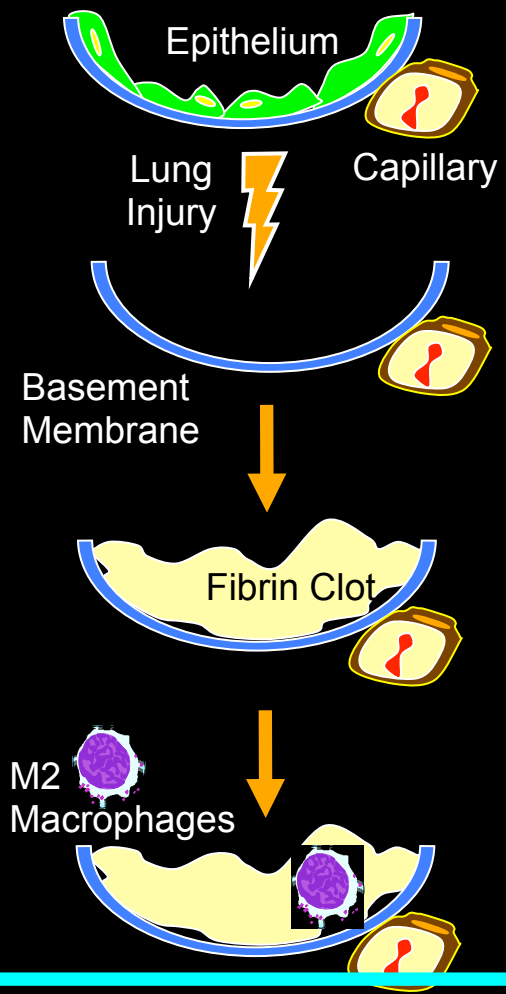
CAPACITY trials

- Two concurrent randomized, double-blind, placebo-controlled trials
- Primary outcome measure: Change in % Predicted FVC at Week 72

	CAPACITY 1 (n = 344)			CAPACITY 2 (n = 348)		
	LS Mean Change		Rank	LS Mean Change		Rank
Week	PFD	Placebo	ANCOVA	PFD	Placebo	ANCOVA
72	-6.49	-7.23	0.501	-6.49	-9.55	0.001

ASCEND Trial of Pirfenidone

Sponsor	InterMune
Mechanisms	Thought to inhibit TGF-β actions among other mechanisms
Trial Design	Phase III, randomized, double blind, placebo controlled
Inclusion Criteria	FVC 50 to 90% and DL_{CO} 30 to 90%
Primary Endpoint	Change in FVC % predicted at week 52
Treatment Arms	Pirfenidone - vs - Placebo
Treatment Duration	52 weeks
Result	Recruitment ongoing



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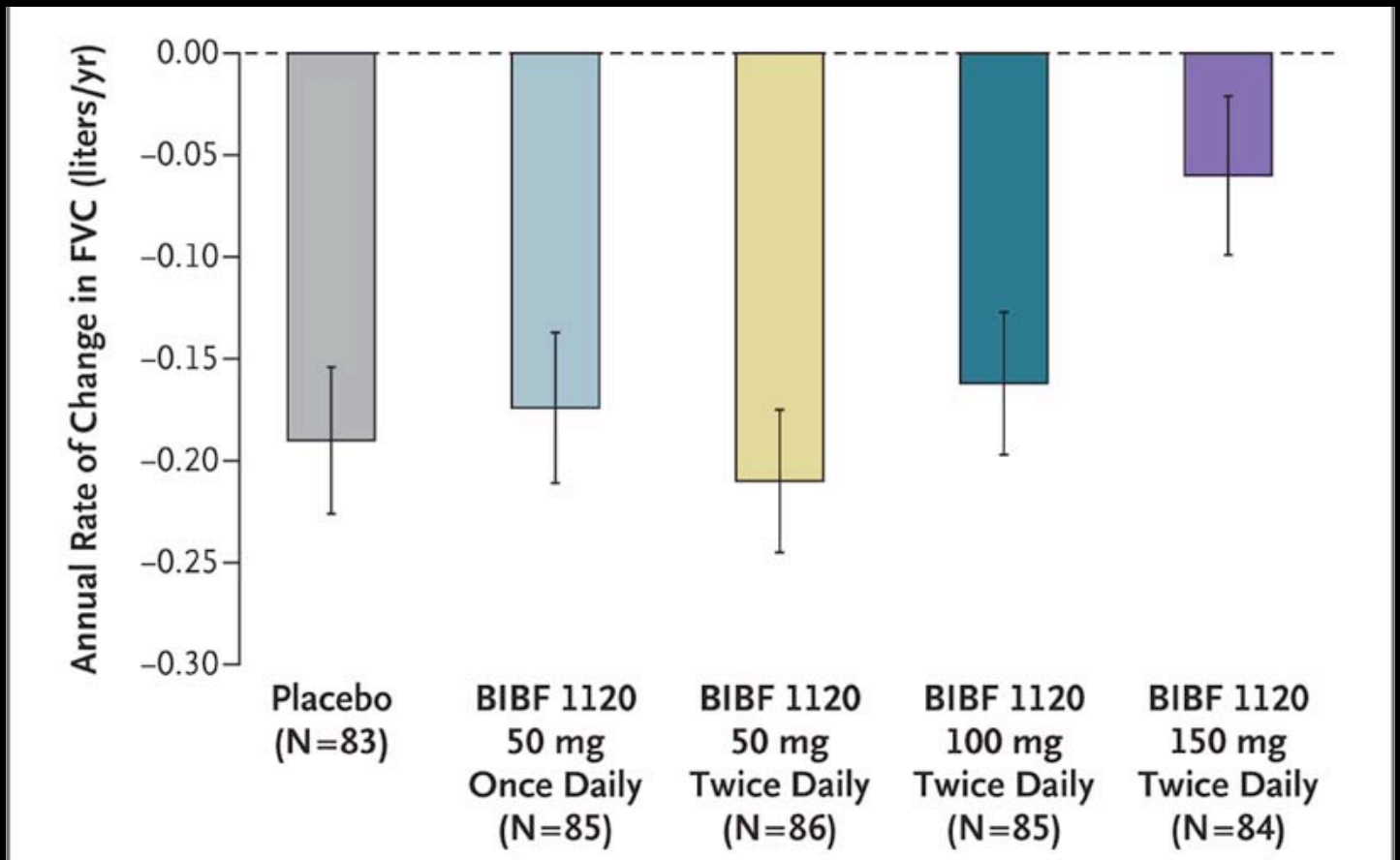
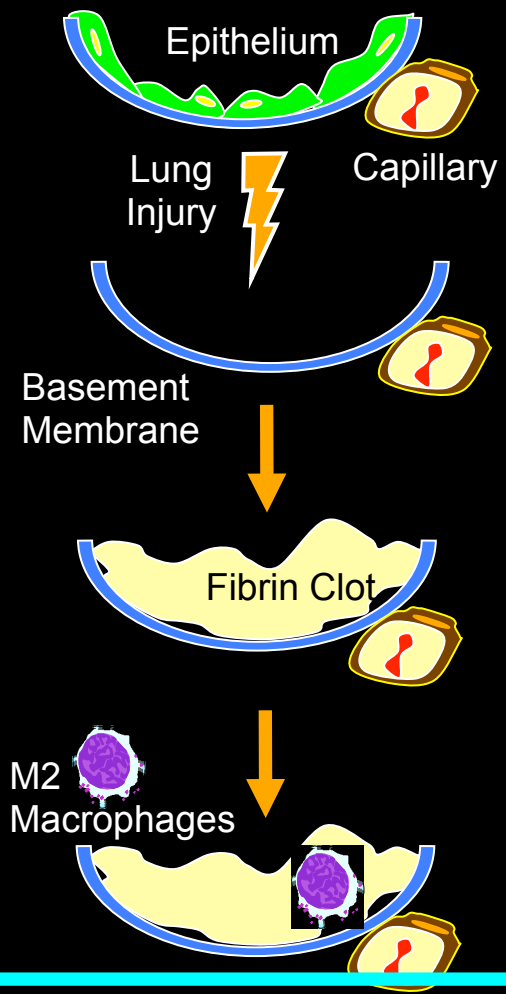
TOMORROW Trial of BIBF 1120



% subjects with ↓FVC >10% or 200ml	44.0%	41.2%	47.7%	35.3%	23.8%**

Phase III Trial of BIBF 1120

Sponsor	Boehringer Ingelheim
Mechanisms	Inhibits FGF, PDGF and VEGF
Trial Design	Phase III, randomized, double blind, placebo-controlled
Inclusion Criteria	FVC ≥ 50 %, DL_{CO} 30 to 79%
Primary Endpoint	annual rate of decline in FVC
Treatment Arms	BIBF 1120 (300 mg/d) - vs - Placebo
Treatment Duration	52 weeks
Result	Recruitment completed



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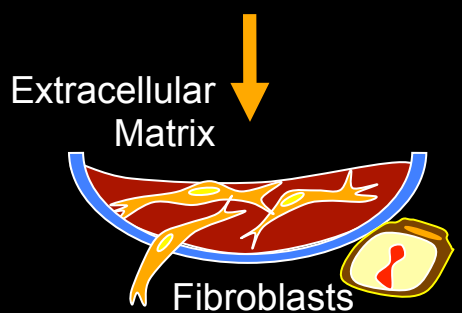

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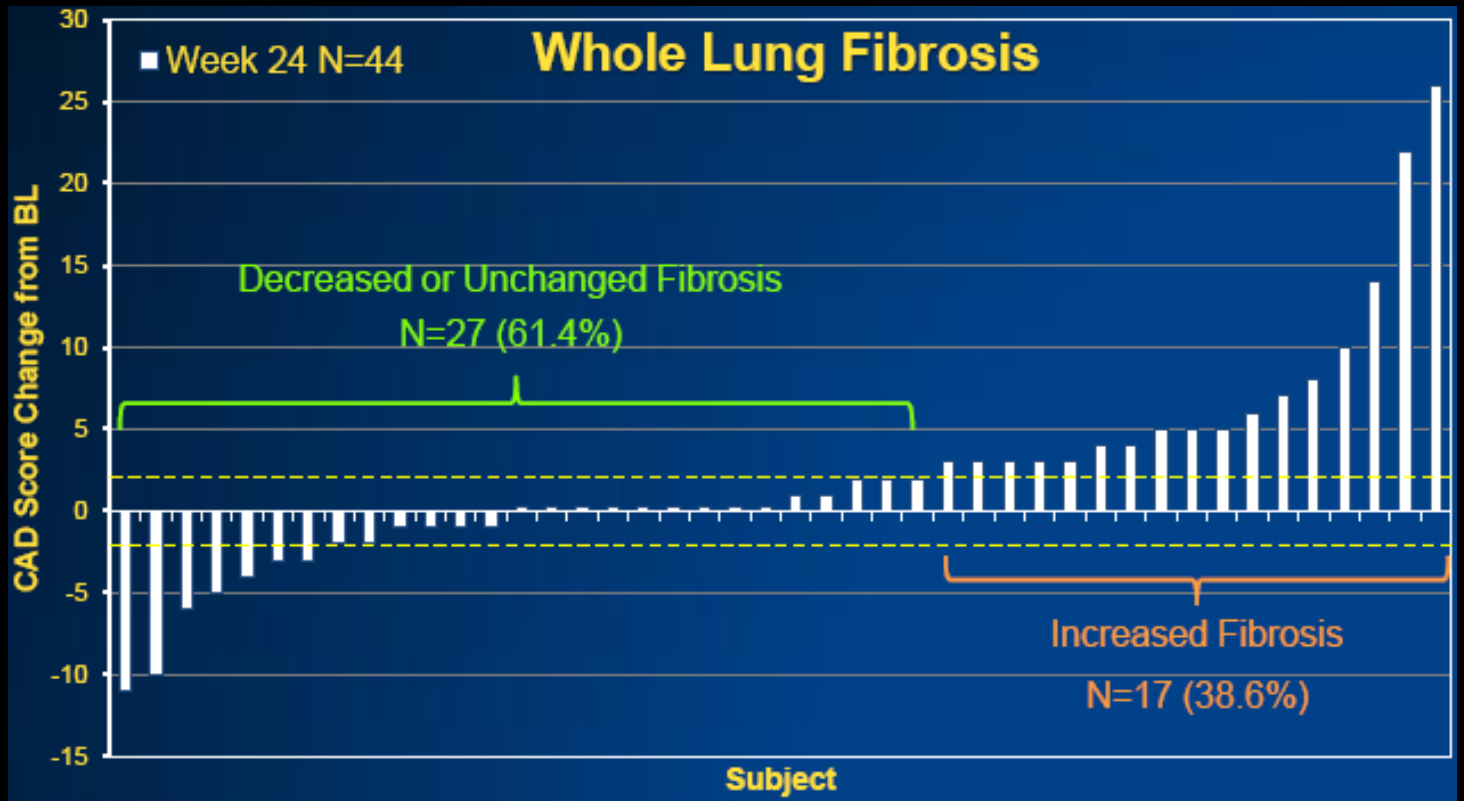
	PDGF FGF-2 VEGF	BIBF 1120
	CTGF	**FG-3019**
	LPA	AM152
	LOXL2	GS-6624

Targeting CTGF to Inhibit Fibroblast Accumulation and Matrix Deposition: Phase II Trial of FG-3019

Sponsor	FibroGen
Mechanisms	Inhibits CTGF
Trial Design	Phase II, single arm, open label
Inclusion Criteria	IPF Duration < 5 years, Progression over last 3 - 12 months
Primary Endpoint	Safety and tolerability of FG-3019 Extent of fibrosis, lung function, dyspnea (2º endpoints)
Treatment Arms	FG-3019 - vs - Placebo
Treatment Duration	45 weeks
Result	Recruitment completed

Evidence of Improvement in Some IPF patients in Phase II Trial of FG-3019



	24 weeks		48 weeks	
Subjects	**Total**	**Δ FVC % Predicted > 0**	**Total**	**Δ FVC % Predicted > 0**
ALL	44	14 (31.8%)	21	5 (23.8%)
BL FVC % Predicted > 55%	34	13 (38.2%)	17	5 (29.4%)

Inhibiting Fibroblast Accumulation and Matrix Deposition with Carbon Monoxide

Sponsor	Brigham and Women's Hospital
Mechanisms	Inhibits fibroblast accumulation and matrix deposition
Trial Design	Phase II, randomized, double blind, placebo-controlled
Inclusion Criteria	FVC ≥ 50% predicted
Primary Endpoint	MMP7 levels Effects on FVC, DLCO, 6MWD and SGRQ (2º endpoints)
Treatment Arms	Inhaled Carbon Monoxide (CO) - vs - placebo
Treatment Duration	12 weeks
Result	Recruitment ongoing

Targeting TGF-β to Inhibit Fibroblast Accumulation and Matrix Deposition: Anti-β6 Integrin Antibody (STX-100)

Sponsor	Stromedix
Mechanisms	Inhibit TGF-β activation
Trial Design	Phase II, randomized, double blind, placebo-controlled
Inclusion Criteria	FVC ≥ 50 %, DL_{CO} ≥ 35%, Room air O_2 saturation ≥ 90%
Primary Endpoint	Incidence and severity of adverse events % change in lung function (secondary endpoint)
Treatment Arms	STX-100 - vs - Placebo
Treatment Duration	8 weeks
Result	Recruitment ongoing

Summary

- Recent advances in understanding IPF progression
- Identification of new drug targets of clinical trials
- Optimism for development of effective treatments for IPF