ILDsym®, a Quantitative Systems Pharmacology (QSP) Platform, Successfully Simulates the Pathophysiology of Systemic Sclerosis-Interstitial Lung Disease (SSc-ILD) and Inter-patient Variability

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ILDsym®, a Quantitative Systems Pharmacology (QSP) Platform, Successfully Simulates the Pathophysiology of Systemic Sclerosis-Interstitial Lung Disease (SSc-ILD) and Inter-patient Variability

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PURPOSE

Systemic sclerosis (SSc) is a rare connective tissue and autoimmune disease associated with inflammation of the skin and internal organs. Interstitial lung disease (ILD), a frequent complication of SSc, is associated with increased risk of morbidity and mortality [1]. The course of SSc-ILD is highly variable; some patients remain stable while others progress rapidly. The two current FDA-approved treatments for SSc-ILD patients, nintedanib and tocilizumab (TCZ), demonstrate efficacy but do not reverse disease [2]. Mechanistic, mathematical modeling approaches can support the development of new drug treatments by improving understanding of disease pathophysiology, identifying mechanistic drivers of SSc-ILD, interpreting clinical treatment results, and assessing efficacy for novel treatments as monotherapies or in combination with existing treatments.

OBJECTIVE

Develop mechanistic representation of SSc-ILD pathophysiology capable of representing responses to existing and novel treatments.

METHODS

ILDsym, a QSP model of SSc-ILD, was developed based on publicly available data. Applications combine predicted drug exposure in the lung with drug pharmacodynamic (PD)properties (mechanism of action) to modulate SSc-ILD pathophysiology and predict efficacy of novel therapeutics. To facilitate evaluating the effects of inter-individual patient variability on predicted treatment response, a simulated population (SimPops™) of SSc-ILD patients was generated reflecting variability in disease pathophysiology. Patients were screened by assessing simultaneous consistency with multiple clinical data sets, including lung function, disease extent, cell populations, biomarkers, and standards of care.

RESULTS

ILDsym dynamically captures changes to lung architecture, susceptibility to inflammation and/or fibrosis, and several key clinical outcome measures such as forced vital capacity (FVC) and diffusing capacity of the lung for carbon monoxide (DLCO). Over 700 simulated patients were generated to represent SSc-ILD patients at various stages of disease (mean ± standard deviation for baseline % predicted FVC and % predicted DLCO values of 74.3% ± 12.2% and 54.8% ± 19.1%, respectively), and the simulated patients span appropriate ranges of alveolar epithelial cells, endothelial cells, macrophages, and myofibroblasts, mediators and biomarkers in accordance with published data for SSc-ILD patients; a selection of these validation results are shown. Over a one-year simulation, lung function remains stable in some patients and declines in others, with average FVC losses of -0.142 ± 0.112 L/year. Simulated patients were sub-selected (i.e., SimCohorts generation) to match the baseline lung function characteristics of clinical patients in phase 3 trials for nintedanib [3] and TCZ [19]. Simulations of compound exposure and PD effects in SimCohorts resulted in lesser lung function decline and stabilized lung function, respectively, consistent with clinical data.

CONCLUSIONS

ILDsym is well-positioned to support SSc-ILD drug development by providing a dynamic representation of SSc-ILD disease progression. The flexible framework of ILDsym enables its use in exploring novel targets and therapies as needed. ILD SimPops capture expected clinical inter-patient variability and can be utilized to optimize clinical trial protocols, explore mechanistic hypotheses, and evaluate combination therapies in addition to monotherapies.

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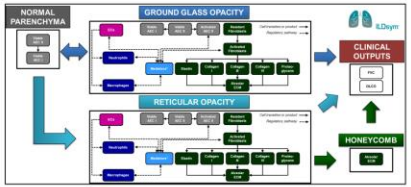
QSP model captures pathophysiology of SSc-ILD and inter-patient variability

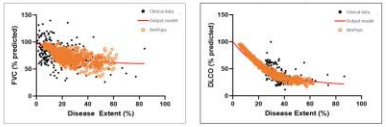
DIAGRAM OF NEWLY DEVELOPED QSP MODEL FOR SSc-ILD



SIMULATED POPULATION CAPTURES CLINICALLY REPORTED RELATIONSHIP BETWEEN DISEASE EXTENT AND CLINICAL OUTPUTS

Key clinical measured FVC and DLCO well-represented

- Baseline relationship developed (red line) captures trend between disease extent and clinical outputs
- SimPops patients (orange circles) designed to span range of clinical data (black circles) [17-18]
- % predicted defined as relative to normal level for person of same gender, height, and age

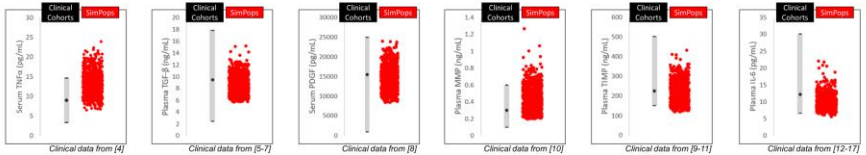


MEDIATOR LEVELS CONSISTENT WITH REPORTED SSc-ILD PATIENT VARIABILITY

Mediators and biomarkers calibrated to represent SSc-ILD patients

Simulated patients (n=780; red dots represent individual simulated patients) generally consistent with clinical data (range and mean indicated), simultaneously across all data comparisons

- Mediators shown demonstrate key inflammatory and fibrotic regulators; produced by various cell types which are also calibrated to align with clinical data

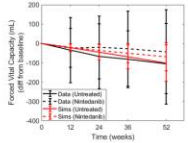


SIMULATED TREATMENT CONSISTENT WITH CLINICAL RESPONSE

Nintedanib treatment response captured by ILDsym

Simulated change in FVC with nintedanib treatment was comparable to clinical data

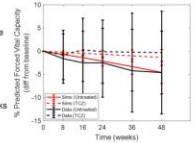
- Clinical untreated and nintedanib groups each composed of n=288 SSc-ILD patients [3]
- ILDsym SimCohorts (n=444) matched to inclusion/exclusion criteria of clinical SSc-ILD patients which were treated with 150 mg BID nintedanib for 52 weeks



Tocilizumab (TCZ) treatment response captured by ILDsym

Simulated change in FVC with TCZ treatment was comparable to intent-to-treat clinical data

- Clinical untreated (n=106) and TCZ (n=104) groups composed of SSc-ILD patients [19]
- ILDsym SimCohorts (n=114) matched to inclusion/exclusion criteria of clinical SSc-ILD patients which were treated with 162 mg SC QW TCZ for 48 weeks



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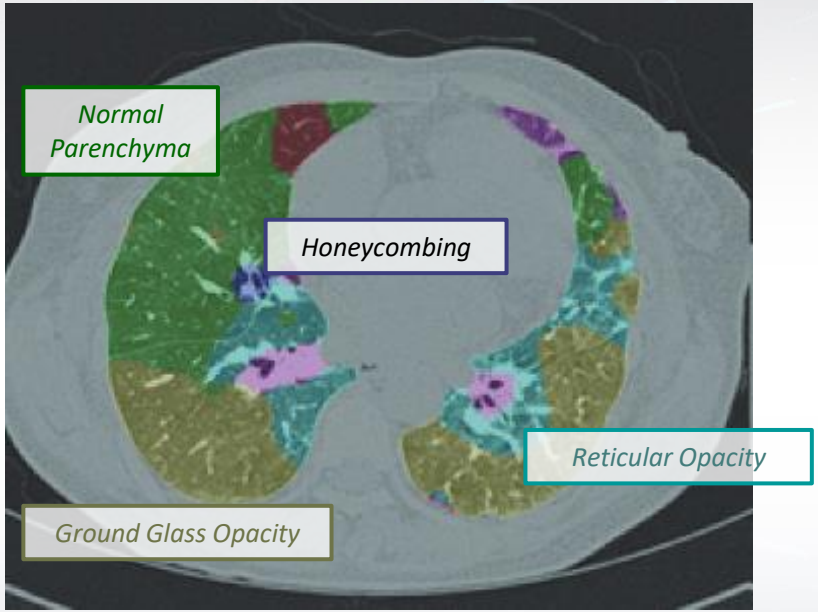
ILDsym Is Designed to Support Drug Development with Efficacy Predictions

- SSc-ILD often presents around age 55, proportionately higher in women, and has higher mortality rates in patients with greater fibrotic lung involvement
  - Often experience other systemic manifestation of pathophysiology before respiratory function is implicated
- ILD in SSc patients has variable course
  - Respiratory function (e.g., FVC) in some patients stable, others decline rapidly over time
- ILDsym is a QSP model of SSc-ILD
  - Includes capabilities of predicting effects of treatments on fibrosis, inflammation, endothelial cells, and epithelial cells of alveoli
  - Includes pathophysiologically diverse simulated patients in SimPops
  - ILDsym v1A available now
- ILDsym can be used to support SSc-ILD 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

Hold 2015

Distinct Functional Zones are Present in Lungs of ILD Patients

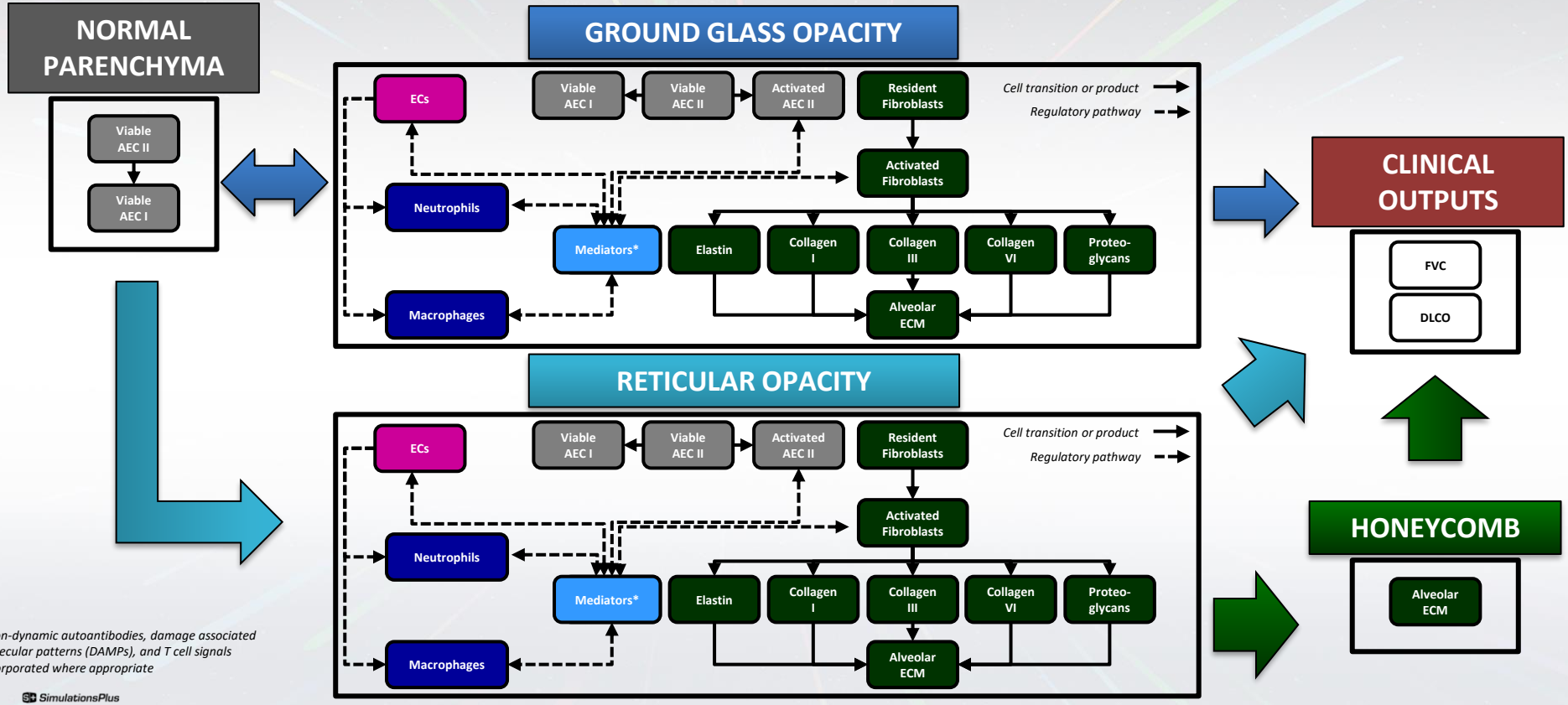
- **Normal parenchyma**
  - Unaffected alveoli
  - Primarily responsible for residual respiratory function
- **Ground Glass Opacity (GGO)**
  - Potentially sites of edema, inflammation, and fibrosis
  - Interstitial thickening due to inflammation and fibrosis
  - Immune response predominant
- **Reticular Opacity (RO)/Fibroblastic Foci (FF)**
  - 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
- **Honeycombing (HC)**
  - Collapsed, non-functional alveoli laden with fibrotic extracellular matrix (ECM) proteins
  - No contribution to respiratory function
  - Relatively rare in SSc-ILD patients



Color code
Normal, NL (green)
Ground-glass opacity, GGO (yellow)
Reticular opacity, RO (cyan)
Honeycombing, HC (blue)
Emphysema, EMPH (red)
Consolidation, CONS (pink)

Park 2011

ILDsym Summary Diagram



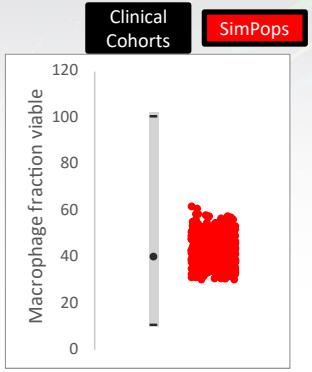
*Non-dynamic autoantibodies, damage associated molecular patterns (DAMPs), and T cell signals incorporated where appropriate

FVC: forced vital capacity
DLCO: diffusing capacity for carbon monoxide

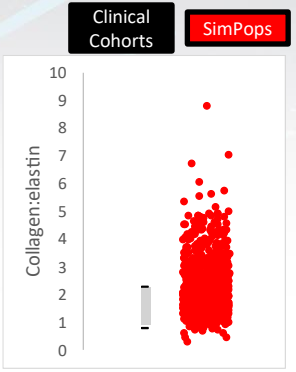
Simulated Immune and Fibrosis Levels for SimPops Compared to Clinical ILD Data

ILDsym

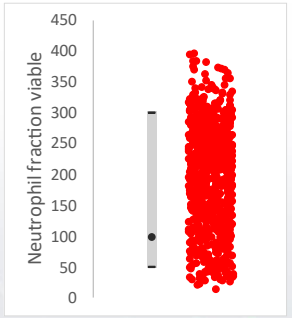
- SimPops patients (n=780) include varying degrees of ILD severity
- Simulated macrophage and neutrophil cell numbers generally near range observed
  - Macrophages and neutrophils quantified from UIP/IPF and NSIP (pattern most similar to GGO) data
  - Mean (•), minimum (-), maximum (-) plotted
- Simulated lung collagen:elastin ratio generally near range of clinical data
- Simulated endothelial mature cell fold changes within range guided by clinical data



Nuono 2019, Parra 2008, Yamashita 2018, Jonigk 2019



DeCarvalho 2008, Parra 2009, Rozin 2005, Parra 2007



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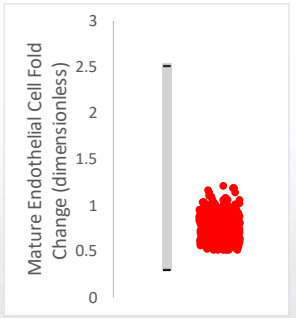

Beon 2004

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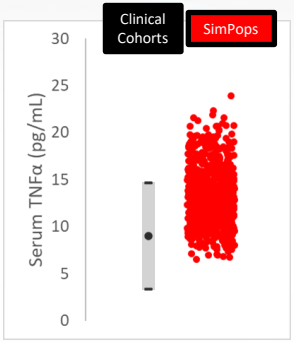
SimPops Mediator and Biomarker Levels Consistent with Clinical ILD Data Ranges (I)

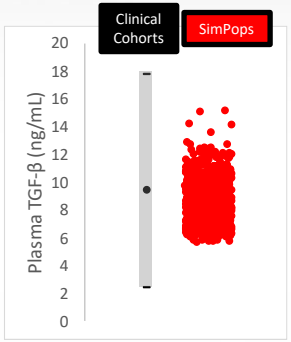
ILDsym

TNF-α



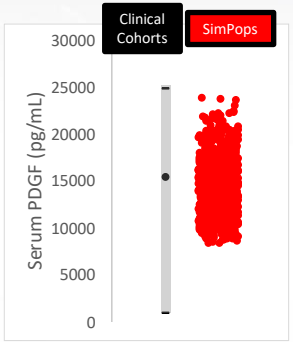
Mathai 2010

TGF-β



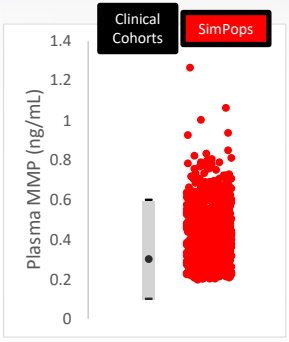
Dantas 2016, Dzaidzio 2005, Kuznik-Trocha 2020

PDGF



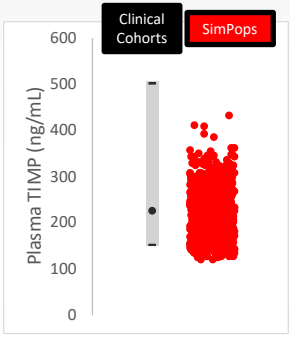
Hoffman-Vold 2019

MMP-1



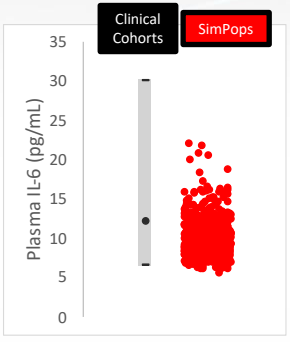
Young-Min 2001

TIMP



Kuznik-Trocha 2020, Montagana 2007, Young-Min 2001

IL-6



Gourh 2009, Wu 2017, De Lauretis 2013, Sato 2001, Clark 2019, Khan 2012, Matsushita 2006

- Simulated mediators and biomarkers from SimPops (n=780) generally consistent with clinical data
  - Mean (•), minimum (-), maximum (-) plotted
  - Clinical data come from variety of sources
  - Other mediators (IL-10, IL-1β, MMP-7, TSP-1, neutrophil elastase, LOX) and biomarkers (ProC3, C3M) also evaluated (not shown)

SimPops Mediator and Biomarker Levels Consistent with Clinical ILD Data Ranges (II)

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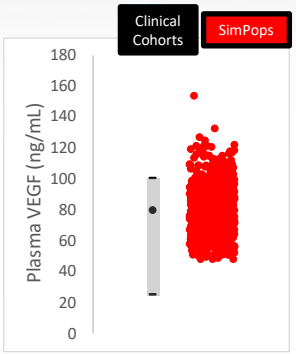
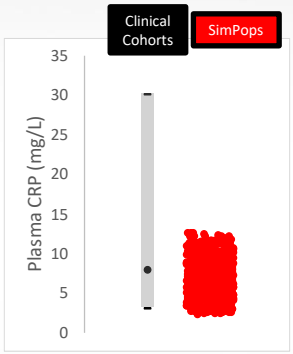
VEGF



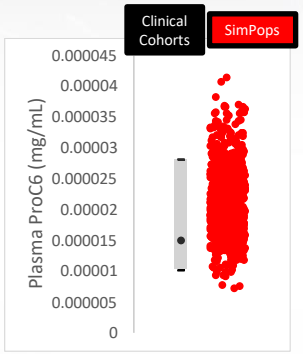
Hoffman-Vold 2019

CRP



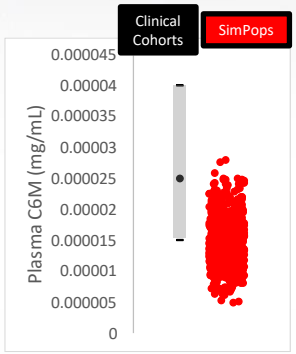
Khanna 2020, Kubo 2020, Apras 2003, Henes 2013, Schiopu 2014, Mitev 2009, Calguneri 2003, Scheja 2000

ProC6



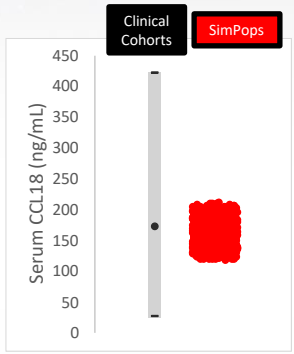
Juhl 2016

C6M



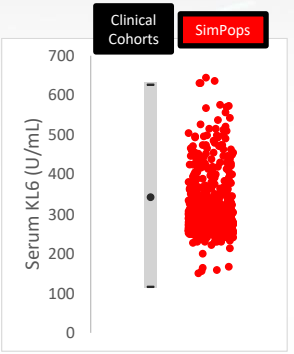
Juhl 2016

CCL18



Mathai 2010, Prasse 2007

KL-6



Benyamine 2018, Kumánovics 2014, Volkmann 2018, Yanaba 2004, Stock 2020, Hara 2009, Cao 2018, Hant 2009, Salazar 2018

- Simulated mediators and biomarkers from SimPops (n=780) generally consistent with clinical data
  - Mean (•), minimum (-), maximum (-) plotted
  - Clinical data come from variety of sources
  - Other mediators (IL-10, IL-1β, MMP-7, TSP-1, neutrophil elastase, LOX) and biomarkers (ProC3, C3M) also evaluated (not shown)

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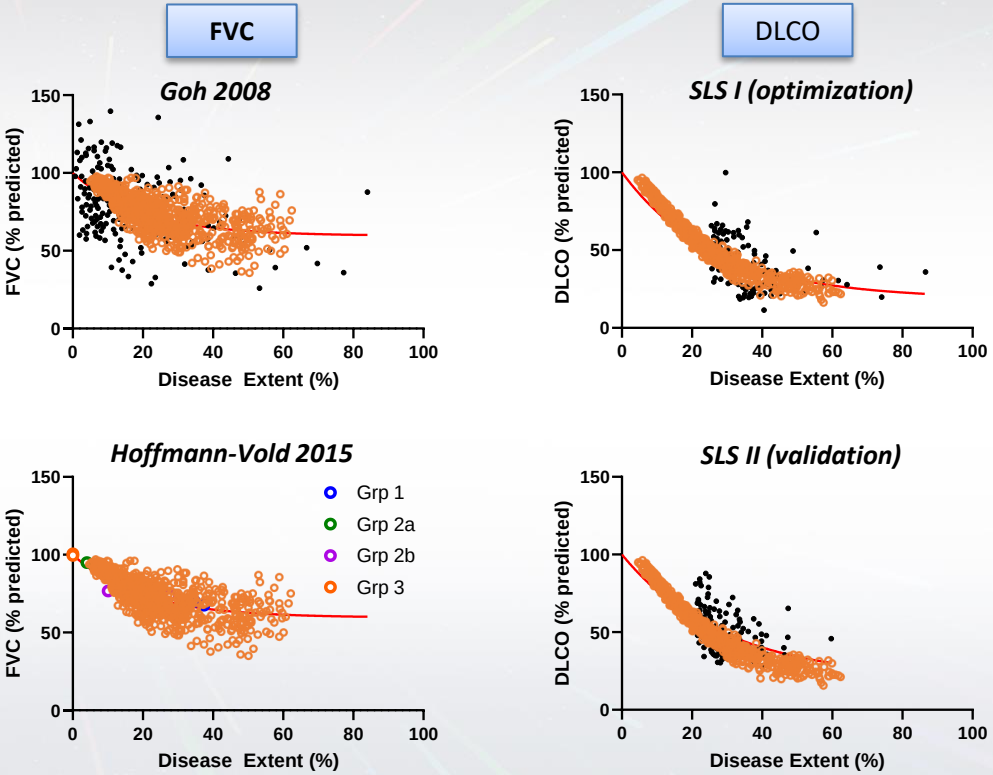
Simulated FVC across SimPops Consistent with Clinical Data

- SimPops patients (n=780) include varying degrees of ILD severity
  - Includes simulated patients early in progression
- Simulated FVC (% predicted) and DLCO (% predicted) consistent with range of reported clinical data
  - FVC and DLCO measurements compared with reference values for untreated patients of similar age, gender, size
  - FVC and DLCO are influenced by extent of GGO, RO, and honeycombing within lungs of SimPops patients (disease extent = GGO+RO+HC)
- ILDsym calibrated base model (red line) and SimPops individuals (orange circles) plotted



FVC: forced vital capacity
DLCO: diffusing capacity for carbon monoxide
SLS: scleroderma lung study

Multiple Available Treatments Have Been Represented in IPFsym and ILDsym

- IPFsym
  - Pirfenidone
  - Nintedanib
  - Multiple proprietary treatments/targets

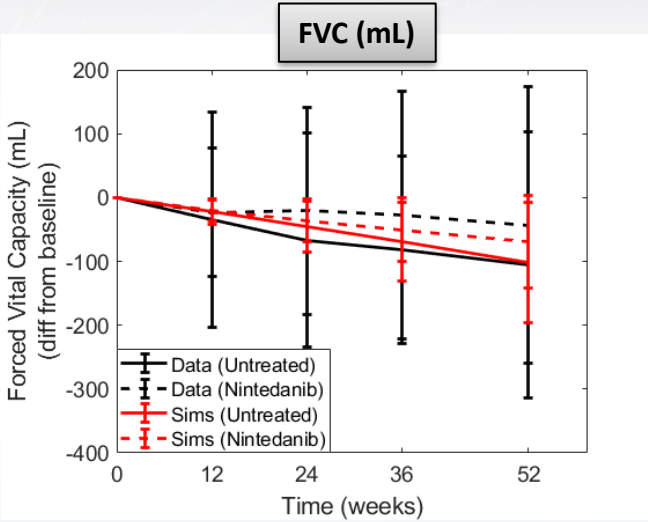
- **ILDsym**
  - **Nintedanib**
  - **Mycophenolate mofetil**
  - **Tocilizumab**
  - **Multiple proprietary treatments/targets**

- *GastroPlus used to simulate compound exposure at site of target*

- *IPFsym/ILDsym model used to simulate response to treatment in appropriate patient types (SimPops)*

Reasonable Simulation of Clinical Response to Nintedanib Treatment

- ILDsym SimCohorts patients (n=444) and clinical ILD patients were treated with 150 mg oral BID nintedanib for 52 weeks
  - Distler 2019 untreated and nintedanib groups each composed of n=288 patients
  - SimPops selected to match inclusion/exclusion criteria of study
- Simulated change in FVC on nintedanib treatment was comparable to clinical data
- Differences in simulations versus data potentially due to clinical trial structure
  - 48% of patients co-administered MMF; group examined separately and nintedanib shown to increase efficacy beyond MMF alone (not separately simulated)

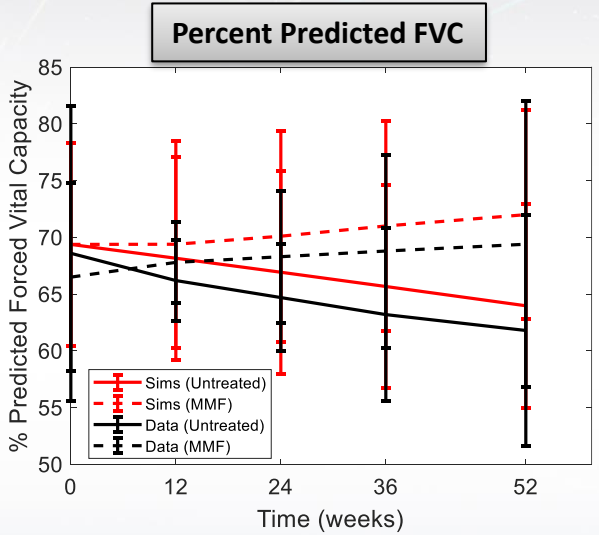


Distler 2019

Treatment Naïve

Reasonable Simulation of Clinical Response to MMF Treatment

- ILDsym SimCohorts patients (n=71) and clinical ILD patients were treated with 1500 mg oral BID MMF for 104 weeks
  - Assessed through 52 weeks as placebo group (n=79) demonstrated increase in percent predicted FVC increased in the 2nd year, as did the MMF group (n=69)
  - SimCohorts selected to match inclusion/exclusion criteria of study
- Simulated change in percent predicted FVC on MMF treatment generally matches clinical data
  - Data and simulations compared as changes in percent predicted FVC based on assessments of SLS I/II by Volkmann 2017
  - Difference in MMF simulated versus data due to modest offset in starting percent predicted FVC
    - Potential to add patients with more severe lung impairment in order to improve comparison

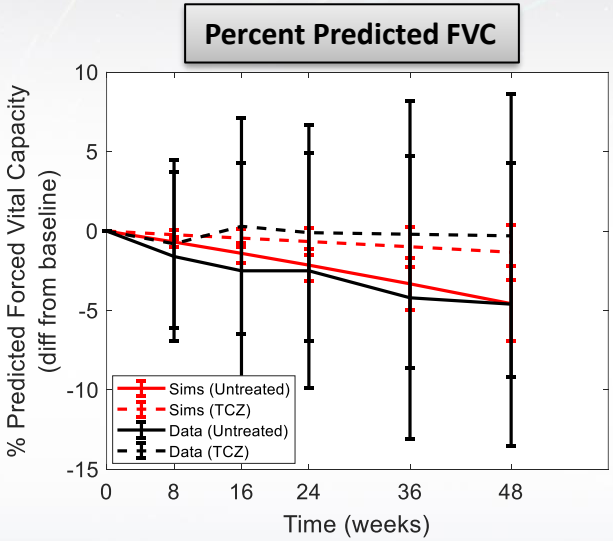


Volkmann 2017

Treatment Naïve

Reasonable Simulation of Clinical Response to TCZ Treatment

- SimCohorts patients (n=114) and clinical ILD patients were treated with 162 mg SC QW for 48 weeks
  - Compared with clinical ITT data, placebo group (n=106) and TCZ group (n=104)
  - SimCohorts selected to match inclusion/exclusion criteria of study
- Simulated change in percent predicted FVC on TCZ treatment is consistent with clinical data
  - Data and simulations compared as differences from baseline percent predicted FVC based on assessments in the focuSSced phase 3 trial reported by Khanna 2020
  - Potential to improve comparison through inclusion of additional patient variability



Khanna 2020

Acknowledgements and Future Directions

ILDsym development team

- Kyunghee Yang
- Christina Battista
- Diane Longo
- Zack Kenz
- Scott Siler
- Lisl Shoda

Future Directions

- ILDsym poised to evaluate novel targets for SSc-ILD
  - Potential to extend model to dynamically represent other organ (i.e., skin) pathophysiology
- Utilize model, with appropriate updates and recalibration, in other interstitial lung diseases