Developing Novel Treatments for Fibrotic Diseases

Fireside Chat
20th Annual Needham and Co. Healthcare Conference

April 13, 2021

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THERAPEUTICS

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Pliant – Company Highlights

Cutting Edge Science Focused on Large Markets

- Founded in 2015 by Third Rock Ventures, based in South San Francisco
- Utilizing breakthrough technology from UCSF with a focus on treating fibrosis
- Modulators of integrins and the TGF-β pathway with tissue-targeted antifibrotic activity
- Lead indications in IPF and PSC represent high unmet need

Leading Integrin Platform with Near Term, Potentially High-Impact Catalysts

- Integrin biology, chemistry and screening platform with a compound library of >9,000 integrin binders
- Two clinical-stage assets in four different indications
- Multiple data readouts beginning in the first half of 2021
- Phase 2a 12-week IPF and PSC trials evaluate early efficacy endpoints

De-Risking Pipeline Through Preclinical/ Clinical Tools and Strategic Partnership

- Live patient tissue assays, advanced PET and collagen imaging
- Strategic partnership with NOVARTIS
  - Validation of Pliant R&D platform
  - Significant expense offset to pipeline programs

Strong Financial Position

- Over $385 million raised in four financing rounds including June 2020 IPO
  - NASDAQ: PLRX
- $277 million cash balance as of December 31st, 2020
- Company funded into 2023

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Pliant Development Pipeline

	Program	Indication	Preclinical	Clinical			Anticipated Milestone	Global Rights
				Phase I	Phase II	Phase III		
WHOLLY OWNED	**PLN-74809** Dual selective inhibitor of $\alpha_V\beta_6/\alpha_V\beta_1$	Idiopathic Pulmonary Fibrosis					Phase 2a Data	PLIANT
		Primary Sclerosing Cholangitis					Phase 2a Data	PLIANT
		COVID-19 Related ARDS					Phase 2a Data	PLIANT
	Oncology Inhibitor of $\alpha_V\beta_8$	Solid Tumors					IND Filing	PLIANT
	Muscular Dystrophies Anti-integrin mAb	DMD Other Muscular Dystrophies					IND Filing	PLIANT
PARTNERED	**PLN-1474** Selective inhibitor of $\alpha_V\beta_1$	NASH-Associated Liver Fibrosis					Phase 2 Initiation	NOVARTIS

ARDS: Acute respiratory distress syndrome

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Phase 2a PET Trial – $\alpha_v\beta_6$ Expression Measured by a PET Ligand is Correlated with Extent of Fibrosis in IPF

PET Ligand Uptake Confined to IPF Lung in Unilateral Lung Transplant Patient

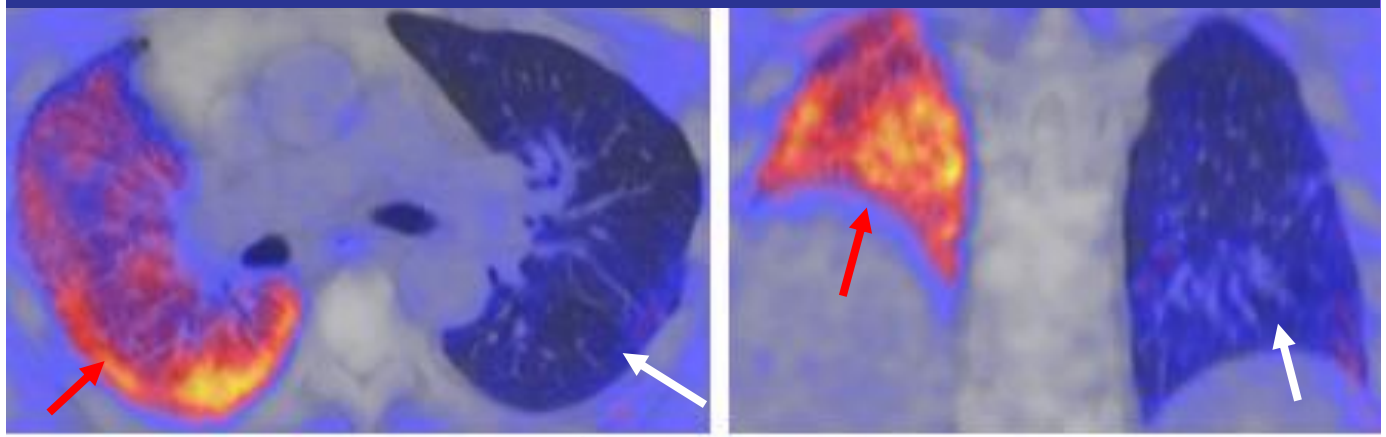
TRIAL DESIGN

- Single-site open-label trial at Stanford University
- Adults with IPF diagnosis (n=12) and FVC ≥ 45% of predicted
- Patients receive single oral dose of PLN-74809 with PET scans prior to dosing and at T_{max} post dose
- Ascending dose cohorts to be explored

ENDPOINTS

- **Primary**: Evaluation of $\alpha_v\beta_6$ receptor occupancy by PLN-74809 assessed by change in PET tracer uptake following a single oral dose
- **Secondary**: Assessment of safety and tolerability of PLN-74809 in IPF patients
- **Exploratory**: Relationship between PLN-74809 systemic exposure and positron emission tomography (PET) imaging and biomarkers in IPF participants

71-y/o ♂ left lung transplant 2yr prior to scan



Red arrows: IPF lung
White arrows: transplant lung

0 **SUV** **5.5**

Kimura et al., *Nature Com*. 2019

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PLN-74809-IPF-202 [INTEGRIS-IPF]
Phase 2a Global Safety-PK-Exploratory Efficacy Trial in IPF

Key inclusion/exclusion criteria

- Adults with IPF diagnosis
- FVC ≥ 45% of predicted
- Stratified for pirfenidone or nintedanib use

Randomization 3:1 (PLN-74809:placebo)

- Placebo (n=21)
- PLN-74809 40 mg (n=21)
- PLN-74809 80 mg (n=21)
- PLN-74809 160 mg (n=21)

Primary and secondary endpoints

- Safety, tolerability, PK

Exploratory endpoints

- Change in FVC over 12 weeks
- High Resolution CT-based Quantitative Lung Fibrosis (QLF) imaging
- Effect on selected biomarkers

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Additional References

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The Pliant Team
Highly Experienced in Fibrosis and Drug Development

Core Team

Bernard Coulie, M.D., Ph.D., M.B.A.
President, CEO, and Director

Hans Hull, J.D.
Chief Business Officer

Éric Lefebvre, M.D.
Chief Medical Officer

Keith Cummings, M.D., M.B.A.
Chief Financial Officer

Greg Cosgrove, M.D., FCCP
Vice President, Clinical Development (IPF)

Scott Turner, Ph.D.
Vice President, Biology & Translational Sciences

Founders

Dean Sheppard, M.D.
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William DeGrado, Ph.D.
Professor of Pharmaceutical Chemistry

Rik Derynck, Ph.D.
Professor, Cell and Tissue Biology, Co-Director of the Eli and Edythe Broad Center of Regeneration Medicine and Stem Cell Research

Harold Chapman, M.D.
Professor of Medicine, Division of Pulmonary, Critical Care, Allergy and Sleep

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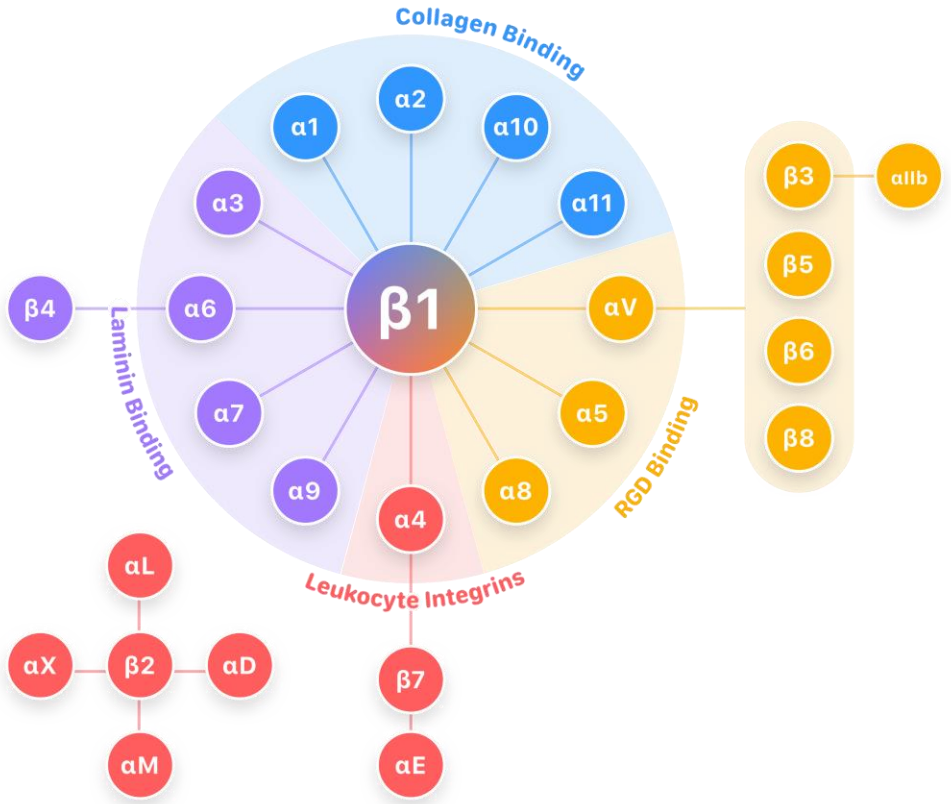
Pliant's Integrin Focused Library
Core Platform for Novel Pipeline and Partner Programs



Expanded library of >9,000 compounds

- Emphasis on structural diversity
- Expands beyond α_V integrins including collagen binders

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Global License & Collaboration Agreement

NOVARTIS

Collaboration Overview

- Global license on PLN-1474
- Collaboration on three additional integrin targets

Deal Terms

- **$80 million up-front**, including $50 million license fee and $30 million equity[1]
- Full reimbursement of R&D
- **$416 million** of total potential milestones ($25 million received to date)
- Mid-single digit to low teens tiered royalties on product sales

Key Points

- Research collaboration validates Pliant's powerful integrin development platform
- Remainder of wholly-owned pipeline remains unencumbered

1 – Included $20 million investment in Series C and $10 million investment in concurrent private placement.

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Integrin-mediated TGF-β Activation Plays a Crucial Role in Fibrosis

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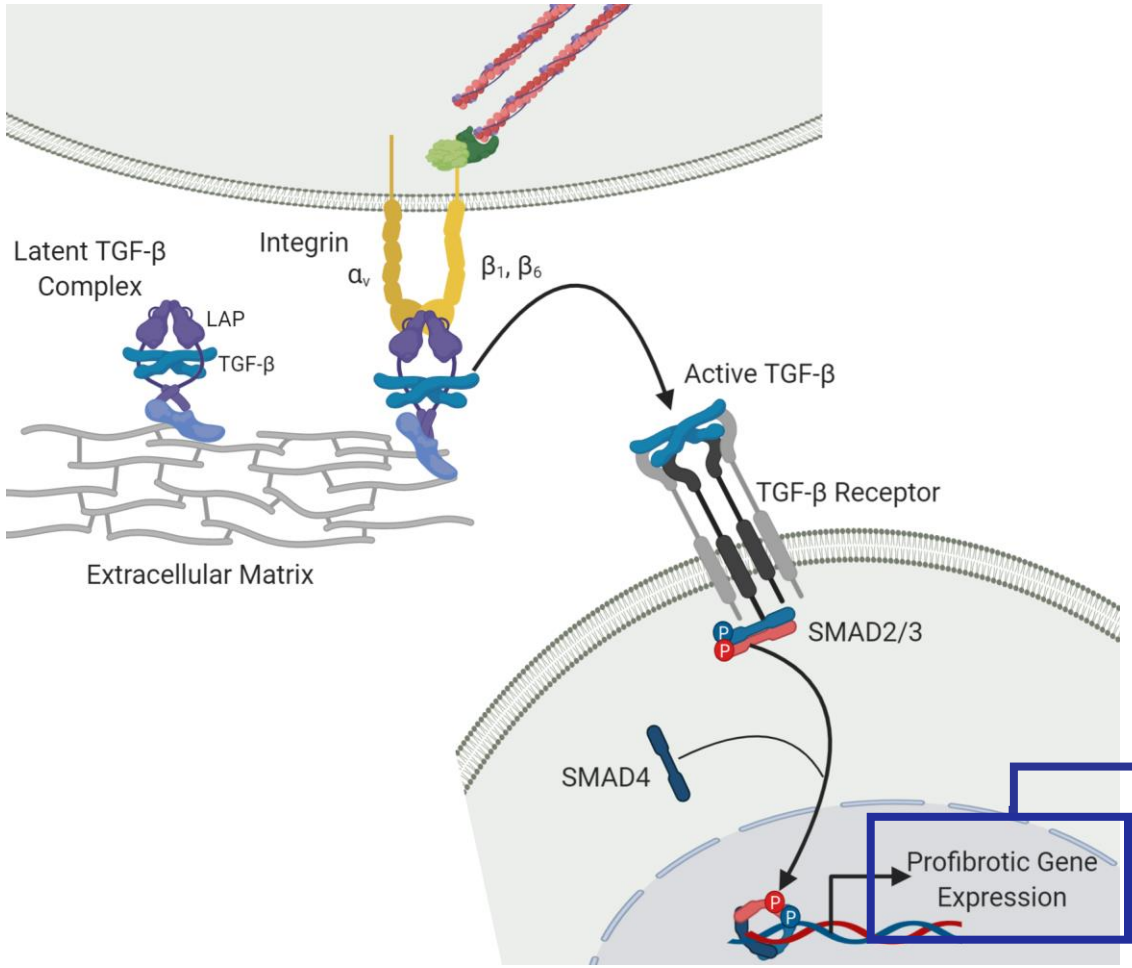
$\alpha_v\beta_6$ / $\alpha_v\beta_1$ Integrins Drive Cell-Matrix Interactions in Fibrosis

$\alpha_v\beta_6$ / $\alpha_v\beta_1$ Integrins promote fibrosis by TGF-β activation

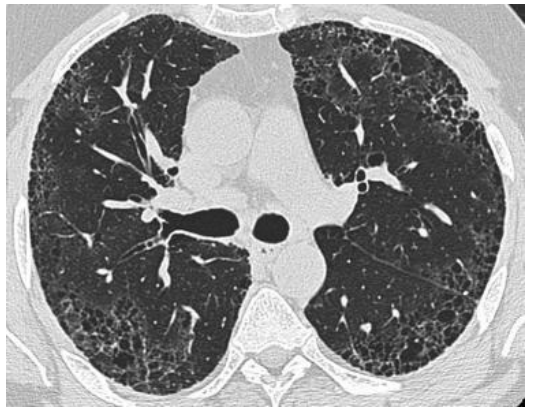


- TGF-β is central mediator of fibrosis
- $\alpha_v\beta_6$ /$\alpha_v\beta_1$ Integrins activate latent TGF-β only in fibrotic tissue
- Systemic TGF-β blockade carries toxicity risks

Selectively blocking TGF-β in fibrotic tissues may provide a low risk, effective antifibrotic approach

Col1a1
Col3a1
Timp1
CTGF
ATX
…

FIBROSIS



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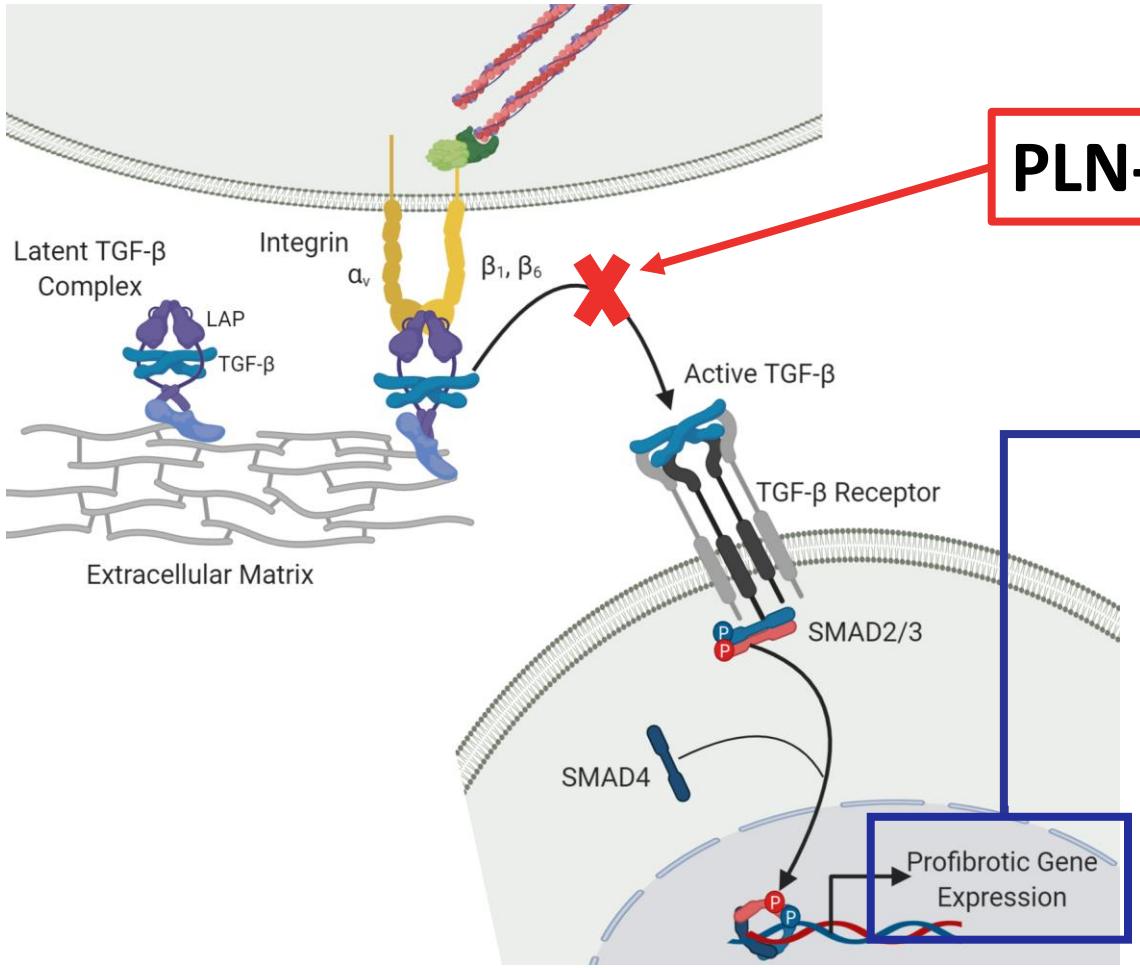
PLN-74809 Provides Profound Antifibrotic Activity through Upstream Inhibition of TGF-β Activation

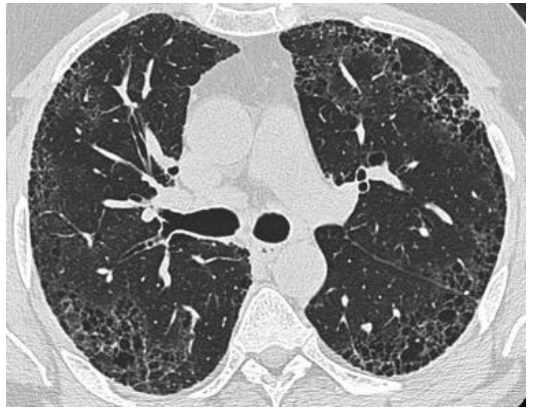


PLN-74809

Pamrevlumab

- Col1a1
- Col3a1
- Timp1
- CTGF
- ATX
- …

FIBROSIS



Upstream inhibition of TGF-β leads to reduction of multiple profibrotic genes

Competitor programs only block one of multiple profibrotic gene products

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Pliant Compounds Have Not Shown Adverse Effects of Systemic Inhibition of TGF-β Pathways

By targeting integrins that are upregulated specifically in fibrotic tissues, Pliant's small molecule compounds may avoid toxicities associated with systemic TGF-β blockade*

Affected Organ System	Systemic TGF-β Blockade	Observed with Pliant Compounds?
Cardiovascular System	Cardiotoxicity	No
Immune System	Autoimmunity/Inflammation	No
GI System	Autoimmunity/Inflammation	No
Skin	Keratoacanthomas/SCC	No
Hematology	Thrombocytopenia/Anemia	No

* Based on preclinical GLP tox studies

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PLN-74809
A Dual Selective $\alpha_v\beta_6/\alpha_v\beta_1$ Inhibitor for the Treatment of IPF and PSC

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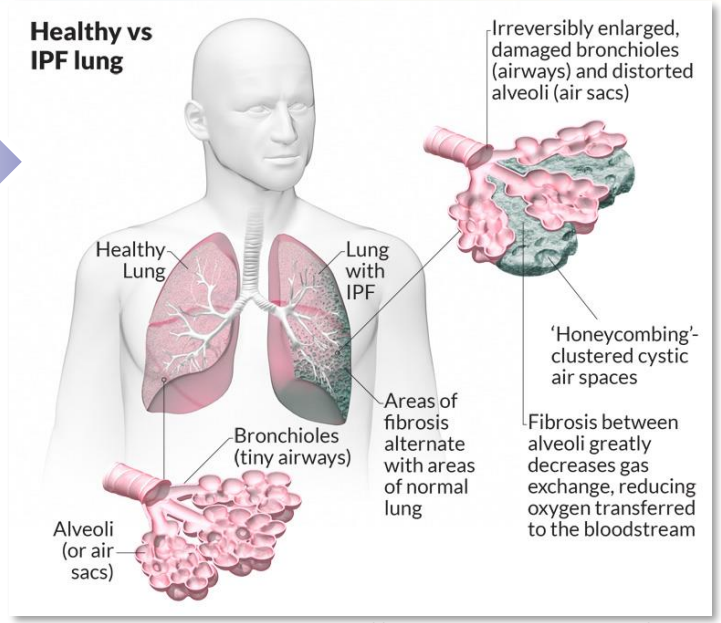
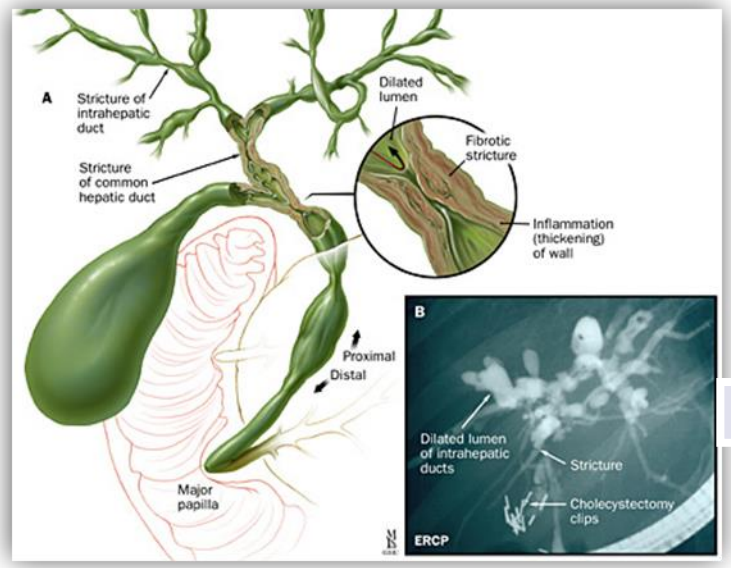
Fibrosis, the Silent Killer

Idiopathic Pulmonary Fibrosis (IPF) is a lethal pathological process with limited therapeutic options

- 140k patients in the U.S.; 30k-40k new cases/yr; 40k deaths/yr
- **Median survival: 3–5 years** - Worse than some common cancers
- 2 FDA approved therapeutics generate **annual revenues >$2.7 billion** despite remaining unmet medical need



https://www.lungsandyou.com/ipf



www.jhmicall.org

Primary Sclerosing Cholangitis (PSC) is a progressive inflammatory liver disease resulting in scarring of bile ducts, and cirrhosis

- Currently **no FDA approved therapeutics**
- 30k-45k patients in the U.S.
- **Median survival: 10-12 years** without intervention

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PLN-74809 – Dual Selective $\alpha_v\beta_6$ /$\alpha_v\beta_1$ Inhibitor

Key Drug-like Properties

- **Favorable tolerability and PK profile**
- Good oral bio-availability and long half life – **potential once-daily dosing**
- **No treatment related effects** in 13-wk GLP tox – NOAEL set at highest dose

Multiple Target Indications

- **Profound antifibrotic effect in live patient tissue explants:**
  - Lung (IPF, Systemic Sclerosis), and liver (PSC, PBC) tissues

Reduced Development Risk Profile

- Human biological proof-of-mechanism established: **reduction of alveolar pSMAD**
- Phase 2a study in IPF: $\alpha_v\beta_6$ PET ligand evaluating **target engagement**

Development Status

- **Phase 2a trials in IPF, PSC and COVID-19 related ARDS enrolling**
- **Orphan Drug Designation** for IPF and PSC granted

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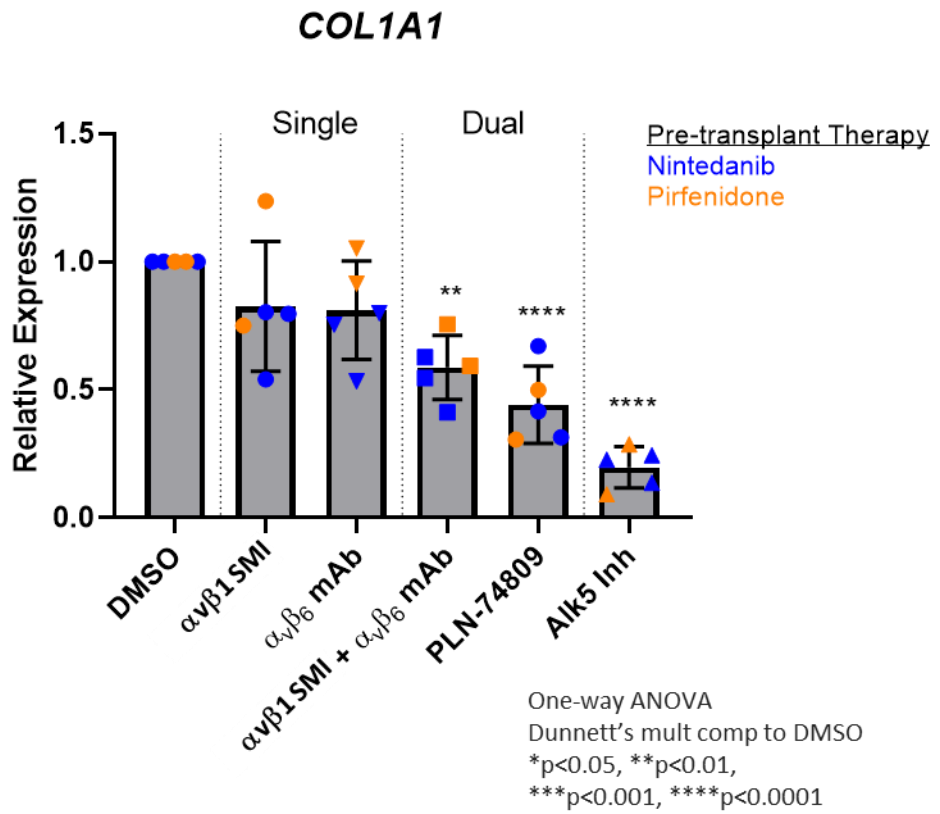
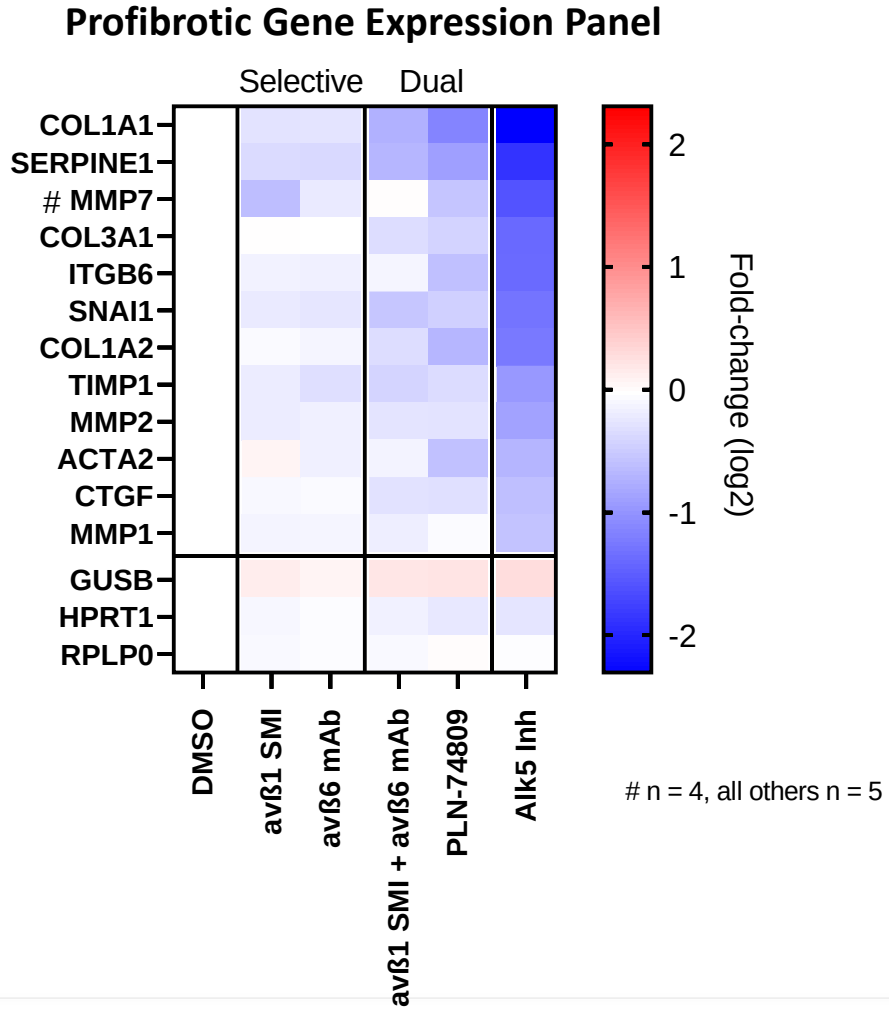
Dual $\alpha_v\beta_6/\alpha_v\beta_1$ Inhibition Blocks COL1A1 Gene Expression More than Single Inhibition in Human IPF Tissue

- **Ex-planted lungs from 5 IPF patients**
- **Sliced and cultured for 7 days**



One-way ANOVA
Dunnett's mult comp to DMSO
*p<0.05, **p<0.01,
***p<0.001, ****p<0.0001



n = 4, all others n = 5

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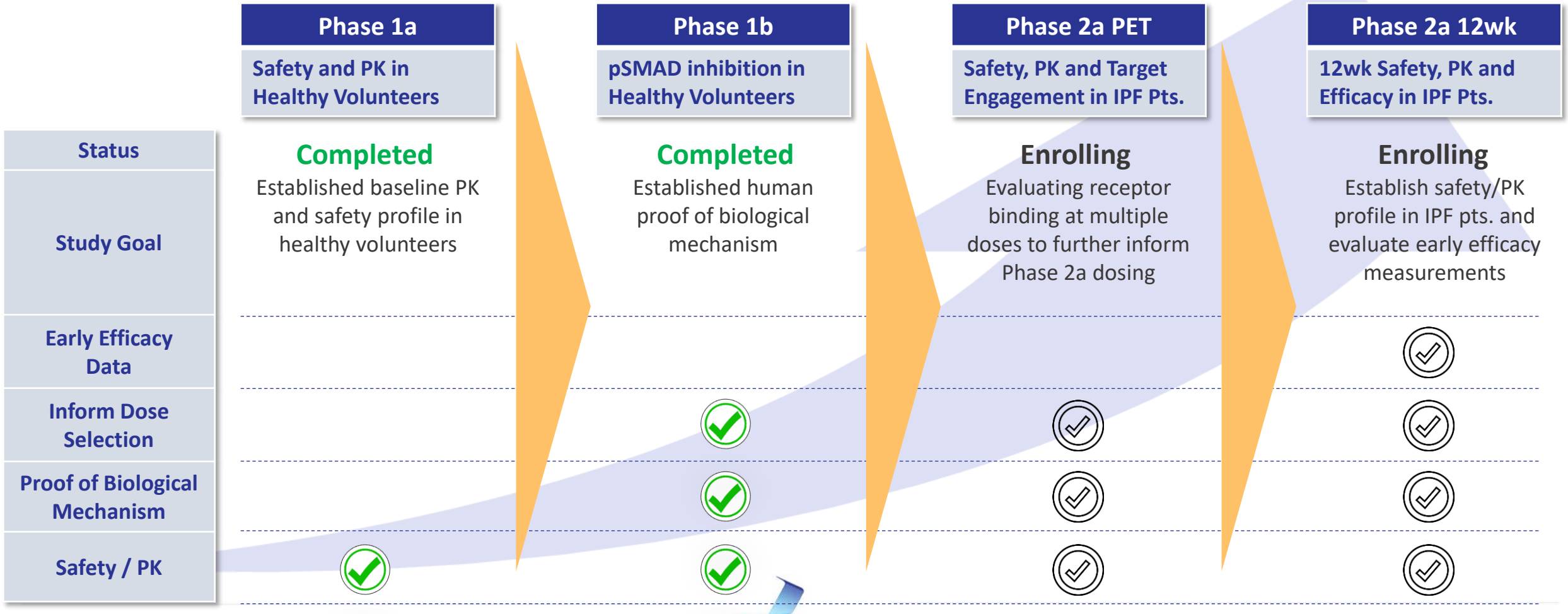
PLN-74809 – Rational Clinical Development in IPF
Step-by-Step De-risking

Maximize Phase 2b POS Through Intelligent Early Trial Design



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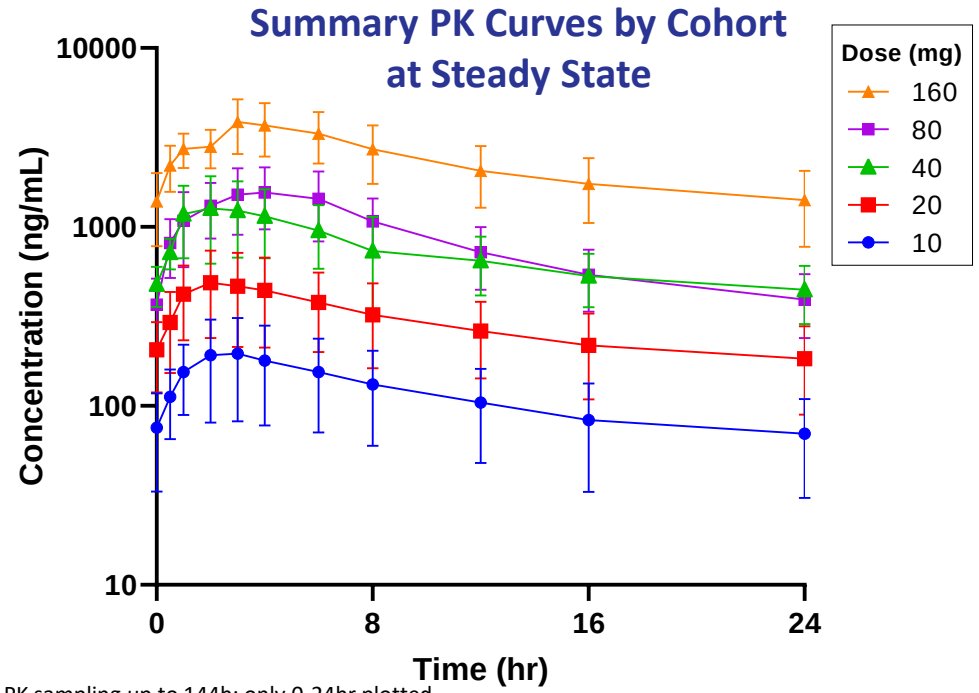
PLN-74809 – Extended Phase 1a Data Summary

Pharmacokinetics

- Well absorbed, orally bio-available
- Long $T_{1/2}$: ~50 hrs – QD dosing



PK sampling up to 144h; only 0-24hr plotted.
Doses 10mg to 40mg from Study PLN-74809-P1-01, Day 14
Doses 80mg and 160mg from Study PLN-74809-104, Day 7

Safety

- Administered to over 180 healthy volunteers to date
- Generally well tolerated
- Most frequently reported AEs were headache and constipation with no drug-related severe AEs reported

Safety Summary (Participants with drug-related TEAEs)

AE Severity	Multiple Ascending QD Doses				
	10 mg (N=9)	20 mg (N=9)	40 mg (N=9)	80 mg (N=8)	160 mg (N=16)
Mild	--	11%	--	13%	19%
Moderate	--	--	--	25%	6%
Severe	--	--	--	--	--

* Excludes AEs reported in fewer than 2% of participants

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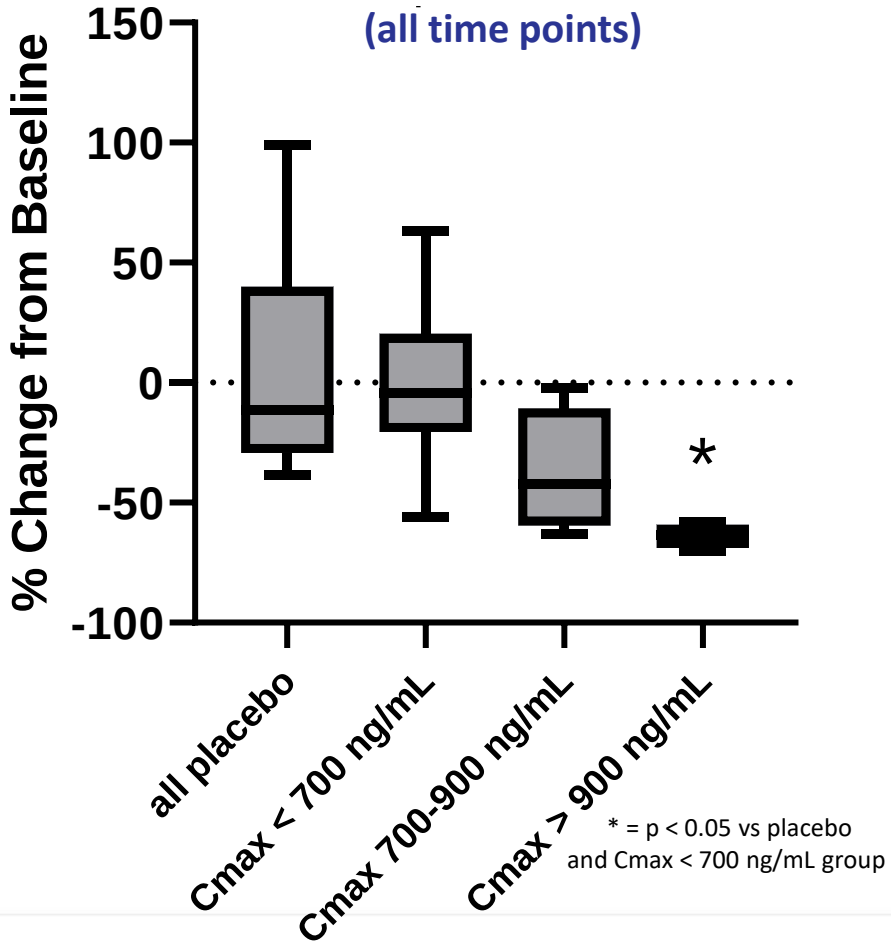
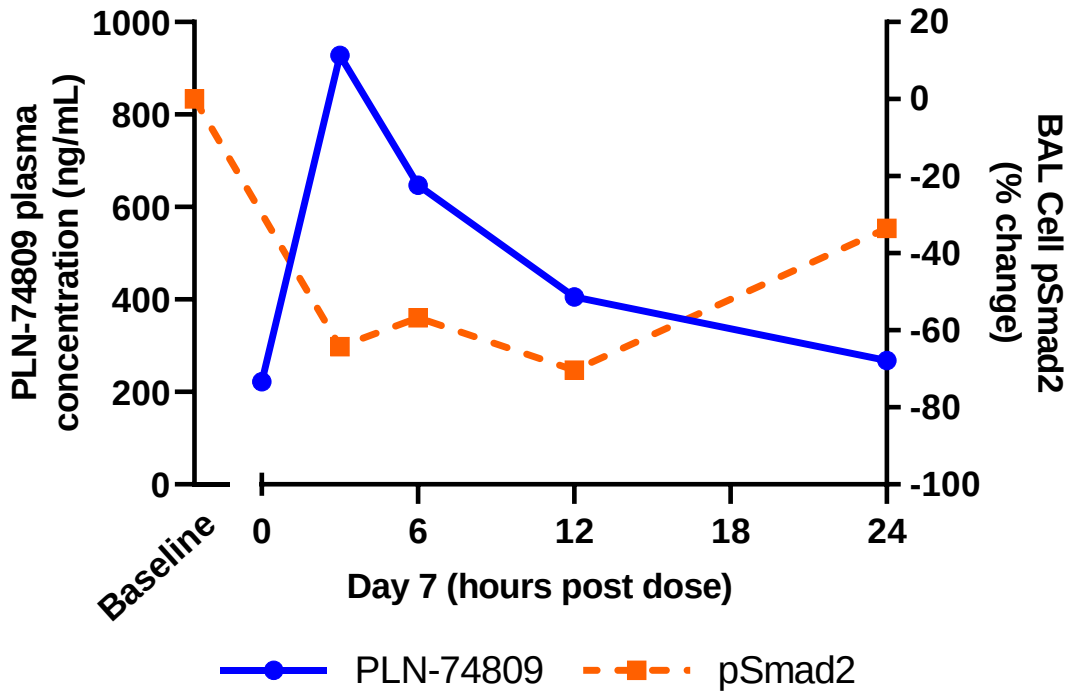
PLN-74809 – Phase 1b Proof of Biological Mechanism

Strong PK/PD Relationship – C_{max} above IC_{60} Results in Predicted Biological Effect

Alveolar pSMAD2/SMAD2 (all time points)



Mean PK/PD Response in Subjects with Cmax > 700ng/mL



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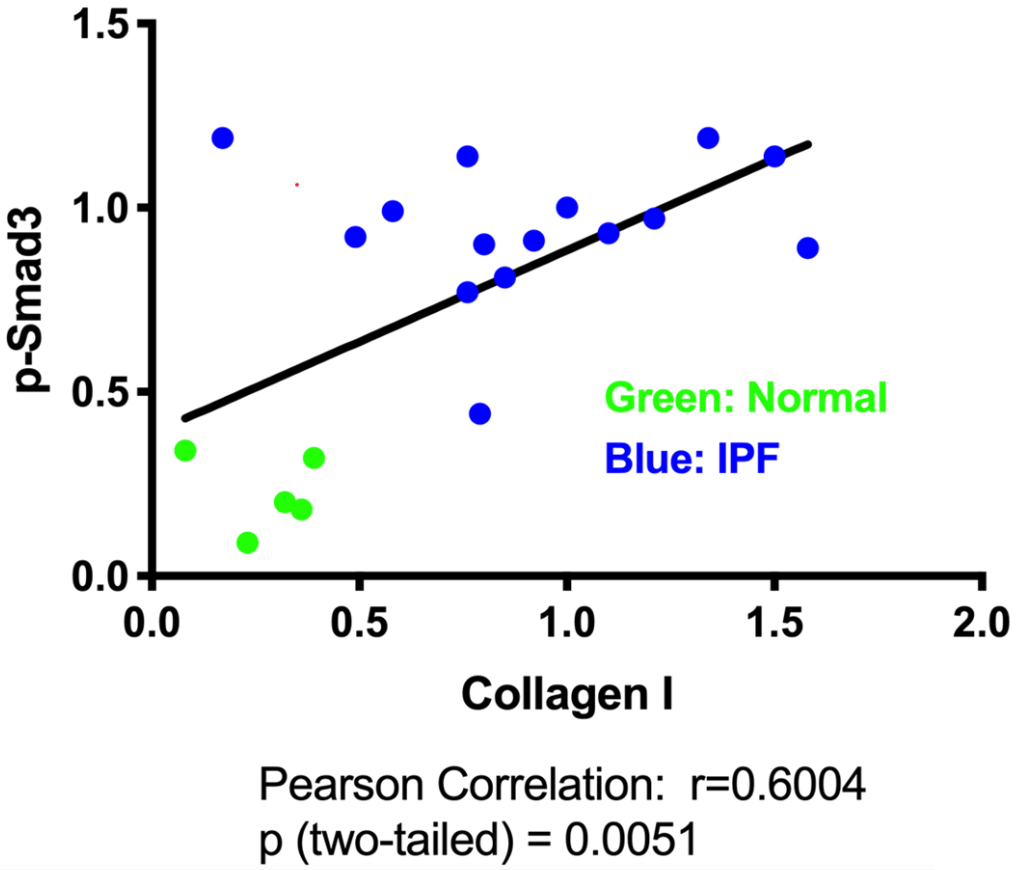
Tissue pSMAD Levels Are Highly Significantly Correlated with Extractable Collagen Levels in Normal and Fibrotic Lungs

Reduction in Pulmonary pSMAD Appears to Be a Marker for Reduction of Fibrosis



- Diagnostic open lung biopsies from 9 patients with ILD and suspected IPF
- 2-3 distinct lung regions sampled from each patient
- 5 controls (non-transplanted lungs)
- Total pSMAD3 had a strong correlation vs. extractable Collagen I (Western Blot)

Adapted from Chapman HA et al. March 12, 2020; 382:1068-1070

The NEW ENGLAND JOURNAL of MEDICINE

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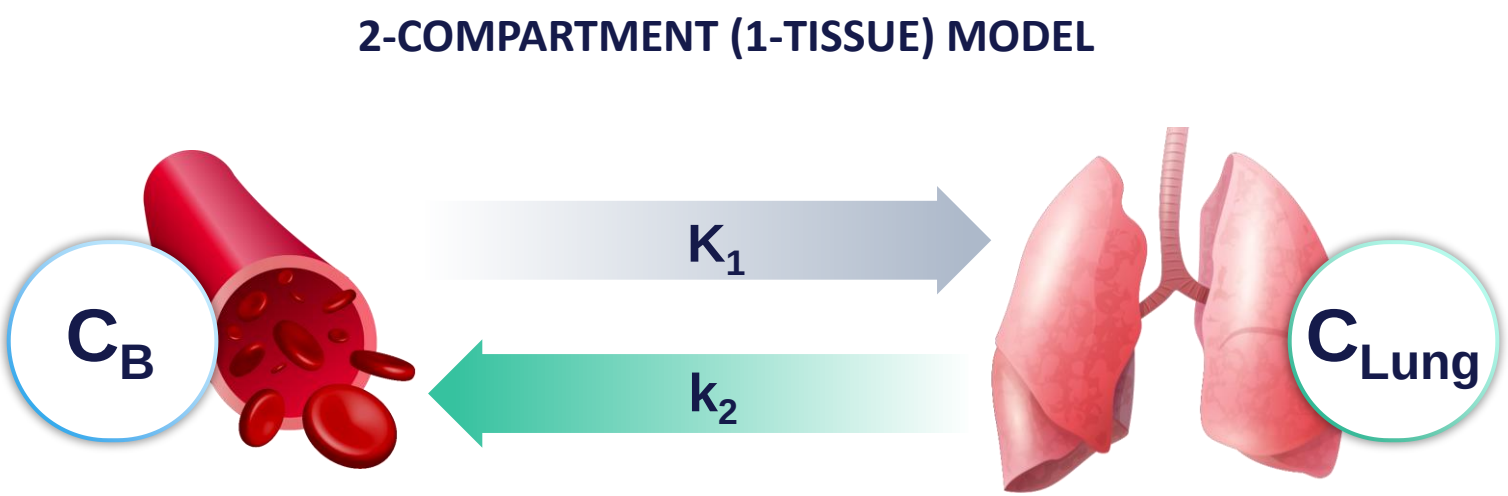
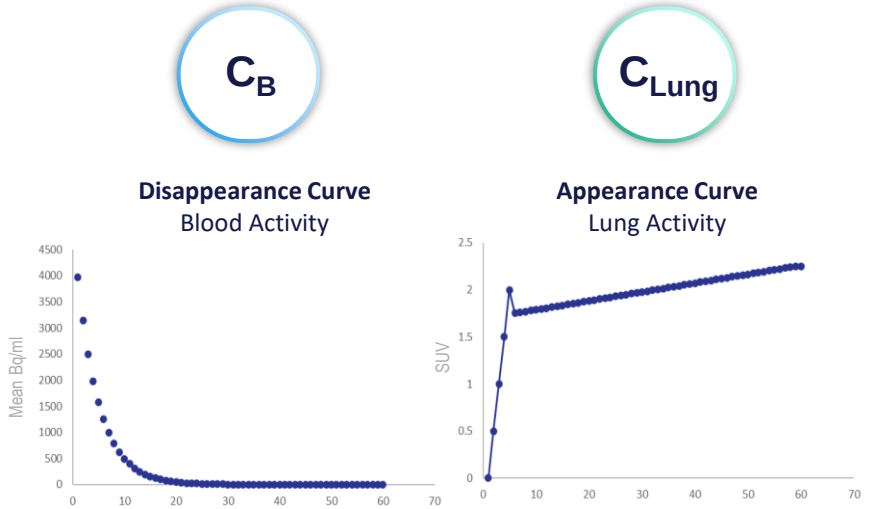
Dynamic PET Quantifies the Total Amount of Tracer Binding [V_t] to $\alpha_v\beta_6$





Illustrative Model

- K_1 represents influx of PET tracer moving into the lung
- k_2 represents the efflux of tracer leaving the lung

- K_1/k_2 ratio is equal the volume of distribution (V_t) which is the total amount of tracer binding in the lung

- Change in V_t from baseline to post-dose PET scan indicates degree of target engagement of PLN-74809 in the lung

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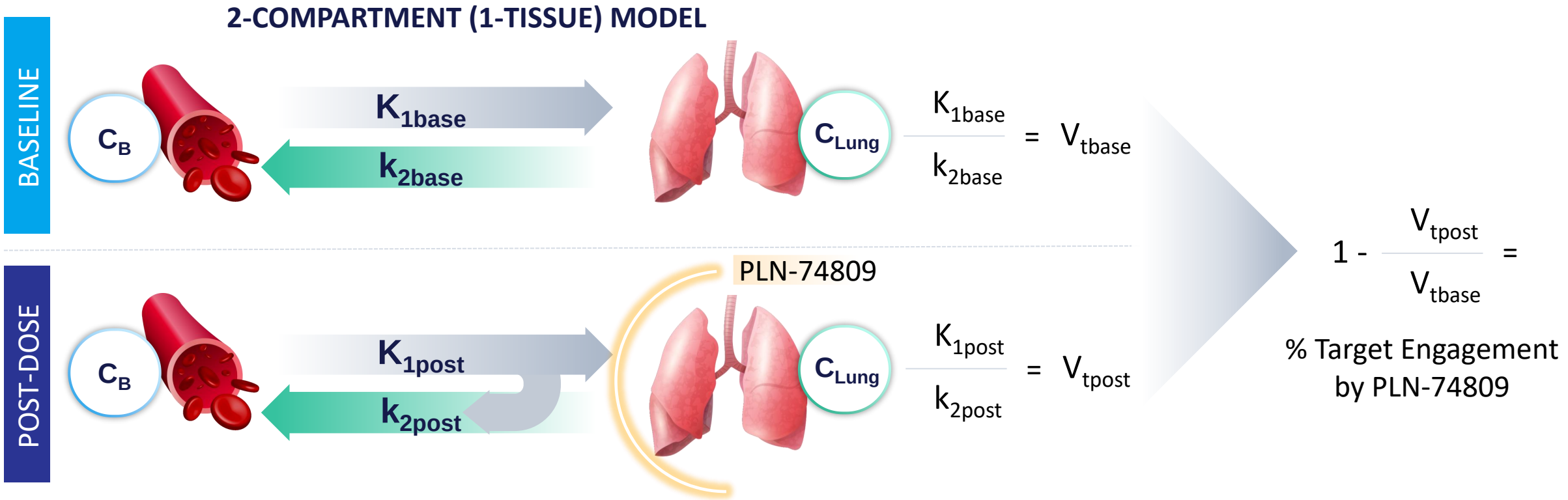
Change in Calculated V_t from Baseline to Post-dose PET Scan Indicates Target Engagement Level of PLN-74809 in the Lung



- We are performing repeat PET scans on IPF patients at baseline and after a single dose of PLN-74809

- Inhibition of tracer binding will reduce K_1 and increase k_2, reflected in a reduction in the V_t measurement of tracer binding

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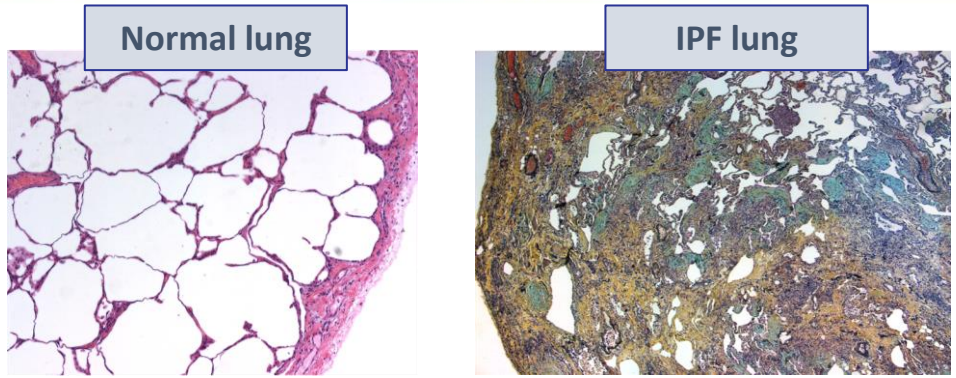
Stanford University

Clinical Implications of Quantitative Reduction of $\alpha_v\beta_6$ PET Tracer Uptake by PLN-74809

Confirm that PLN-74809 penetrates into highly fibrotic areas of the lung where $\alpha_v\beta_6$ expression is the highest



Establish PK/PD relationship between PLN-74809 plasma exposure and $\alpha_v\beta_6$ target engagement – **Build** PK/PD model predicting the full exposure-response curve

Link biological activity (reduction in alveolar TGF-β signaling) shown in the Phase 1b healthy volunteer BAL study to $\alpha_v\beta_6$ target engagement in fibrotic IPF lungs

Inform dose selection in Phase 2b trials and beyond

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PLN-74809-PSC-203 [INTEGRIS-PSC]
Phase 2a Global Safety-PK-Fibrosis and Cholestasis Biomarker Trial in PSC

Key inclusion/exclusion criteria

- Adults with large duct PSC
- Pre-cirrhotic/no hepatic impairment
- Stratified for UDCA use

Randomization 3:1 (PLN-74809:placebo)

- Placebo (n=21)
- PLN-74809 40 mg (n=21)
- PLN-74809 80 mg (n=21)
- PLN-74809 160 mg (n=21)

Primary and secondary endpoints

- Safety, tolerability, PK

Exploratory endpoints

- Effect on fibrosis biomarkers (e.g., Pro-C3, ELF)
- Change in ALP over 12 weeks
- Imaging

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PLN-74809
Rationale for Treatment of ARDS in COVID-19

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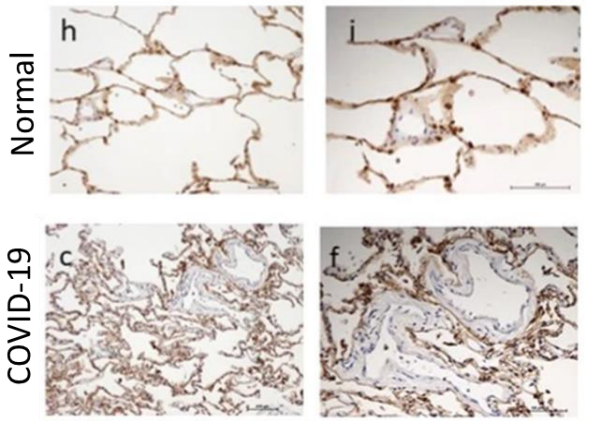
Acute Respiratory Distress Syndrome (ARDS) in COVID-19

- Acute Respiratory Distress Syndrome (ARDS) is a major cause of death in patients with COVID-19
- SARS-COV-2 infection increases $\alpha_V\beta_6$ expression in lung alveoli (Nottingham Covid Research Group)
- ARDS patients have dramatically elevated lung TGF-β levels
- $\alpha_V\beta_6$ knockout mice are protected from multiple lung pathogens

$\alpha_V\beta_6$ expression in COVID-19 ARDS



https://www.nottinghamcrg.info/

Active TGF-1 in ARDS Lung

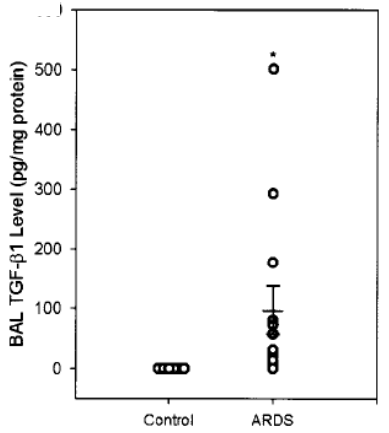
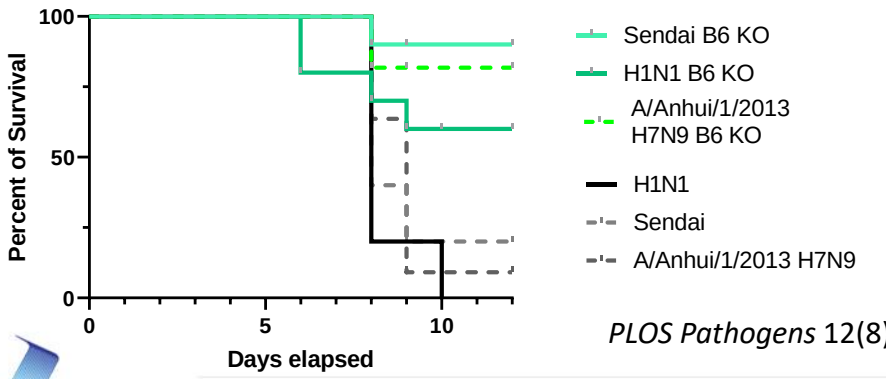


Figure 3. Active TGF-β1 levels in BAL samples in ARDS cases (n = 13) and controls (n = 7) standardized to BAL fluid protein. Mean and SEM are shown. *Significantly greater than control ($P < 0.0001$).

Am. J. Respir. Cell Mol. Biol. **28**, 499–503 (2003).

Protection of $\alpha_V\beta_6$ knock-out mice



PLOS Pathogens 12(8): e1005804

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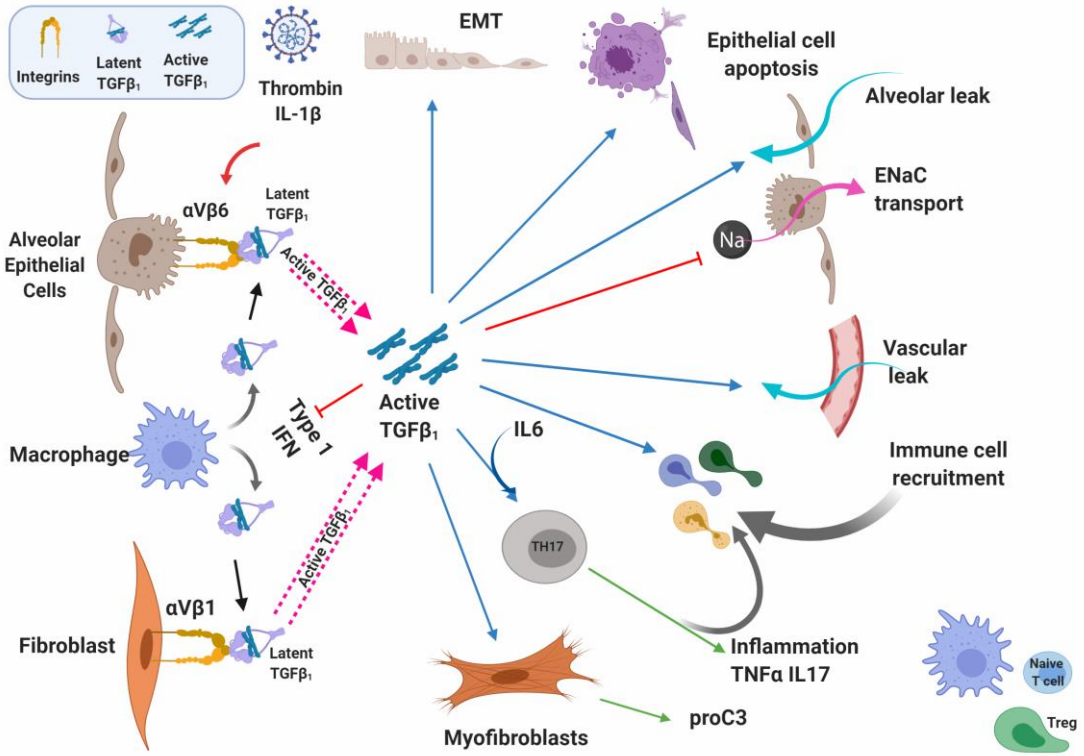
$\alpha_V\beta_6$ Activated TGF-β May Contribute to ARDS in COVID-19

- SARS-COV-2 infection increases $\alpha_V\beta_6$ expression in lung alveoli
- Increased thrombin and IL-1β activate $\alpha_V\beta_6$ increasing TGF-β levels
- Increased TGF-β levels in ARDS lead to:
  - Epithelial cell death
  - Alveolar and vascular leak
  - Reduced interferon expression
  - Increased immune cell infiltration
  - Inhibition of ENaC (sodium transport)
  - Fibroproliferation
- Inhibiting integrin binding to latent TGF-β complex may safely block TGF-β activation and may prevent progression from pneumonia to ARDS
- Phase 2a Trial (CT.gov Identifier NCT04565249)
  - Randomized, placebo controlled, dose ranging trial
  - 36 patients/ three cohorts, 7 to 14-day treatment, 90-day follow-up
  - Primary endpoints: safety, tolerability, and PK (evaluate exploratory outcomes measures)

Integrin Activation of TGF-β **Effects of TGF-β Activation**



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Pliant's Integrin-Based Oncology Program

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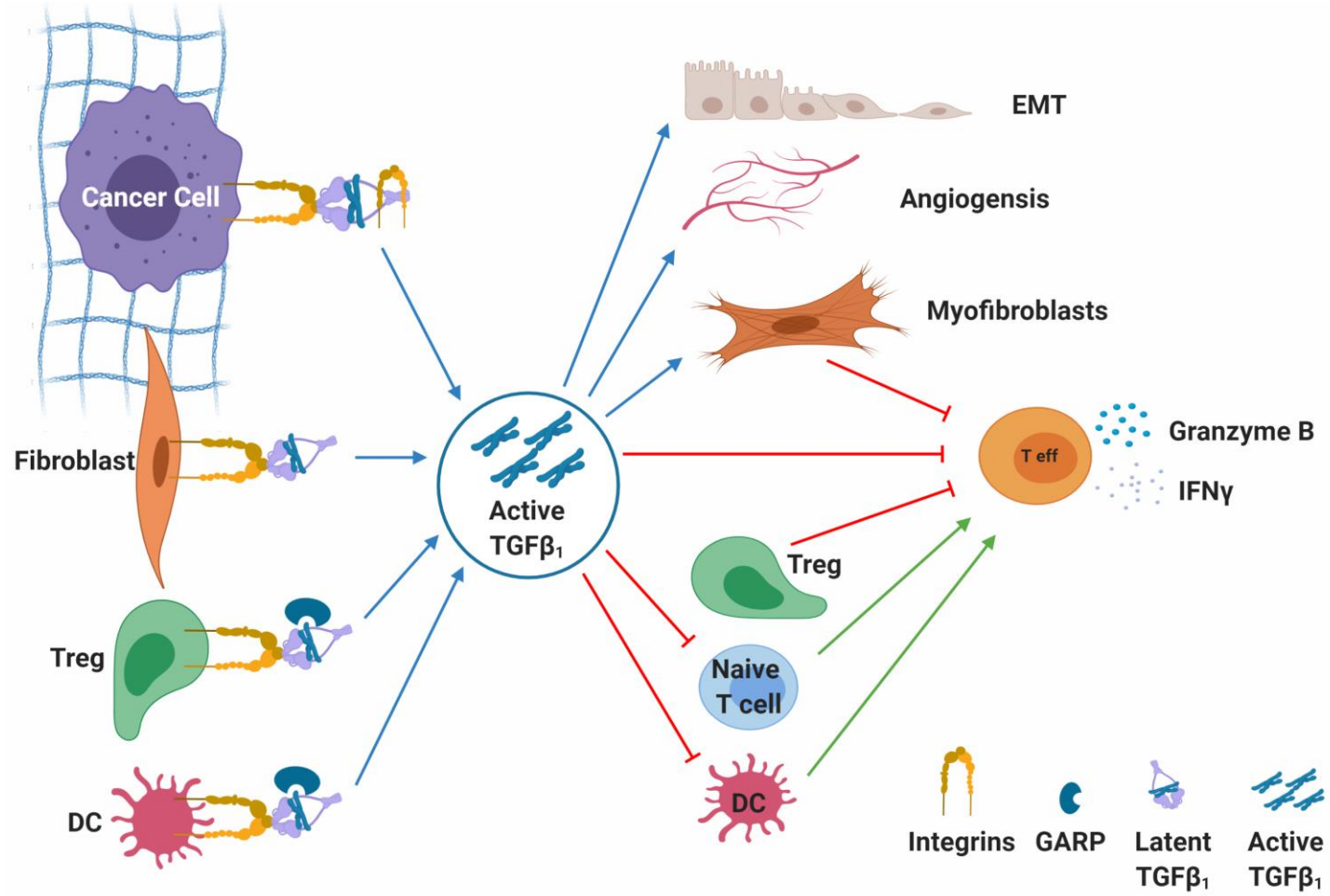
Activated TGF-β Contributes to Immune Exclusion & Evasion, Tumor Metastasis and Angiogenesis

- **Integrins activate TGF-β on cancer cells and multiple cell types in the tumor micro-environment**
- **This leads to immune suppression and resistance to I/O therapies**
- **Selectively inhibiting integrin binding to latent TGF-β complex has potential to:**
  - Safely block TGF-β activation
  - Enhance efficacy of multiple checkpoint inhibition pathways

Integrin Activation of TGF-β **Oncogenic Effects of TGF-β Activation**



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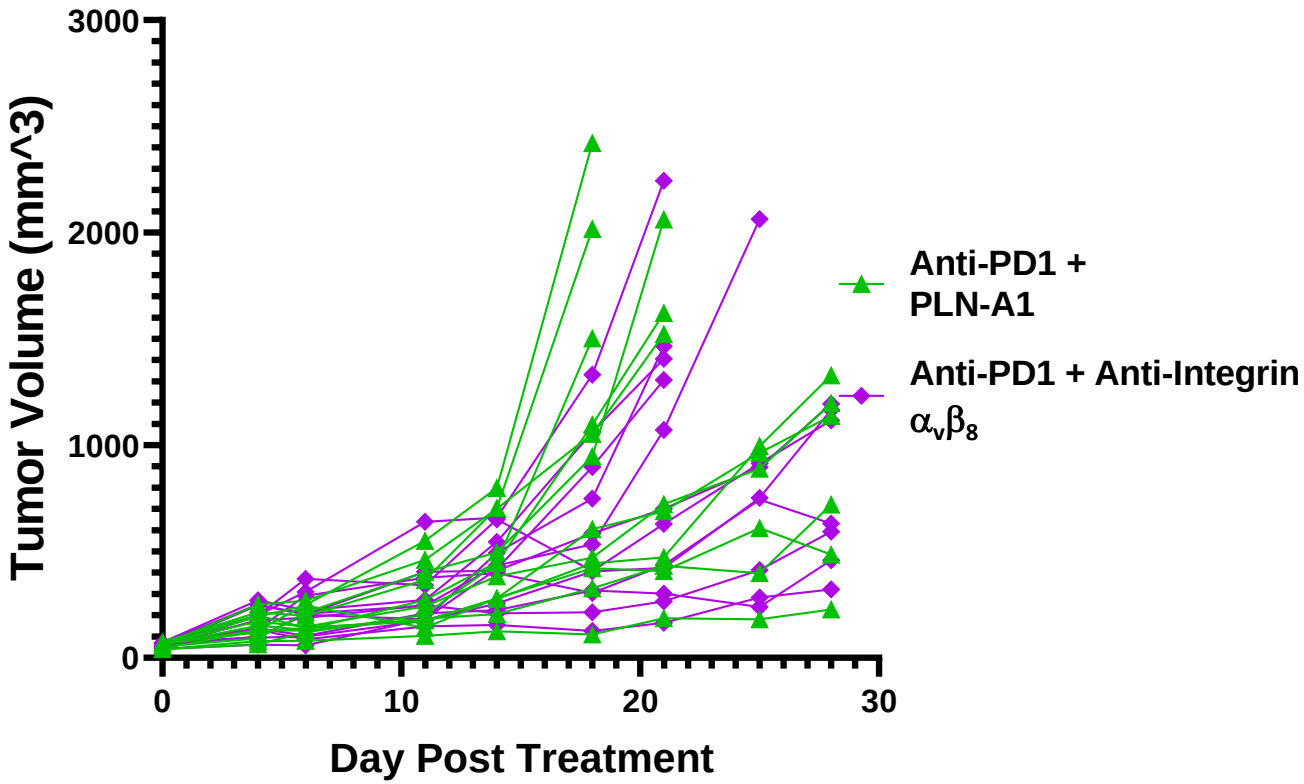
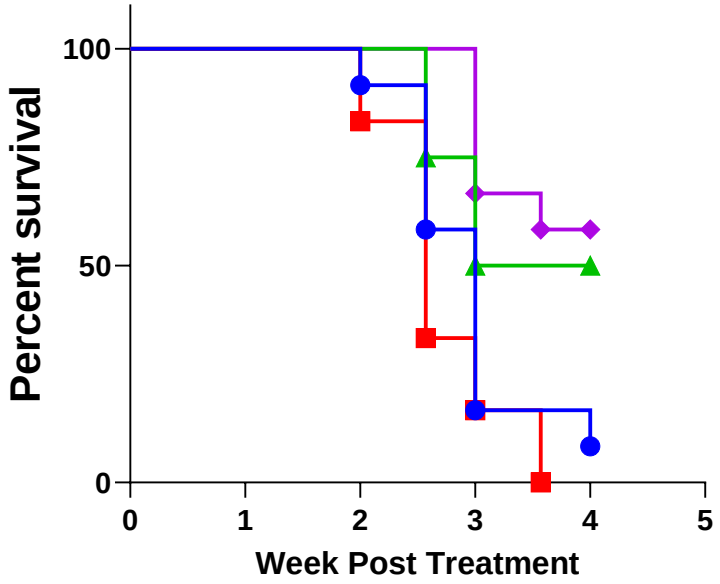
PLN-A1 Reduced Tumor Burden and Increased Survival in Preclinical Models

EMT-6 Syngeneic Model



EMT-6 Syngeneic Model



		Survival Percentage
Rat IgG2b + Vehicle		8%
Anti-PD1 + Vehicle		0%
Anti-PD1 + PLN-A1	**	50%
Anti-PD1 + Anti-Integrin $\alpha_v\beta_8$	***	58%

Log-rank test
** p<.01 *** p<.001 vs PD1+vehicle

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Selective Muscle Cell Integrin Agonism for the Treatment of Muscular Dystrophies

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Pliant's Muscular Dystrophy Program – Overview

Targeting an integrin receptor on the muscle cell surface

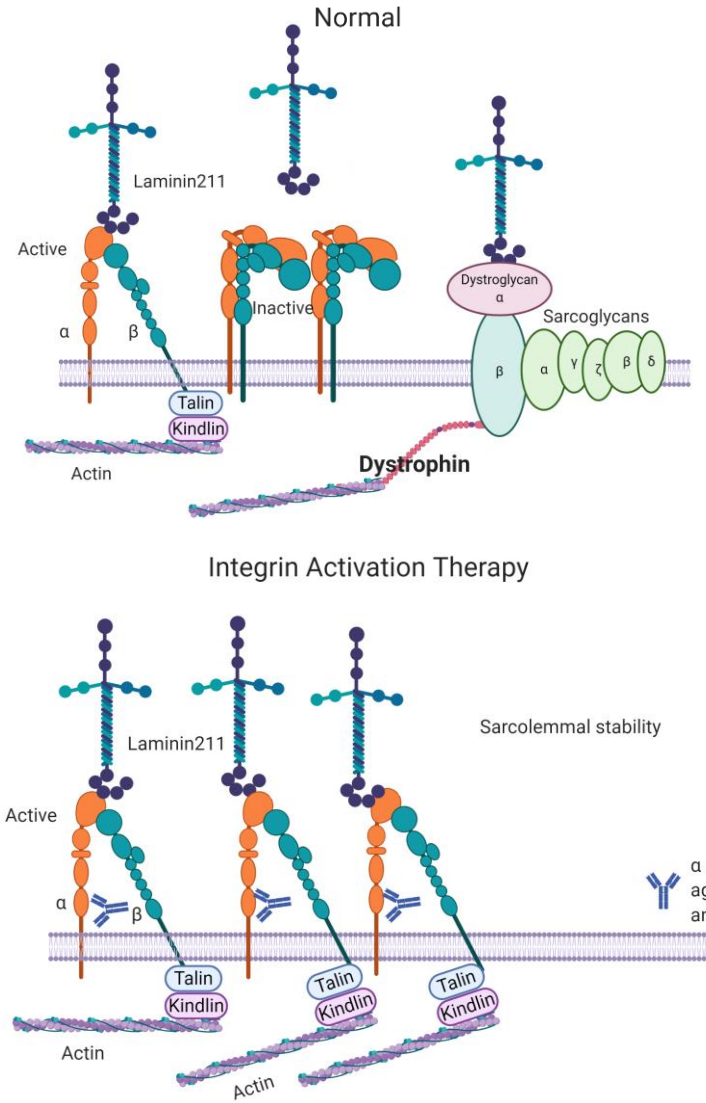
- Integrin target is upregulated as a **compensatory mechanism** in **different types of muscular dystrophy**
- Acts as a **substitute for dystrophin**, helping to stabilize the muscle membrane, decreasing muscle damage
- **Mutations in the target result in human congenital myopathy**

Allosteric agonistic monoclonal antibody

- Activates the target to **augment the compensatory mechanism**

Potential to combine across multiple muscular dystrophy indications

- Target is **upregulated across different forms of muscular dystrophy**
- Mechanism is unrelated to underlying gene mutation
- May be **combined with existing therapies** as well as new modalities (CRISPR, gene therapy,…)



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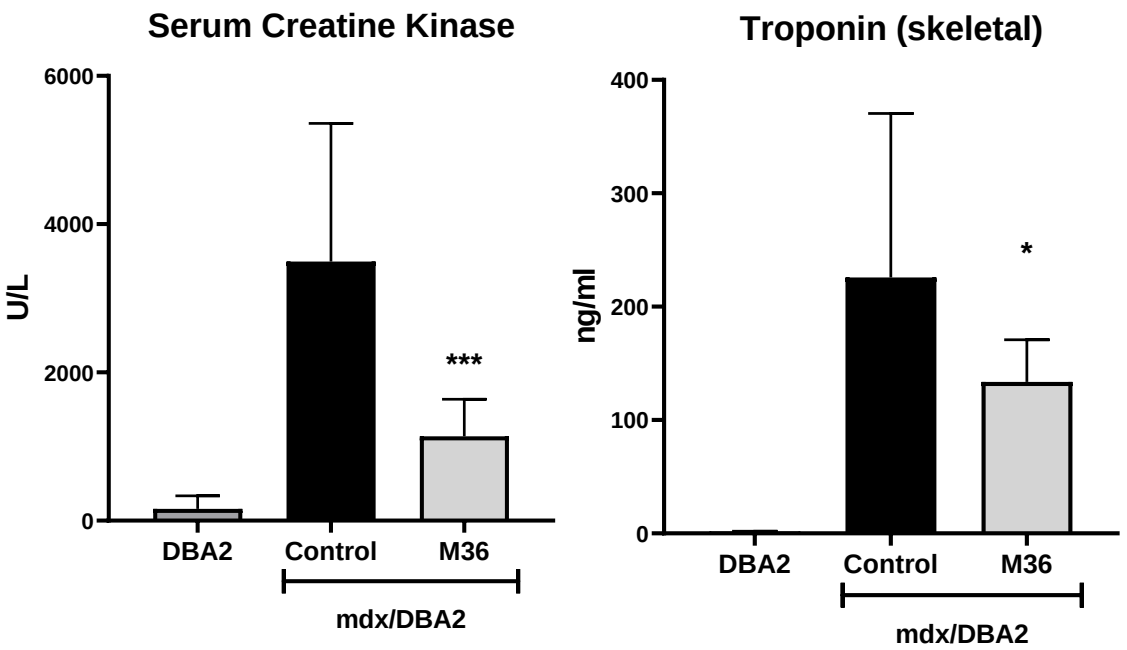
Pliant's mAb Improved Muscle Membrane Integrity and Diaphragm Function in Mouse DMD Model

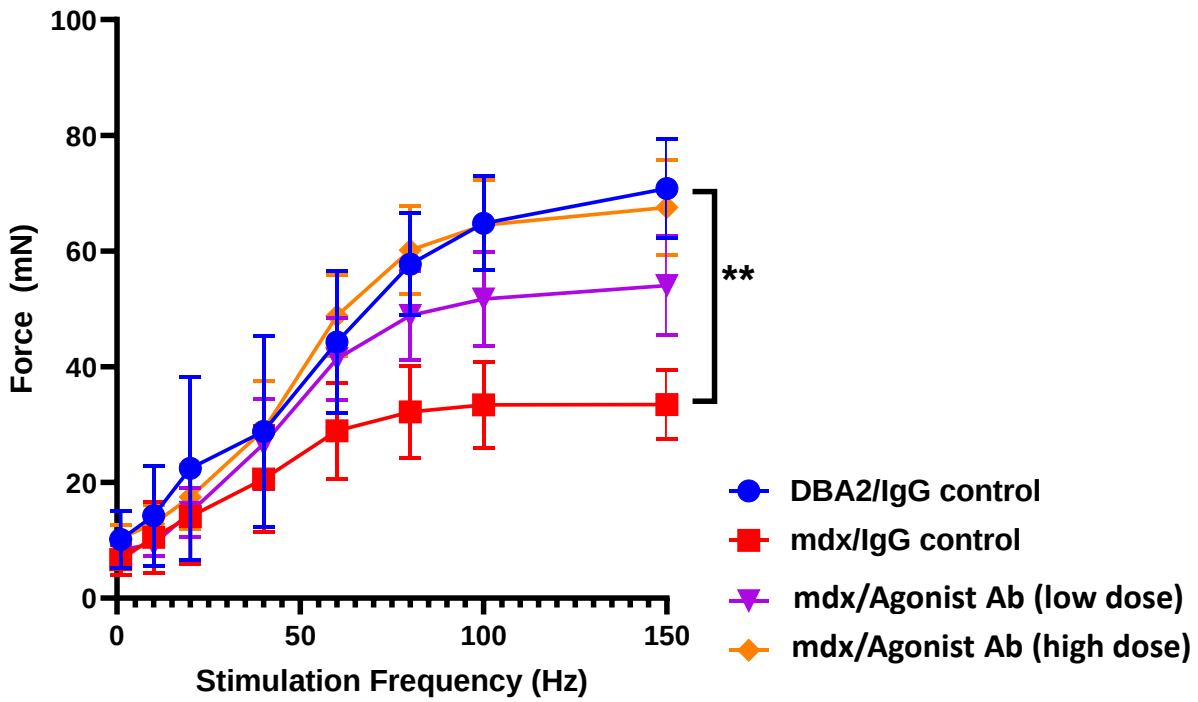
Antibody treatment protected against muscle damage

- Reduction of clinical biomarkers including serum creatine kinase and skeletal troponin

Duchenne muscular dystrophy causes progressive wasting of cardiac and respiratory muscles (main cause of death)

- Improvement in diaphragm function is expected to significantly improve patient pulmonary function





Mean +/- SD n=10/group

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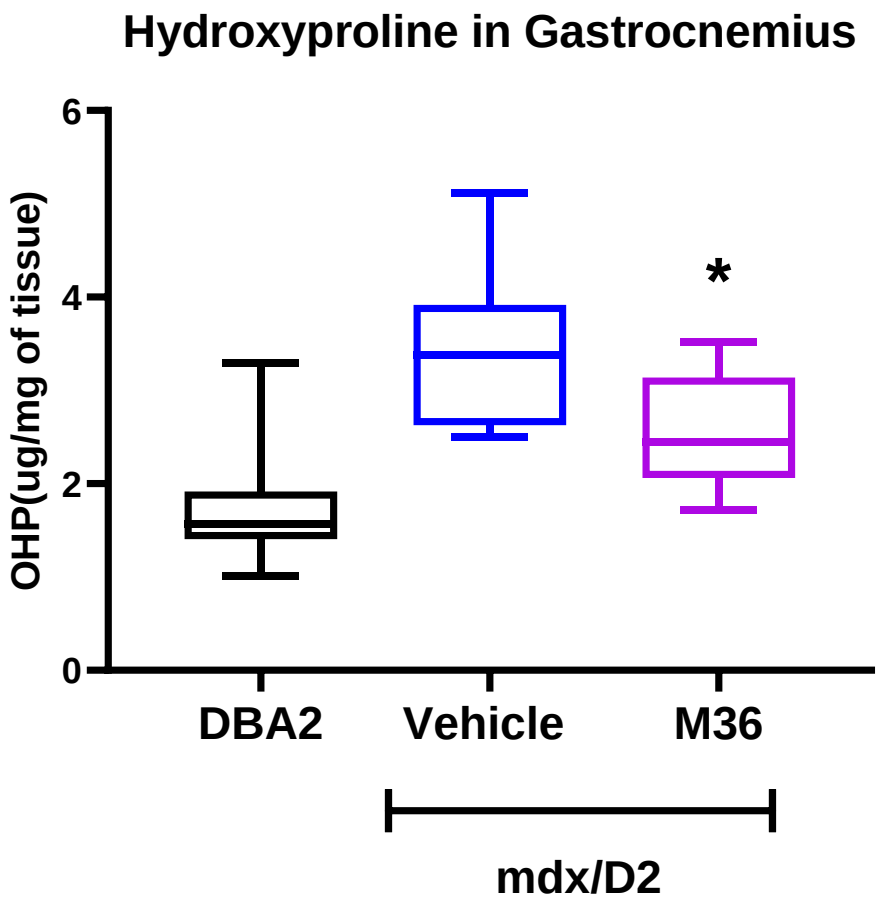
Pliant's mAb Showed Decrease in Collagen Content in Muscles in Mouse DMD Model

Agonistic mAb significantly reduced the collagen content in gastrocnemius of treated mice



Mean +/- min.max n=10/group

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