DILIsym Services

A SIMULATIONS PLUS COMPANY

IPFsym
A Platform to Support the Development of Effective Treatments for IPF Patients

Scott Q Siler

February 18, 2021

Disclaimer: DILIsym Services are developed and provided as an educational tool based on assessment of the current scientific and clinical information, and accepted approaches for drug safety and efficacy. The resultant data, suggestions, and conclusions ("Guidelines") should not be considered inclusive of all proper approaches or methods, and they cannot guarantee any specific outcome, nor establish a standard of care. These Guidelines are not intended to dictate the treatment of any particular patient. Patient care and treatment decisions should always be based on the independent medical judgment of health care providers, given each patient's individual clinical circumstances.

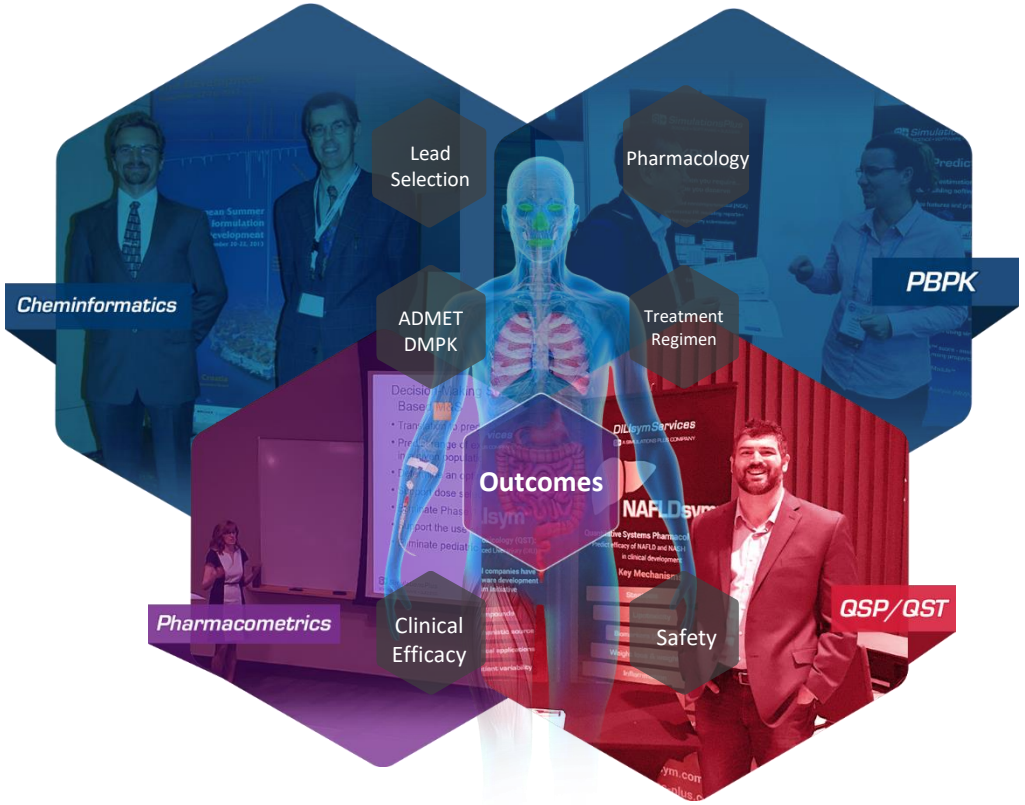
Agenda

- Introduction to DILIsym Services
- Overview of IPFsym v1A
- Simulating Treatment in IPFsym v1A
- IPFsym Licensing and Services
- Q & A

At SimulationsPlus We Put It All Together

Science

- Seamless collaboration
- Integrated, innovative solutions to meet <u>your</u> needs



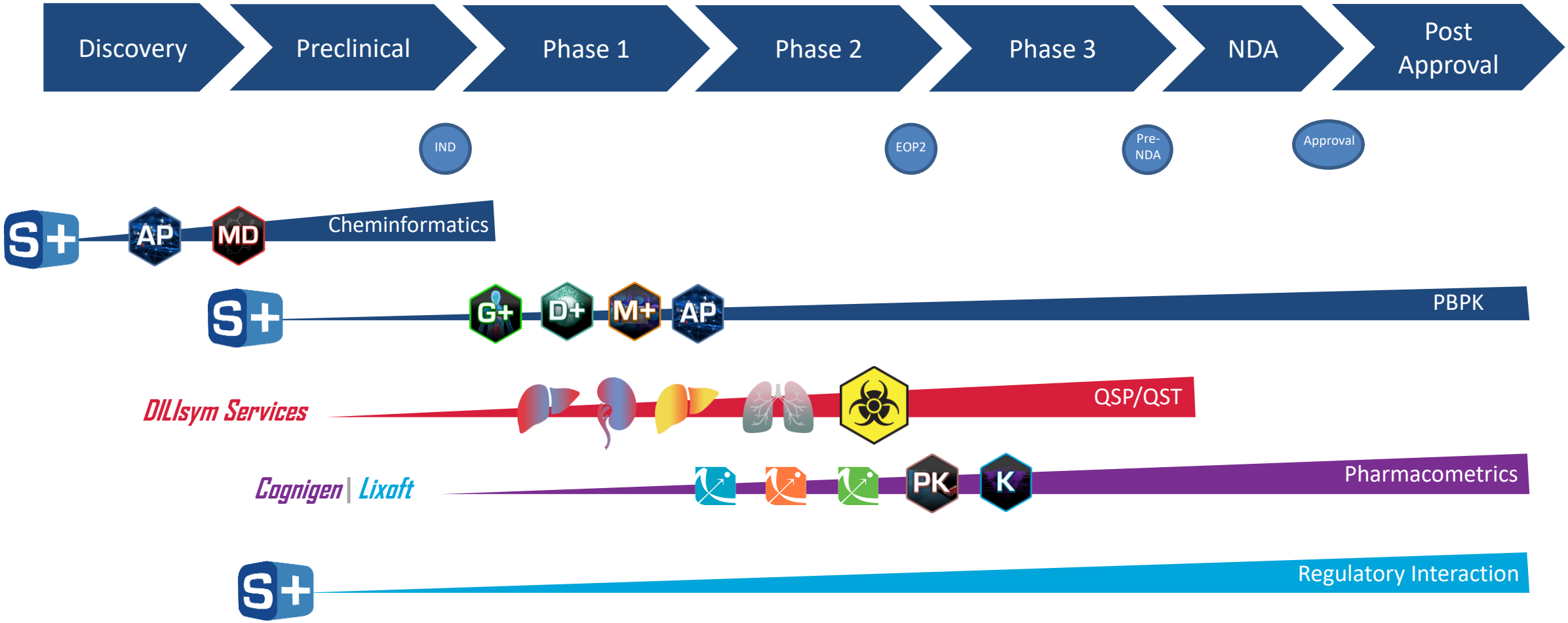
Business

- Resources available to get the job done on time
- One-stop shopping – single vendor for all of your *in silico* drug development needs

We have the *Solutions* and the *People* to Address *<u>Your</u>* Drug Development Questions!

NASDAQ: SLP

Our Solutions Inform the Entire Drug Development Process



NASDAQ: SLP

DILIsym Services Division of Simulations Plus: Mechanistic, QSP/QST Modeling

***Innovation*: pursuing novel and creative solutions to positively impact the world**

***Respect*: promoting a diverse workforce and inclusive culture, while serving our communities**

***Integrity*: thoroughly and accurately communicate with uncompromised truth and honesty**

***Commitment*: providing quality products and exceptional services that deliver value to our partners and the people we serve**

DILIsym™ RENAsym™ IPFsym™ NAFLDsym™ RADAsym™

- **DILIsym** software licensing, training, development (DILI-sim, RENAsym consortia)
- **NAFLDsym** and **IPFsym** software licensing, training, development
- **DILIsym, NAFLDsym,** and **IPFsym** simulation consulting projects
- **Custom QSP model** development and simulation consulting projects
- Drug development consulting and data interpretation; *in vitro* assay experimental design and management
- **RENAsym** and **RADAsym** software in development

NASDAQ: SLP

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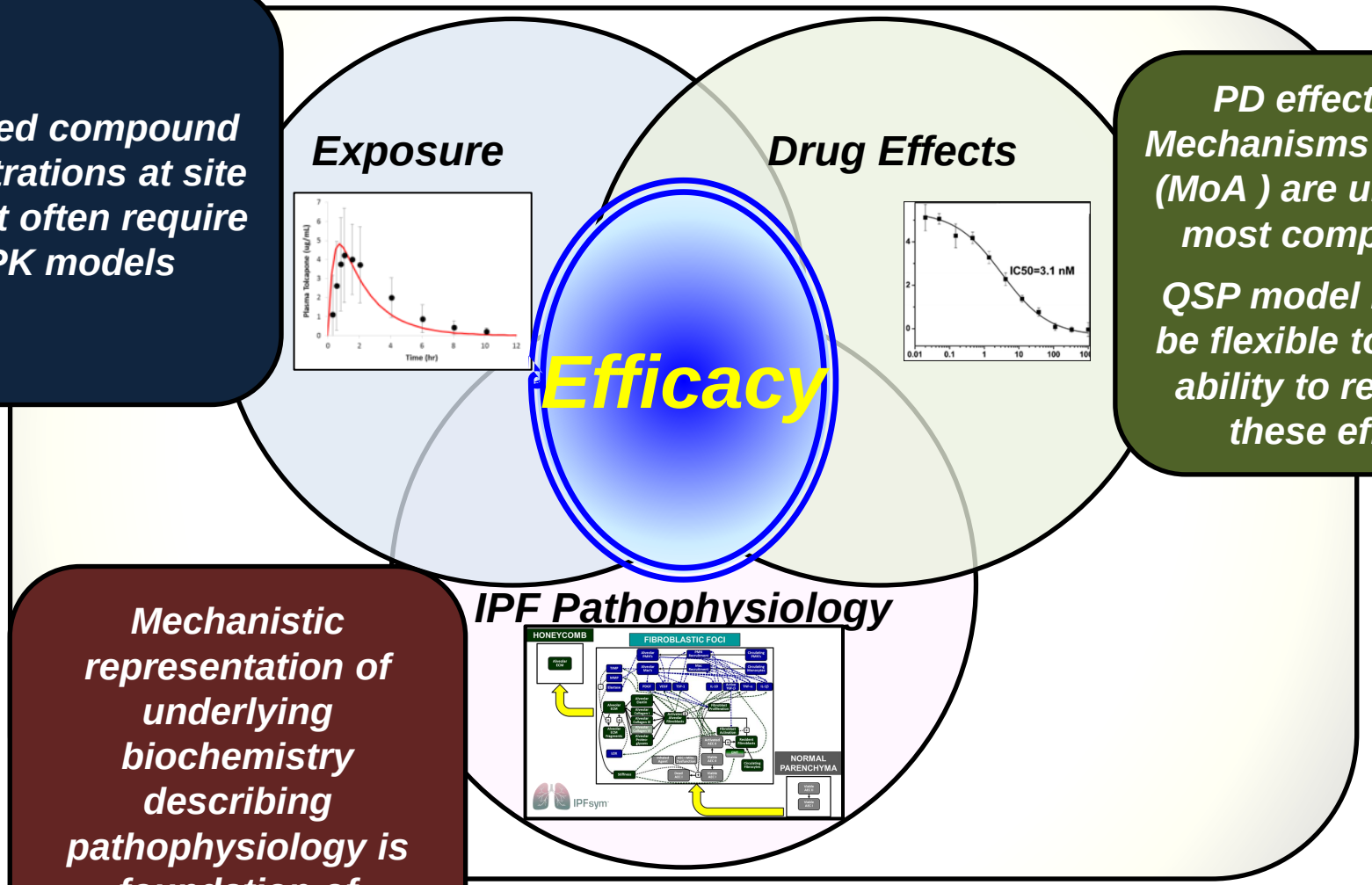
DILIsym Services Is Using QSP Modeling to Predict Efficacy and Safety of Drugs in Development

Predicted compound concentrations at site of target often require PBPK models



PD effects and Mechanisms of Action (MoA) are unique for most compounds;

QSP model needs to be flexible to provide ability to represent these effects

Mechanistic representation of underlying biochemistry describing pathophysiology is foundation of QSP models

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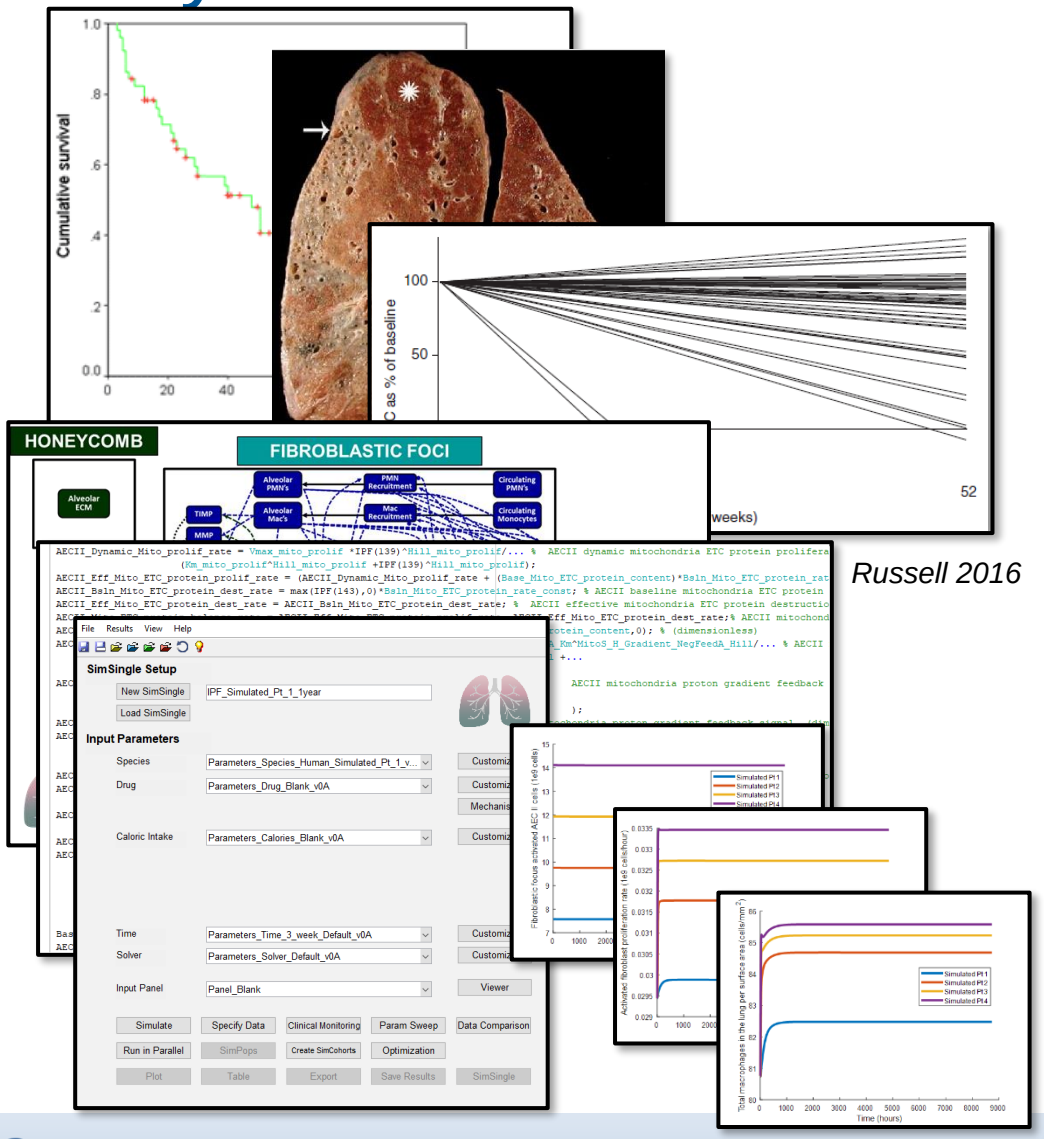
IPFsym Is Designed to Support Drug Development with Efficacy Predictions

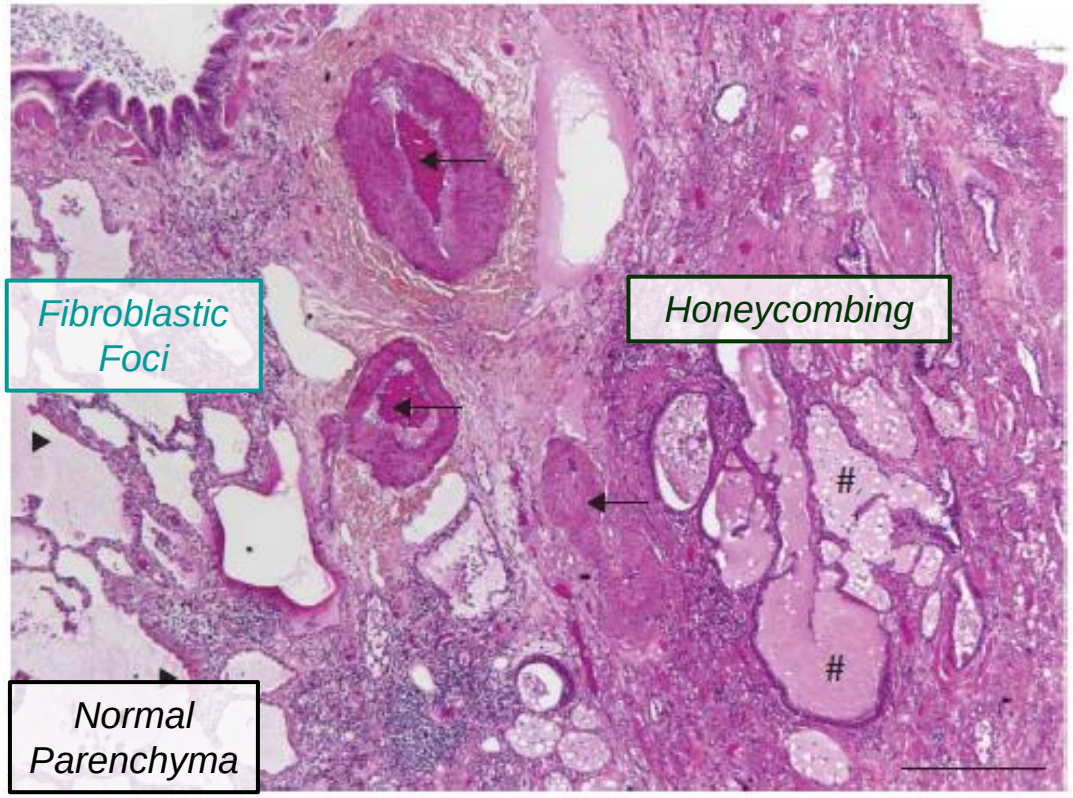
- IPF afflicts elderly patients, with extremely high mortality rates following diagnosis
  - Substantial manifestation of pathophysiology before respiratory function is compromised enough to motivate diagnosis
- IPF is progressive disease
  - Respiratory function (e.g., FVC) declines over time
- IPFsym is a QSP model of IPF
  - Includes capabilities of predicting effects of treatments on fibrosis, inflammation, and epithelial cells of alveoli
  - Includes pathophysiologically diverse simulated patients in SimPops
  - IPFsym v1A to be released in Q1 2021
- IPFsym can be used to support IPF drug development
  - Combines PK, PD, pathophysiology to predict efficacy of novel treatments
  - Flexible framework facilitates addition of new targets as needed
  - Can be used to optimize clinical trial protocols and identify key hypotheses related to mechanistic underpinnings of predicted response to treatment
  - Provides ability to evaluate combinations of treatments with different mechanisms of action



Russell 2016

Three Distinct Functional Zones Are Present In Lungs of IPF Patients

- **Normal parenchyma**
  - Unaffected alveoli
  - Primarily responsible for residual respiratory function
- **Honeycombing**
  - Collapsed, non-functional alveoli laden with fibrotic extracellular matrix (ECM) proteins
  - No contribution to respiratory function
- **Fibroblastic foci**
  - Site of active remodeling of lung
  - Change in cellular composition of alveolar epithelium
  - Activated myofibroblasts synthesizing ECM proteins
  - Immune system active in supporting fibrotic deposition



Plantier 2018

IPFsym Summary Diagram

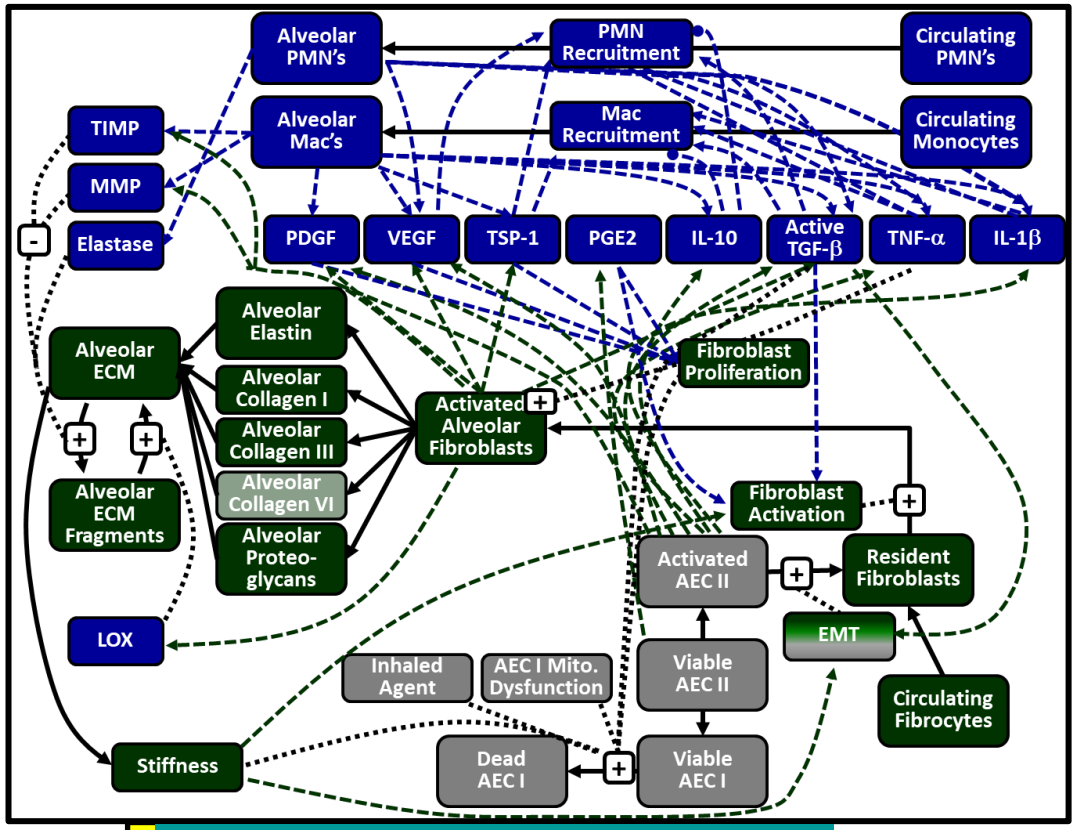
Clinical | Fibrosis | Immune | AEC

HONEYCOMB

Alveolar ECM

- *Comprised of ECM*
- *Devoid of functional immune cells and AEC's*
- *Increases with ECM persistence and stiffness*
- *No contribution to respiratory function*

FIBROBLASTIC FOCI



- *Active AEC loss/activation*
- *Active inflammation, mediator production*
- *Activated fibroblasts*
- *Active ECM deposition*
- *Contributes to respiratory function*

CLINICAL OUTPUTS

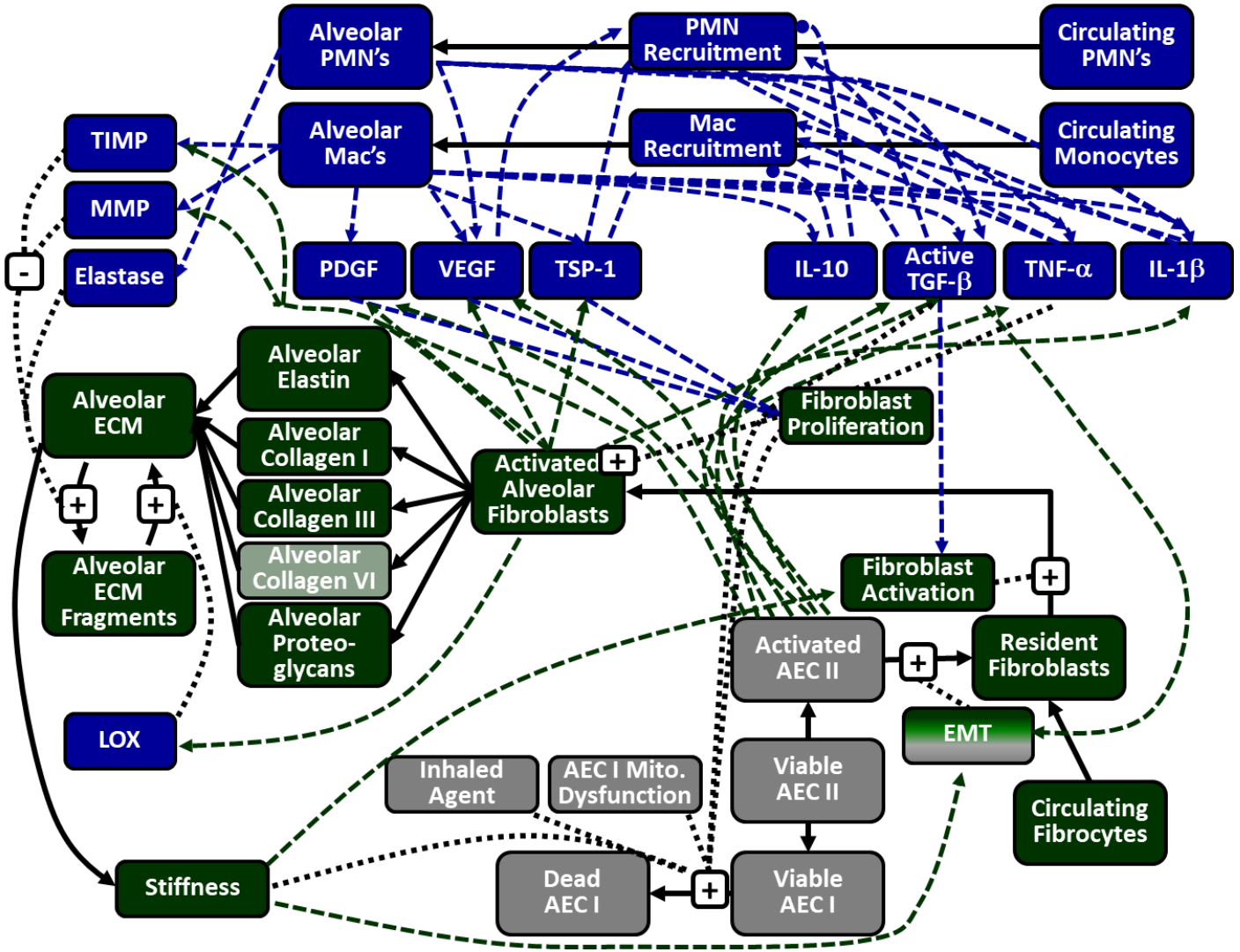
FVC | HRCT | D_{LCO} | 6 Min Walk Dist.

- *Normal alveolar biochemistry*
- *Steady state life cycle of alveolar macrophages represented*
- *Steady state life cycle of AECI and AECII represented*
- *AEC's adjacent to FF vulnerable to apoptosis*
- *Contributes to respiratory function*

NORMAL PARENCHYMA

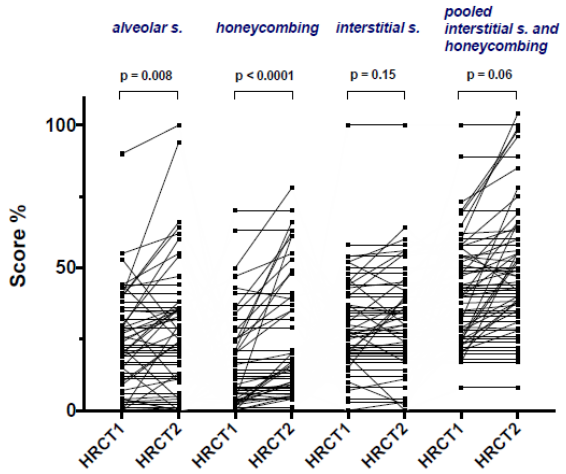
Viable AEC II → Viable AEC I

IPFsym Fibroblastic Foci Diagram

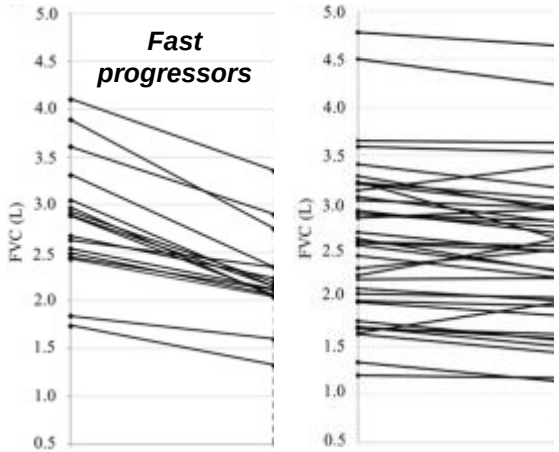


Substantial Inter-Patient Variability in IPF Disease Progression

- Patients can remain stable, with minimal change in clinical outputs
  - Typical period of data collection is 1 year
- Patients can show rapid decline in disease status and pulmonary function
  - Potential for mortality is high in this subset of patients
- IPFsym includes simulated patients that progress slowly or rapidly
- IPFsym v1A does not include acute exacerbation events
  - Destruction of endothelial wall, pneumonitis likely to be added in subsequent versions of IPFsym

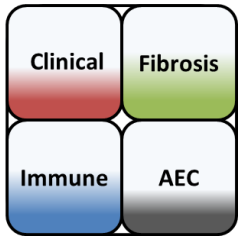


Balestro 2019

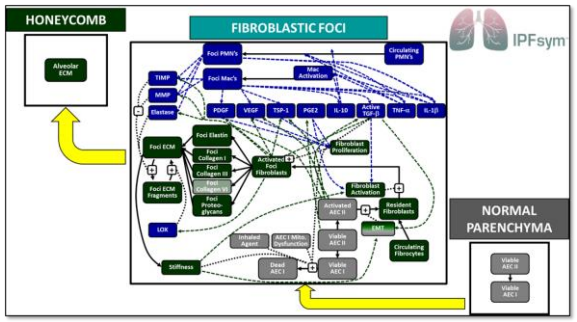


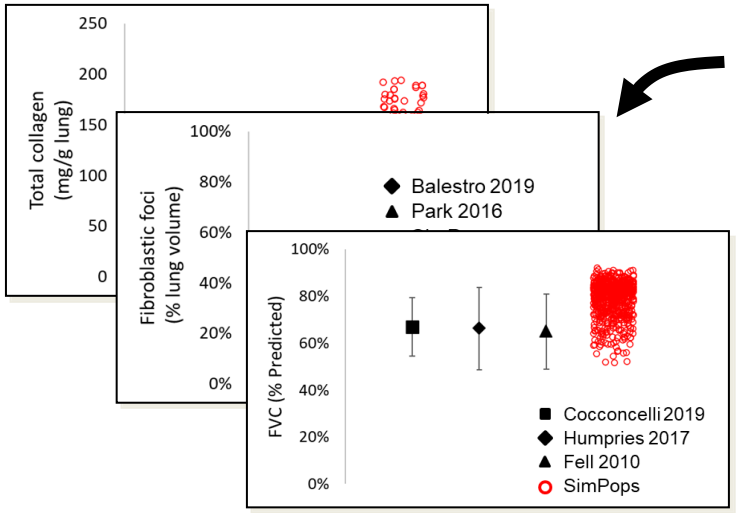
Biondini 2018

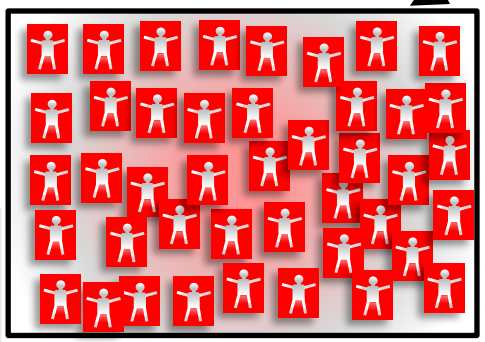
Pathophysiologic Variability Represented in IPFsym SimPops



- SimPops are population samples with variability across key areas of IPF pathophysiology
- Multiple parameters are varied to produce diverse possible simulated patients
- Simulated patients are compared with a multitude of clinical data to validate pathophysiology within model
- Response data (e.g., nintedanib/pirfenidone) used to further validate the SimPops

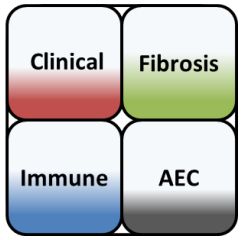




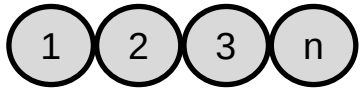


Variables Used to Construct the IPFsym v2A SimPops
Height
Age
AEC apoptosis rates
Immune cell recruitment and activation
Inflammatory mediator production
Fibroblast activation and proliferation
ECM synthesis and degradation
Collagen cross linking and ECM stiffness
Progression rates

Use of Different Categories of SimPops in IPFsym

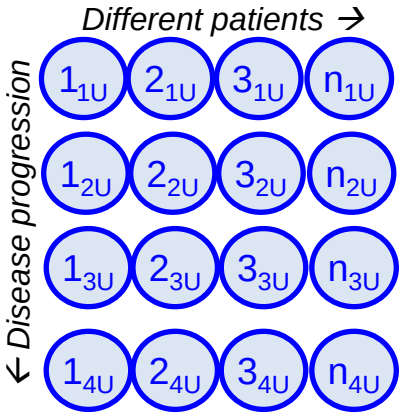


Steady state



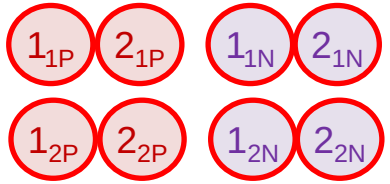
Use for exploration of disease progression

Disease progression With varying trajectories, location in progression trajectory



Use to select cohorts with varying progression trajectories, location in progression spectrum while untreated

Disease progression + standards of care with different location in progression/ treatment trajectory



Use to select cohorts with varying progression trajectories, location in progression spectrum while on treatment

Data to Support Evaluation of IPF SimPops

AEC

- Viable AECI and AECII numbers in fibroblastic foci and normal parenchyma

Immune

- Immune cells in fibroblastic foci
- Circulating mediators

Fibrosis

- Fibroblast numbers in fibroblastic foci
- Total collagen, elastin, proteoglycan (ECM) quantities in fibroblastic foci and/or honeycombed region
- Circulating Pro-C3 and lysyl oxidase-L2
- Stiffness in fibroblastic foci and honeycombed region

Clinical

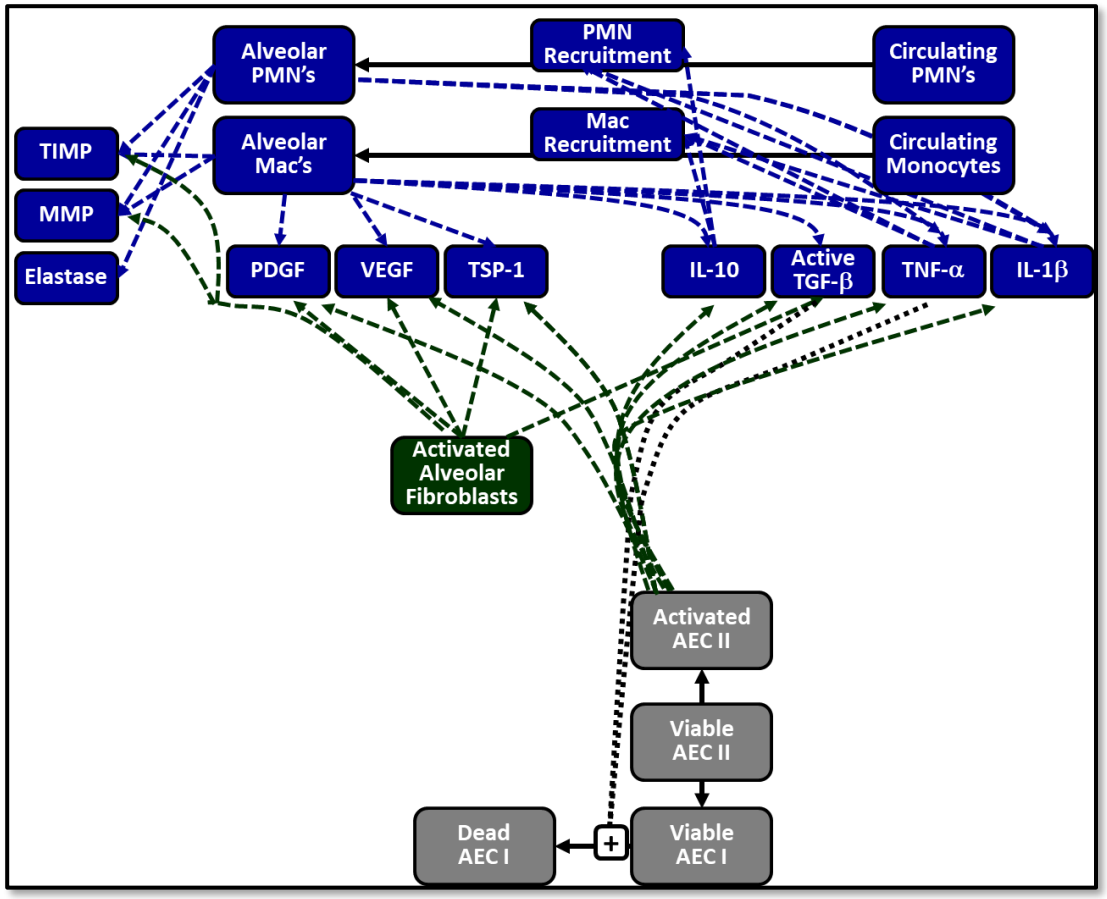
- HRCT determination of honeycombing and fibroblastic foci volumes
- FVC, % predicted FVC in placebo and treated patients
- D_{LCO}, % predicted D_{LCO} in placebo and treated patients
- 6 minute walk distance in placebo and treated patients

Comparisons with clinical data made simultaneously across all axes

IPFsym FF Inflammation Diagram

Immune

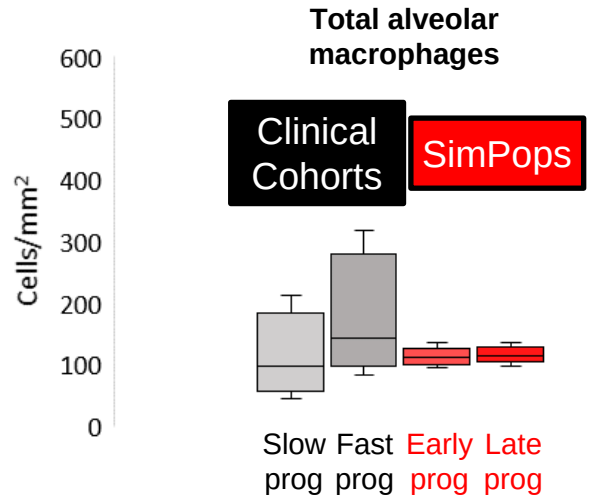
- Representation of immune cells focuses on macrophages and neutrophils
  - Recruitment of circulating monocytes and neutrophils
  - Proliferation of resident and recruited alveolar macrophages
- Inflammation participates in represented pathophysiology largely through production of key mediators
  - Inflammatory mediators produced by multiple cell types, including AECs and fibroblasts
- Mediator effects include
  - Cross-regulation, recruitment, proliferation
  - Pro-fibrotic and pro-apoptotic activity

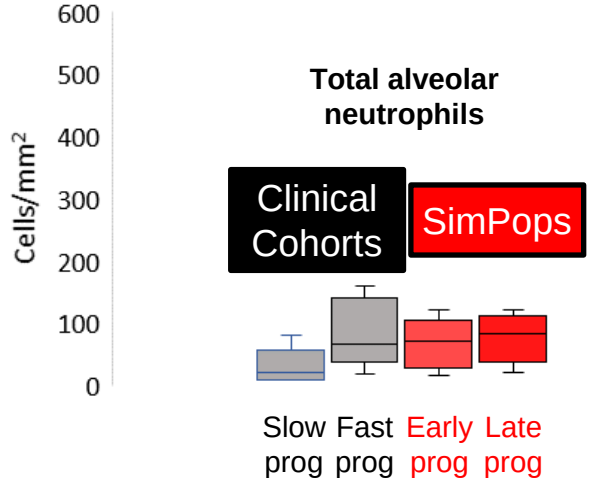


Simulated Cell Numbers for SimPops Are Consistent with Clinical IPF Data

Immune

- SimPops patients (n=716) include varying degrees of IPF severity
  - Includes simulated patients early in progression and later in progression
  - All simulated patients survive 4 years of simulated disease progression
- Simulated cell numbers for SimPops patient macrophages and neutrophils fall within range observed for slow or rapid progressors
  - Macrophages and neutrophils quantified from lung biopsies of IPF patients (slow or fast progressors)



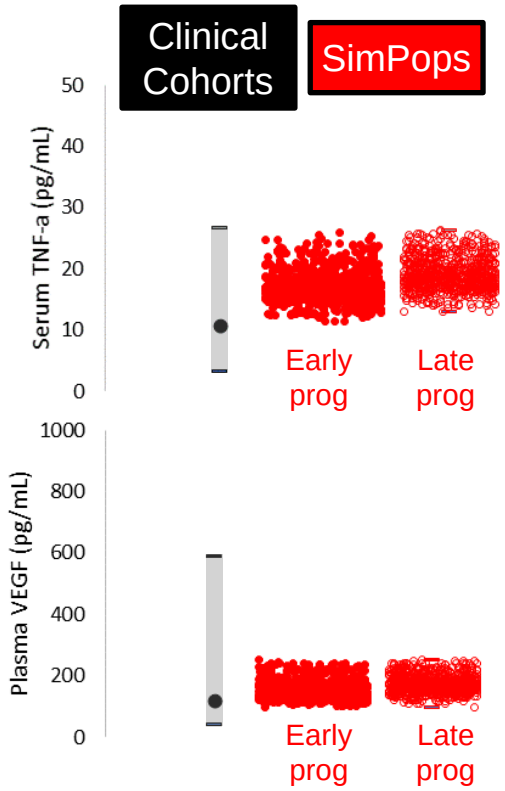


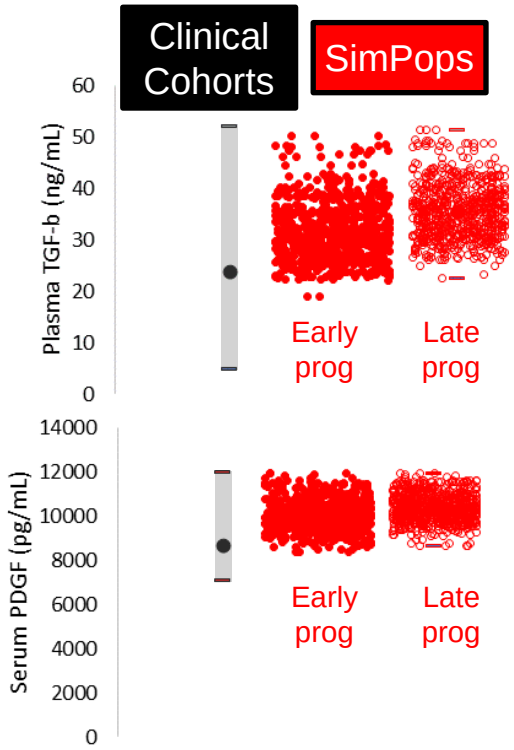
Balestro 2016

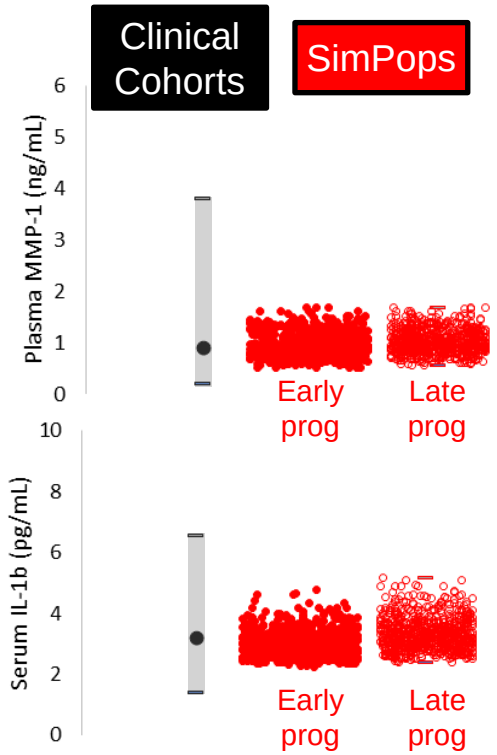
SimPops Mediator Levels Are Consistent with Clinical IPF Data

Immune

- Simulated mediators from preliminary SimPops are consistent with clinical data
  - Mean (•), minimum (-), maximum (-) plotted
  - Clinical data come from variety of sources
  - Other mediators (IL-10, TIMP-1, TSP-1, neutrophil elastase, LOX) also evaluated (*not shown*)



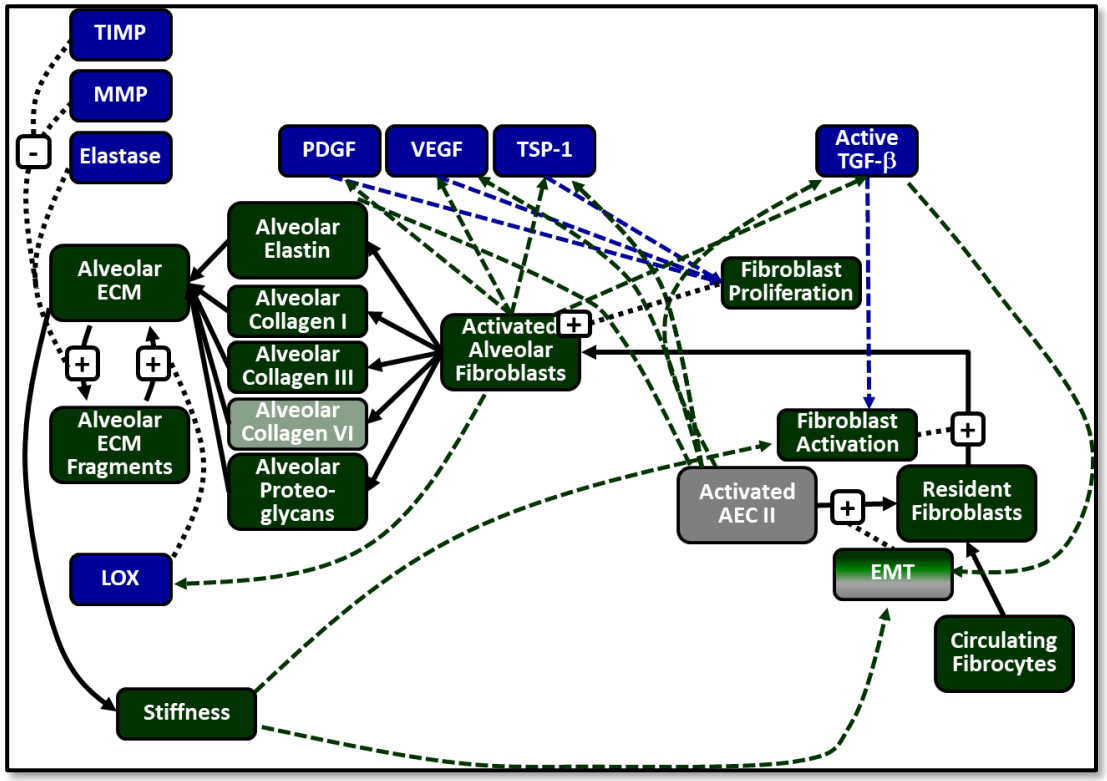




IPFsym FF Fibrosis Diagram

Fibrosis

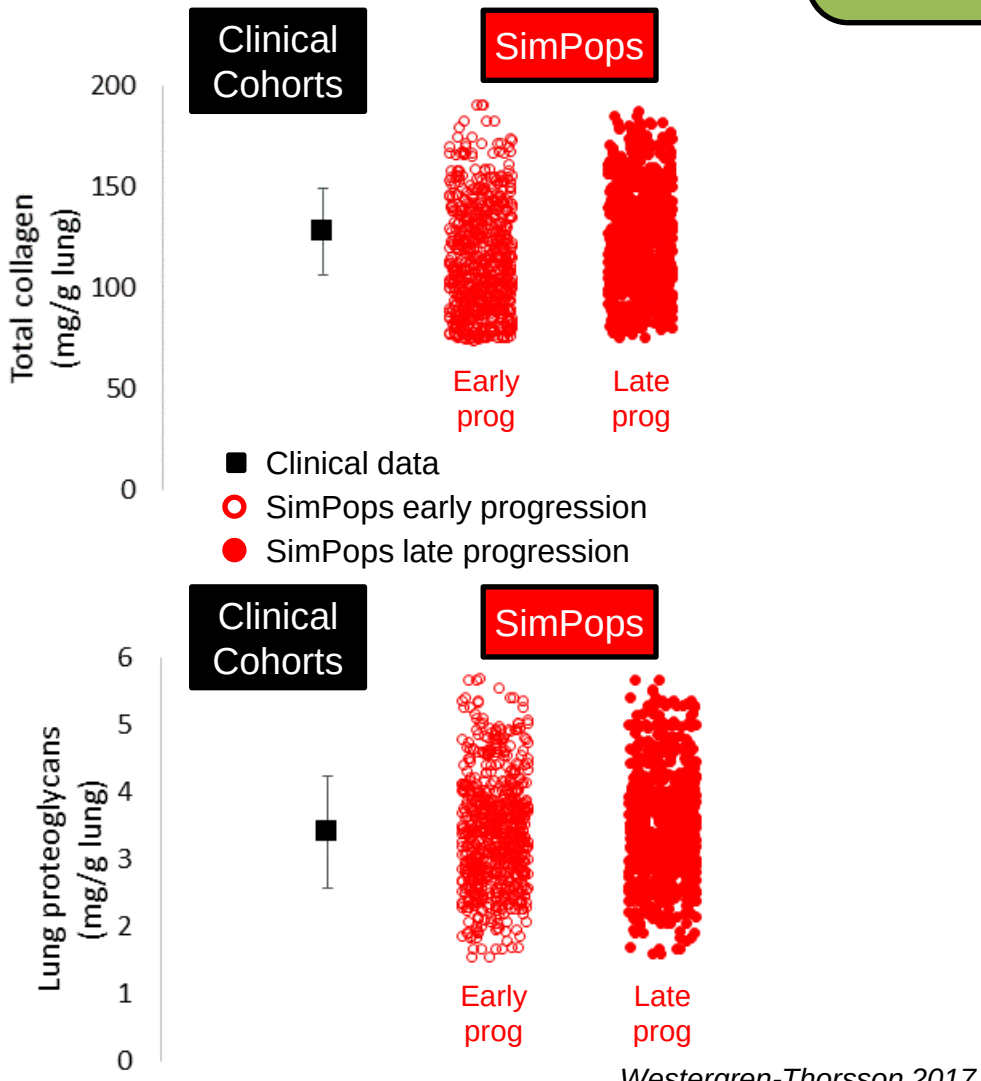
- Resident fibroblasts activated in response to elevated TGF-β levels
- Activated fibroblasts increase proliferation in response to elevated PDGF levels
- Circulating fibrocytes and activated AEC II (via EMT) may contribute to the fibroblast pool
- Activated fibroblasts synthesize ECM
- Elevated ECM increases lung stiffness
  - Stiffness feeds back into fibroblast activation
- Transition of FF alveolar ECM to Honeycombed is dependent upon time and ECM stiffness



Simulated ECM Levels for SimPops Are Consistent with Clinical IPF Data

Fibrosis

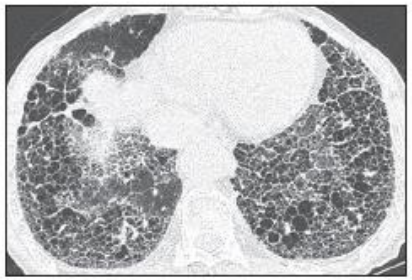
- SimPops patients (n=716) include varying degrees of IPF severity
  - Includes simulated patients early in progression and later in progression
  - All simulated patients survive 4 years of simulated disease progression
- Simulated lung collagen and proteoglycans are consistent with range of clinical data
  - Clinical data measured from lung biopsy and postmortem samples reported in Westergren-Thorsson 2017



Westergren-Thorsson 2017

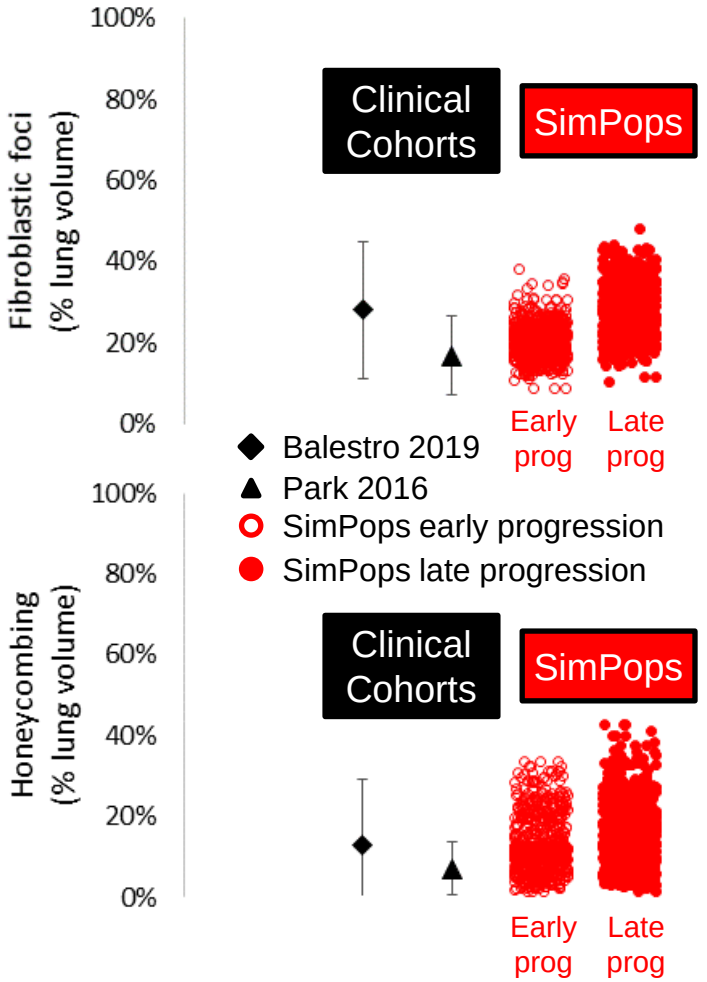
Simulated Fibroblastic Foci and Honeycombing for SimPops Are Consistent with Clinical HRCT Data

Clinical



Park 2016

- SimPops patients (n=716) include varying degrees of IPF severity
  - Includes simulated patients early in progression and later in progression
  - All simulated patients survive 4 years of simulated disease progression
- Simulated volume fractions of fibroblastic foci and honeycombing consistent with range of reported clinical data
  - Clinical data collected via HRCT
  - SimPops patients include variability in body and lung size

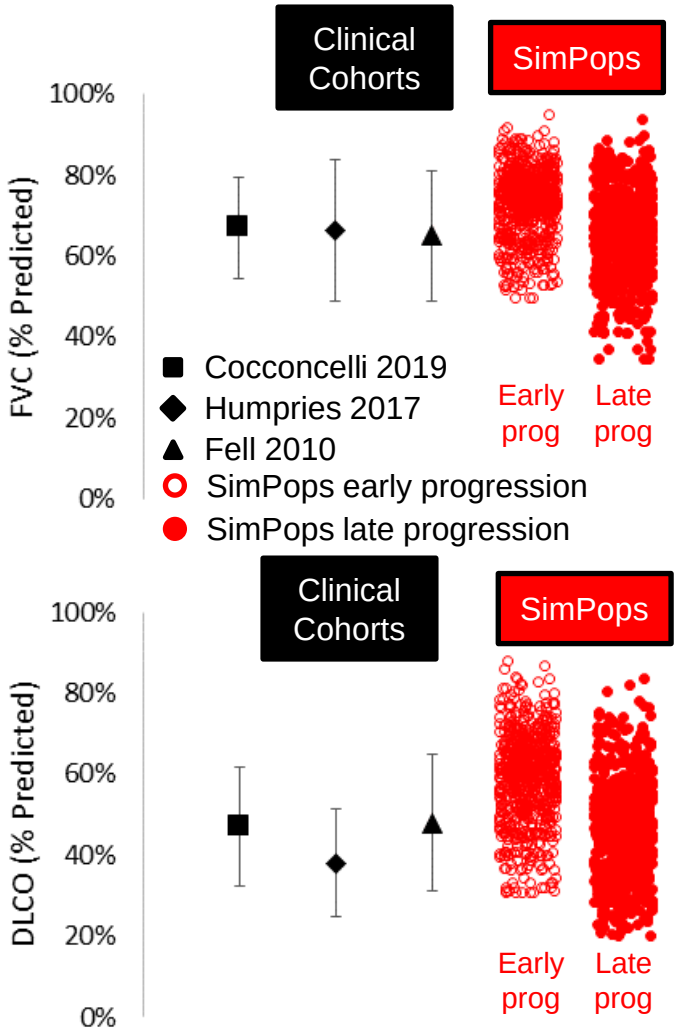


Park 2016, Balestro 2019

Simulated FVC and D_{LCO} for SimPops Are Consistent with Clinical Data

Clinical

- SimPops patients (n=716) include varying degrees of IPF severity
  - Includes simulated patients early in progression and later in progression
  - All simulated patients survive 4 years of simulated disease progression
- Simulated FVC (% predicted) and D_{LCO} (% predicted) consistent with range of reported clinical data
  - FVC and D_{LCO} measurements compared with reference values for untreated patients of similar age, gender, size
  - Absolute FVC and D_{LCO} are also included as IPFsym clinical outputs
  - FVC and D_{LCO} are influenced by extent of fibroblastic foci and honeycombing within lungs of SimPops patients

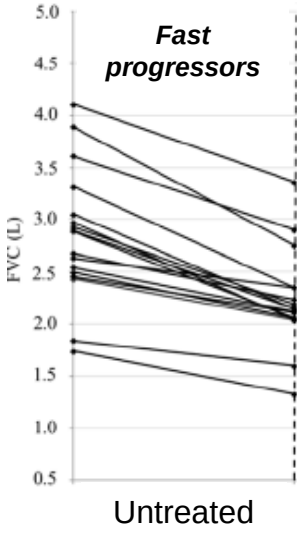


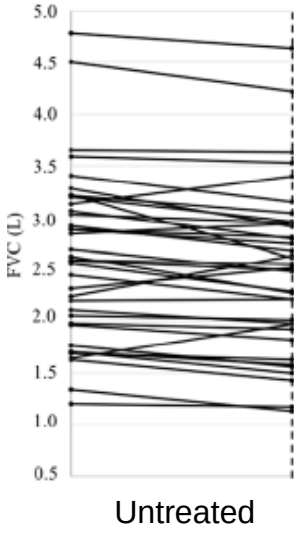
Fell 2010, Humphries 2017, Cocconcelli 2019

SimPops Include Appropriate IPF Progression Rates

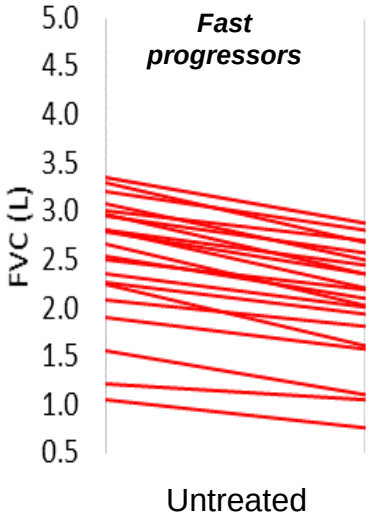
Clinical

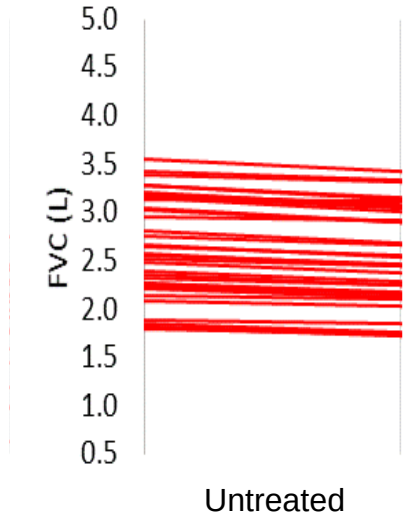
Clinical Cohorts





SimPops





Biondini 2018

- SimPops patients include varying rates of change in fibroblastic foci and honeycombing regions
  - Respiratory measures (e.g., FVC) are dependent upon relative volumes of the functional zones
- Mixture of fast and slow progressors in SimPops (*untreated, 1 year*)
  - Rates consistent with Biondini et al.
    - Fast progressors defined as ΔFVC≥10%; slow progressors defined as ΔFVC≤10%
  - Selected simulated patients displayed

Brief Demonstration of IPFsym v1A Software

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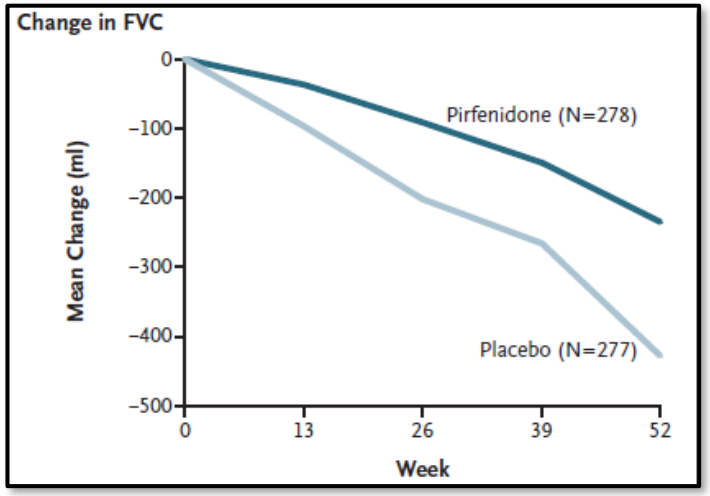
Pirfenidone Overview

Clinical

- Pirfenidone, Esbriet® (Roche/Genentech), approved for treatment of IPF in US and several other countries
- Small molecule with antifibrotic and anti-inflammatory properties
- In IPF patients, pirfenidone mitigated the decline in FVC (King 2014)
- Preclinical data provide evidence that pirfenidone inhibits fibroblast activation and procollagen synthesis
  - Conte 2014
  - Nakayama 2008
- Less evidence exists for alternate mechanisms
  - Inhibition of fibroblast proliferation
  - Inhibition of EMT
  - Inhibition of fibrocyte accumulation
  - Inhibition of inflammatory mediator production

ASCEND

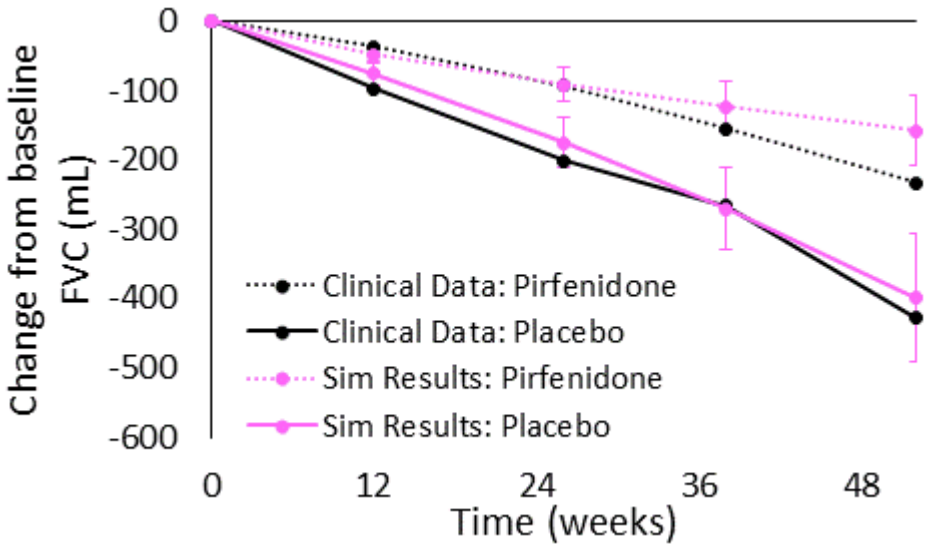


King 2014

Reasonable Simulation of Clinical Response to Pirfenidone Treatment

Clinical

- SimCohorts (n=62) and clinical IPF patients were treated with 801 mg TID pirfenidone for 52 weeks
  - Similar rate of progression between Clinical IPF patients and SimCohorts patients in placebo group
- Simulated change in FVC on pirfenidone treatment was comparable to clinical data
- Simulated change in FVC with placebo was comparable to clinical data

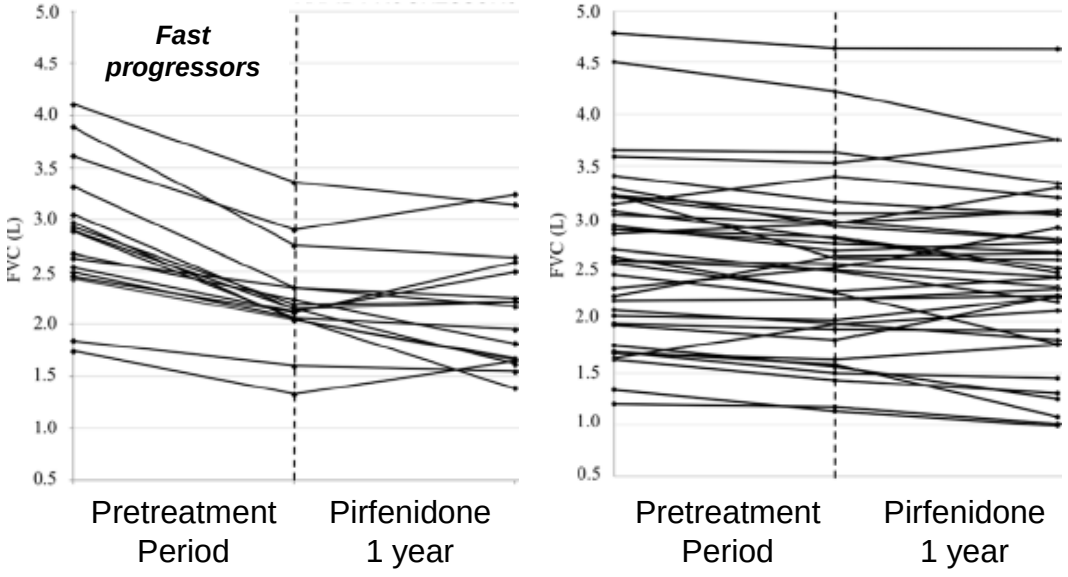


King 2014

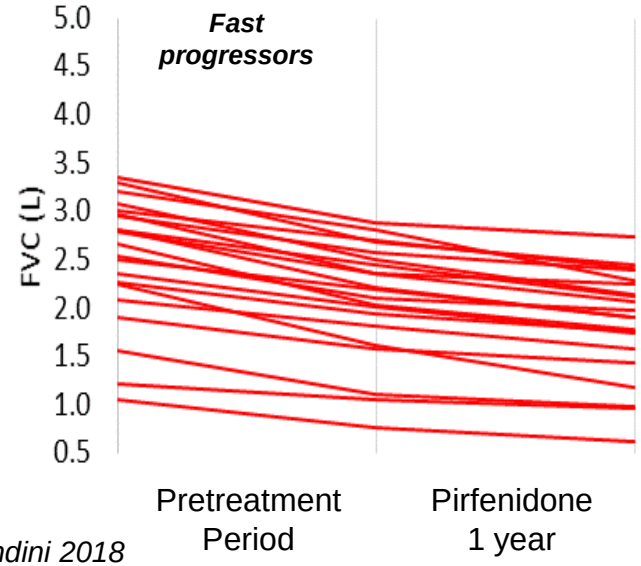
SimPops Include Appropriate Adjustment to IPF Progression Rates with Treatment

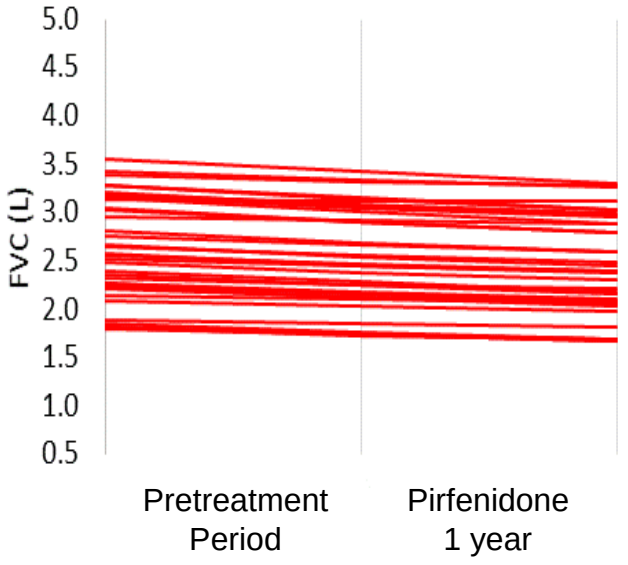
Clinical

Clinical Cohorts



SimPops





Biondini 2018

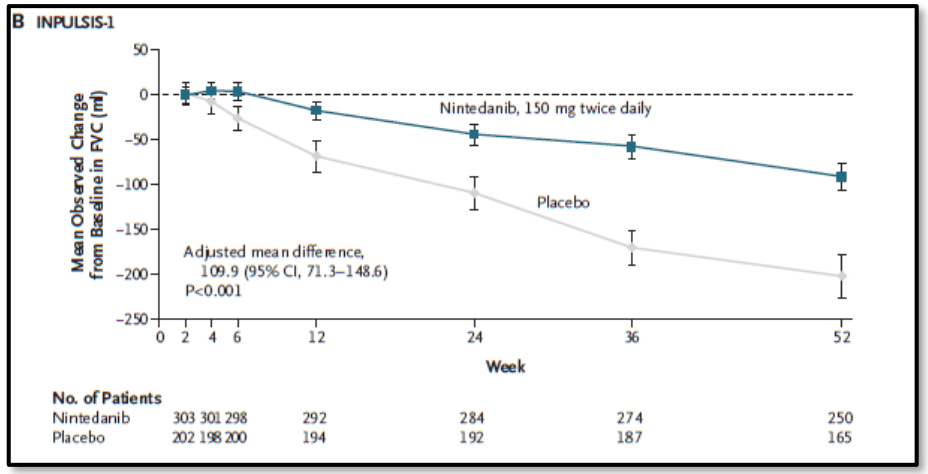
- SimPops patients include varying rates of change in fibroblastic foci and honeycombing regions
  - Respiratory measures (e.g., FVC) are dependent upon relative volumes of the functional zones
- Mixture of fast and slow progressors in SimPops (*untreated 1 yr, Pirfenidone treatment 1 yr*)
  - Reduction in progression rates with pirfenidone treatment consistent with Biondini et al.
  - Fast progressors have greater reduction in progression with treatment than Slow progressors
    - Fast progressors defined as ΔFVC≥10%; slow progressors defined as ΔFVC≤10%
  - Selected simulated patients displayed

Nintedanib Overview

Clinical

- Nintedanib, Ofev® (Boehringer Ingelheim), approved for treatment of IPF in US and several other countries
- Small molecule receptor tyrosine kinase inhibitor targeting PDGFR, FGFR, and VEGFR
- In IPF patients, nintedanib mitigated the decline in FVC (Richeldi 2014)
- Preclinical data provide evidence that nintedanib inhibits fibroblast proliferation and procollagen synthesis
  - Wollin 2014, Hostettler 2014, Rangarajan 2016, Knuppel 2017
- Less evidence exists for alternate mechanisms
  - Inhibition of fibroblast activation
  - Inhibition of collagen synthesis
  - Inhibition of fibrocyte accumulation

INPULSIS

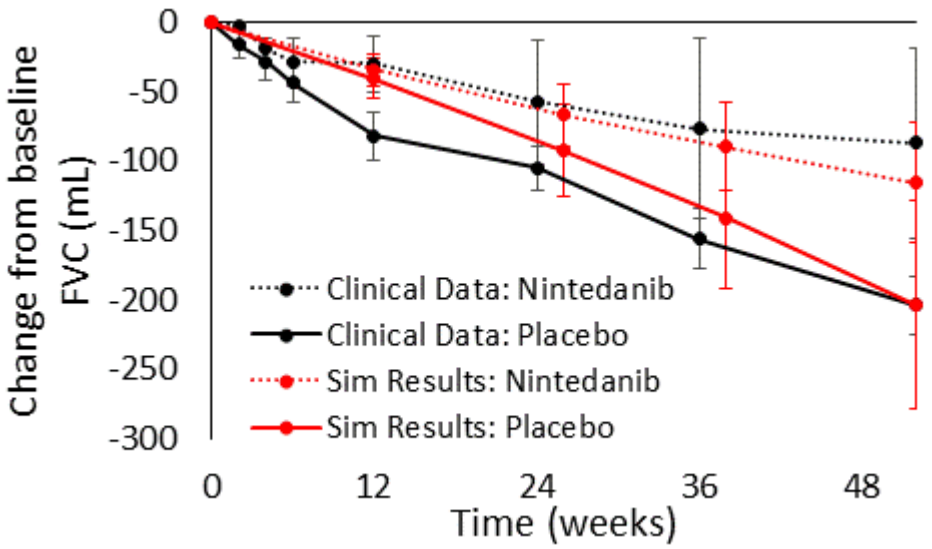


Richeldi 2014

Reasonable Simulation of Clinical Response to Nintedanib Treatment

Clinical

- SimPops patients (n=322) and clinical IPF patients were treated with 150 mg BID nintedanib for 52 weeks
- Simulated change in FVC on nintedanib treatment was comparable to clinical data
- Simulated change in FVC with placebo was comparable to clinical data

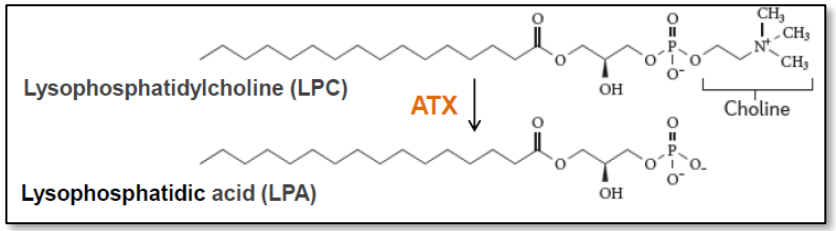


Richeldi 2014

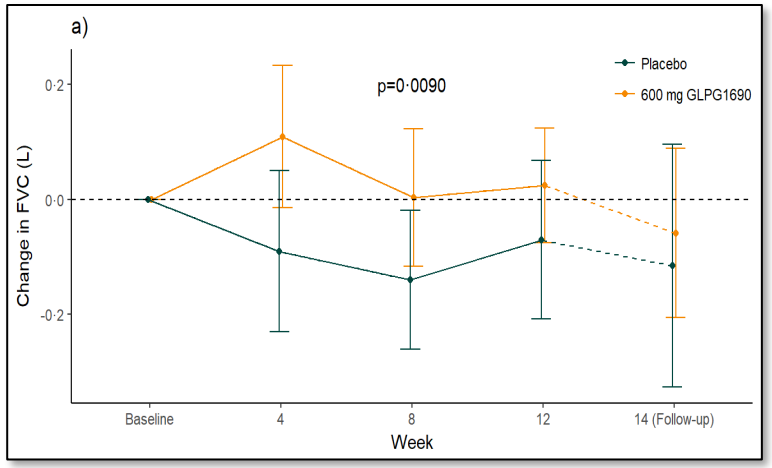
Brief Demonstration of IPFsym v1A Software

Autotaxin Inhibition Is Potential IPF Therapeutic Approach

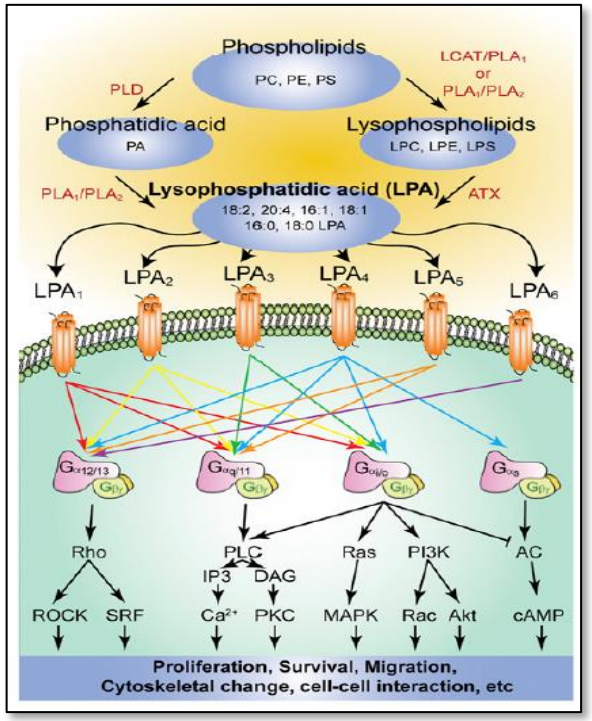
- LPA_1 receptor activation promotes pro-fibrotic processes, including the activation and proliferation of fibroblasts in lungs of IPF patients
  - LPA is substrate
  - Fibroblast proliferation
- Autotaxin (ATX) catalyzes the synthesis of LPA in circulation
- ATX inhibitor, GLPG1690 showed efficacy in Phase II clinical studies



van der Aar 2015

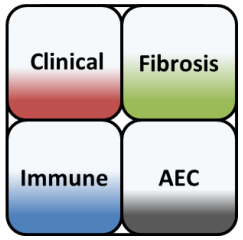


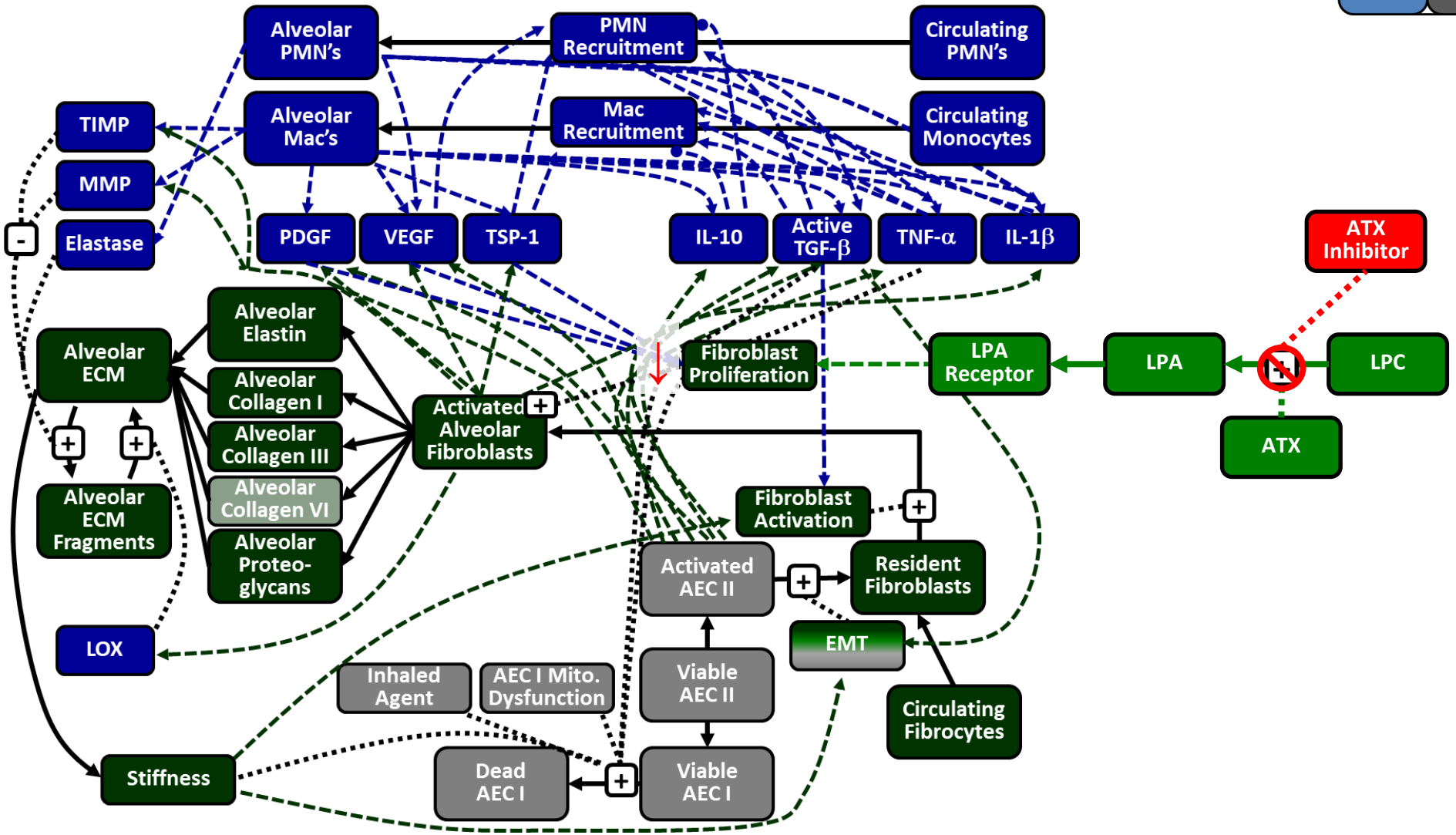
Maher 2018



Yung 2014

IPFsym Framework Allows Addition of New Targets and Compounds Example: Autotaxin Inhibitor





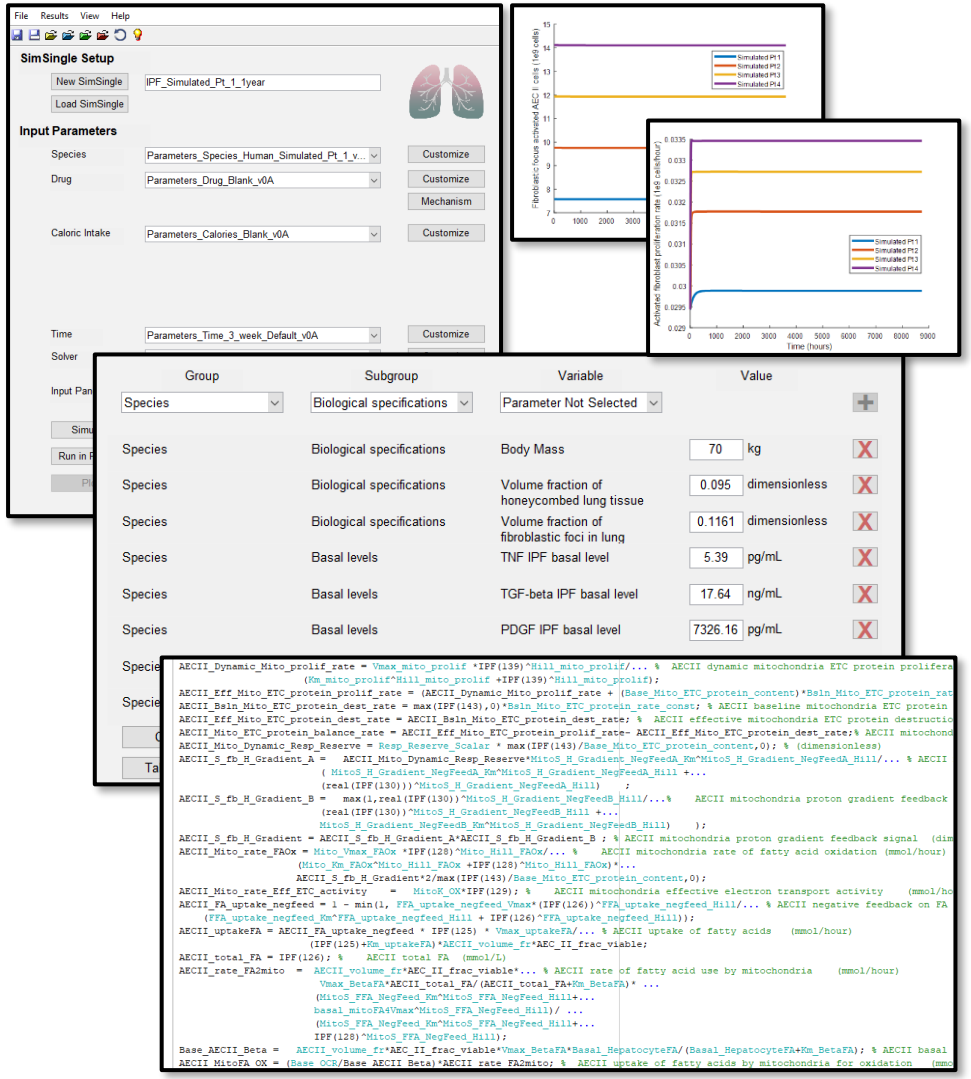
Agenda

- Introduction to DILIsym Services
- Overview of IPFsym v1A
- Simulating Treatment in IPFsym v1A
- IPFsym Licensing and Services
- Q & A

IPFsym v1A License Will Provide Opportunity to Actively Utilize QSP Model

- A license to IPFsym v1A will be $67,500 per year for 1 instance
  - Includes capabilities of predicting effects of treatments on fibrosis, inflammation, and epithelial cells of alveoli
  - Includes 10 hours of training
  - Local desktop installations only
  - No network shareable licenses
  - Must be renewed annually
  - Additional licenses can be made available at reduced, volume pricing

- Equations can be viewed by users
  - Can be modified to represent novel targets within IPFsym v1A
  - No original IPFsym v1A code can be ported out to other MATLAB files or languages without the permission of DILIsym Services



General Project Timeline and Deliverables

Stage I Project Activities
- Updates to IPFsym to represent IPF therapeutic strategies
- Represent Compound A PK and PD

Stage II Project Activities
- Simulations of Compound A prior studies in representative IPF patients
- Simulations of Compound A prior studies in IPF human SimCohorts

Stage III Project Activities
- Simulations of Compound A future clinical trial protocols in representative IPF patients
- Simulations of Compound A future clinical trial protocols in IPF human SimCohorts

Stage 1 | Stage 2 | Stage 3

Kickoff meeting → Milestone 1 meeting → Milestone 2 meeting → Milestone 3 meeting

Project costs are dependent upon required resources

Final Deliverables
- Final report summarizing findings shortly after project completion

Agenda

- Introduction to DILIsym Services
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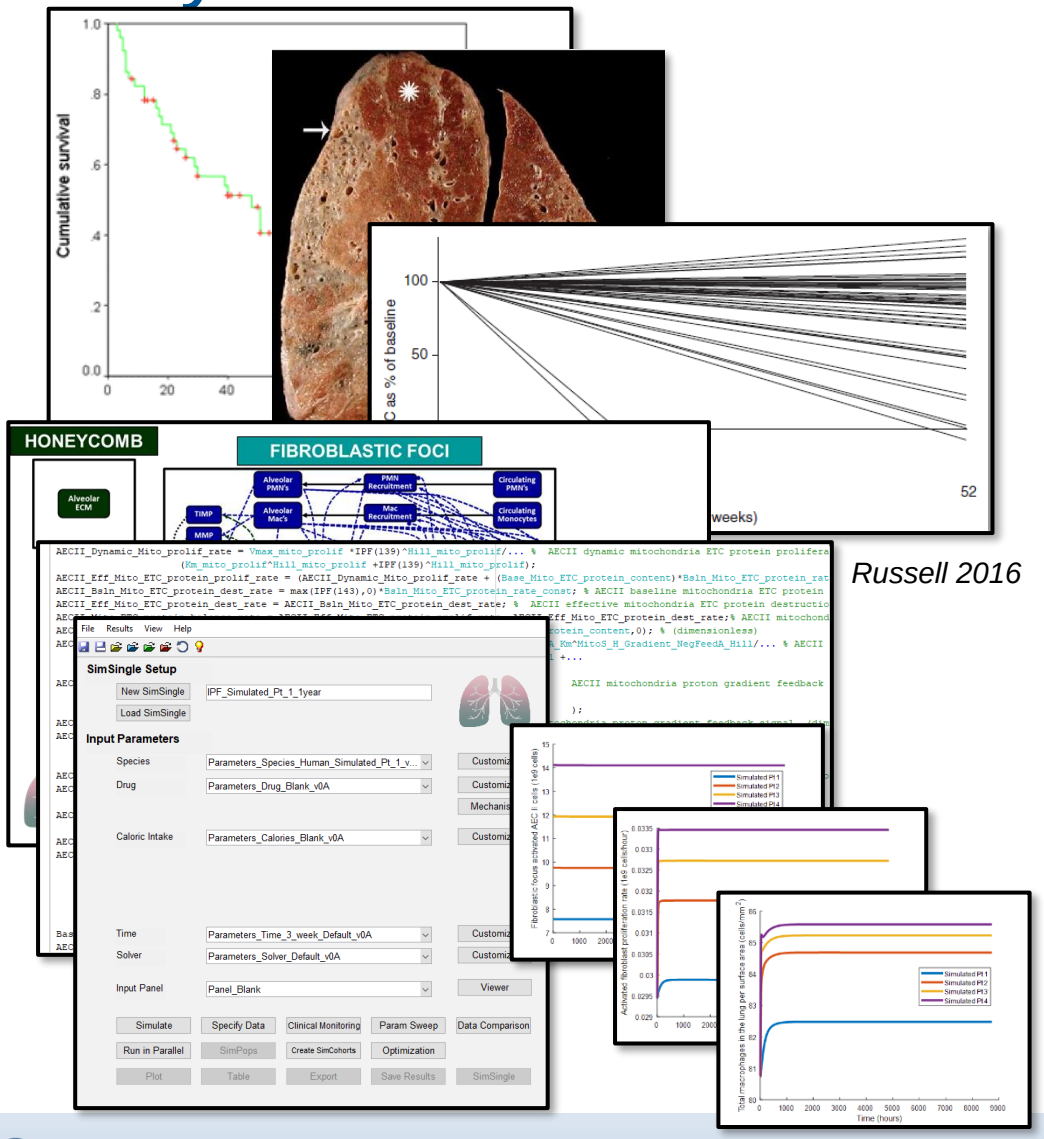
IPFsym Is Designed to Support Drug Development with Efficacy Predictions

- IPF afflicts elderly patients, with extremely high mortality rates following diagnosis
  - Substantial manifestation of pathophysiology before respiratory function is compromised enough to motivate diagnosis
- IPF is progressive disease
  - Respiratory function (e.g., FVC) declines over time
- IPFsym is a QSP model of IPF
  - Includes capabilities of predicting effects of treatments on fibrosis, inflammation, and epithelial cells of alveoli
  - Includes pathophysiologically diverse simulated patients in SimPops
  - IPFsym v1A to be released in Q1 2021
- IPFsym can be used to support IPF drug development
  - Combines PK, PD, pathophysiology to predict efficacy of novel treatments
  - Flexible framework facilitates addition of new targets as needed
  - Can be used to optimize clinical trial protocols and identify key hypotheses related to mechanistic underpinnings of predicted response to treatment
  - Provides ability to evaluate combinations of treatments with different mechanisms of action



Russell 2016