Developing Novel Treatments for Fibrotic Diseases

Piper | Sandler 32nd Annual Healthcare Conference

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THERAPEUTICS

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Pliant – The Fibrosis Company

Founded on Cutting Edge Research in Fibrosis

- Founded in 2015 by **Third Rock Ventures** – Located in South San Francisco – 78 FTEs
- Based on **technology from UCSF**, Pliant was founded to target fibrosis, with a focus on integrin targets

Leading Integrin Platform with World-Class Fibrosis Drug Development Capabilities

- Two clinical-stage assets in development for four different indications
- Integrin biology, chemistry and screening platform with a compound **library of >7,000 integrin binders**
- Early pre-clinical and clinical de-risking tools: **live patient tissue assays**, advanced **PET** and collagen imaging

History of Delivering Results

- Since our founding, we have built a **broad pipeline of multiple programs, with four open INDs**
- 2019 License and Collaboration agreement with **Novartis**

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Pliant – Company Highlights

Cutting Edge Science Focused on Large Markets

- Modulators of integrins and the TGF-β pathway with tissue-targeted antifibrotic activity
- Lead indications IPF and PSC represent high unmet need

Near Term, Potentially High-Impact Catalysts

- Multiple data readouts beginning in the first half of 2021
- Phase 2a 12-week IPF and PSC trials will evaluate early efficacy endpoints

Strategic Partnership De-Risks Pipeline

NOVARTIS

- Validation of the 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
- $294 million cash balance as of September 30th, 2020
- Company funded into 2023

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The Pliant Team
Highly Experienced in Fibrosis and Drug Development

Management Team

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

Hans Hull, J.D.
Chief Business Officer

Eric Lefebvre, M.D.
Chief Medical Officer

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

Barbara Howes
Chief HR Officer

Eve-Irene Lepist, Ph.D
Vice President, Non-Clinical Development

Marzena Jurek
Vice President, Clinical Operations

Katerina Leftheris, Ph.D.
Vice President, Medicinal Chemistry

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

Michael Holfinger, Ph.D.
Vice President, CMC

Stephen Rossi, Pharm.D.
Vice President, Clinical Development

Founders

UCSF

Dean Sheppard, M.D
Professor of Medicine, Chief of the Division of Pulmonary, Critical Care, Allergy and Sleep, and director of the Lung Biology Center.

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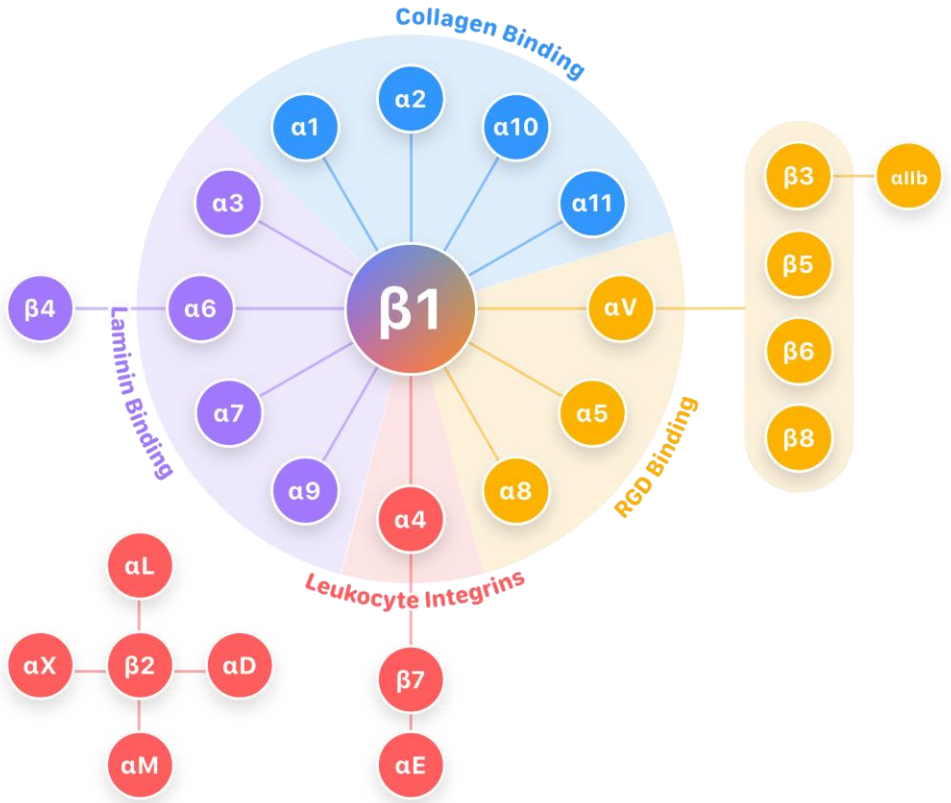
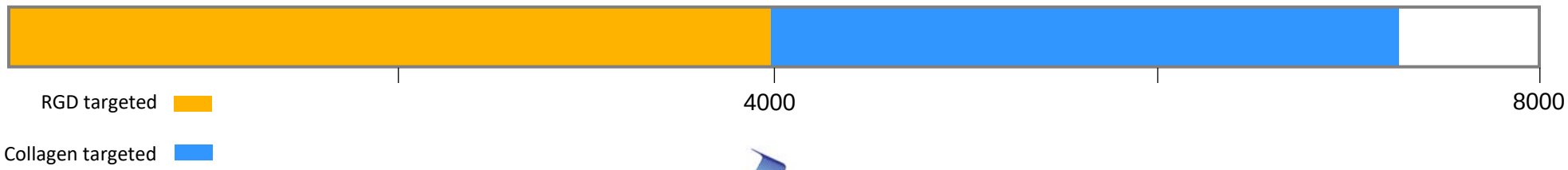
Pliant's Integrin Focused Library
Core Platform for Novel Pipeline and Partner Programs



Expanded library of >7,000 compounds

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



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Pliant Development Pipeline

Program	Indication	Preclinical	IND enabling	Clinical			Anticipated Milestone	Global Rights
				Phase I	*Phase II*	*Phase III*		
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						Phase2 Initiation	PLIANT
PLN-1474 *Selective inhibitor of $\alpha_V\beta_1$*	**NASH-Associated Liver Fibrosis**						Phase 1 Data	NOVARTIS
Oncology *Inhibitor of $\alpha_V\beta_8$*	**Solid Tumors**						IND	PLIANT
Muscular Dystrophies *Anti-integrin mAb*	**DMD and Others**						Candidate Selection	PLIANT

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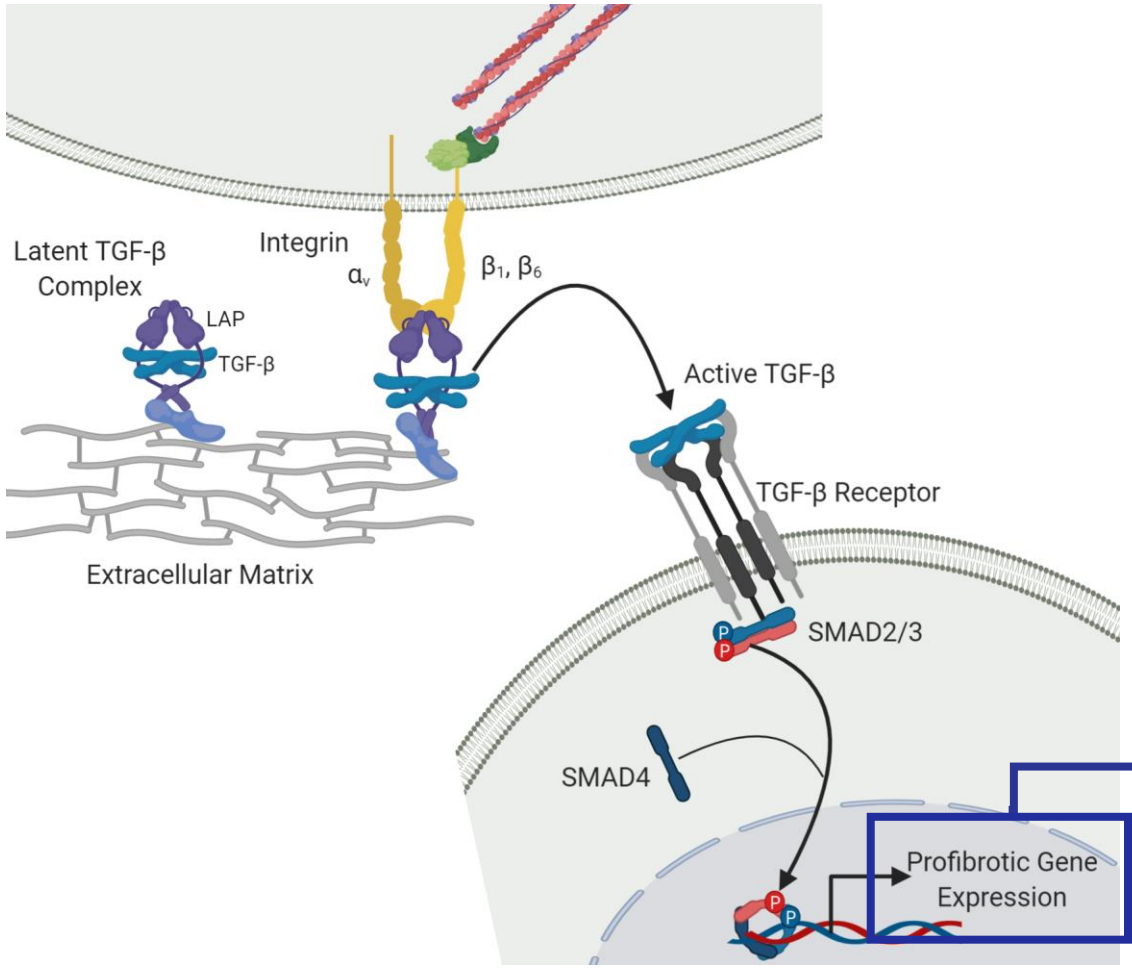
$\alpha_v\beta_6$ / $\alpha_v\beta_1$ Integrins Drive Cell-Matrix Interactions in Fibrosis

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

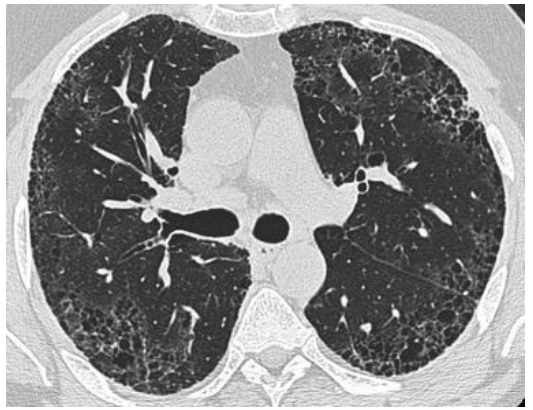


- TGF-β is central mediator of fibrosis
- $\alpha_v\beta_6$ /$\alpha_v\beta_1$ Integrins activate latent TGF-β only in fibrotic tissue
- Systemic TGF-β blockade carries toxicity risks

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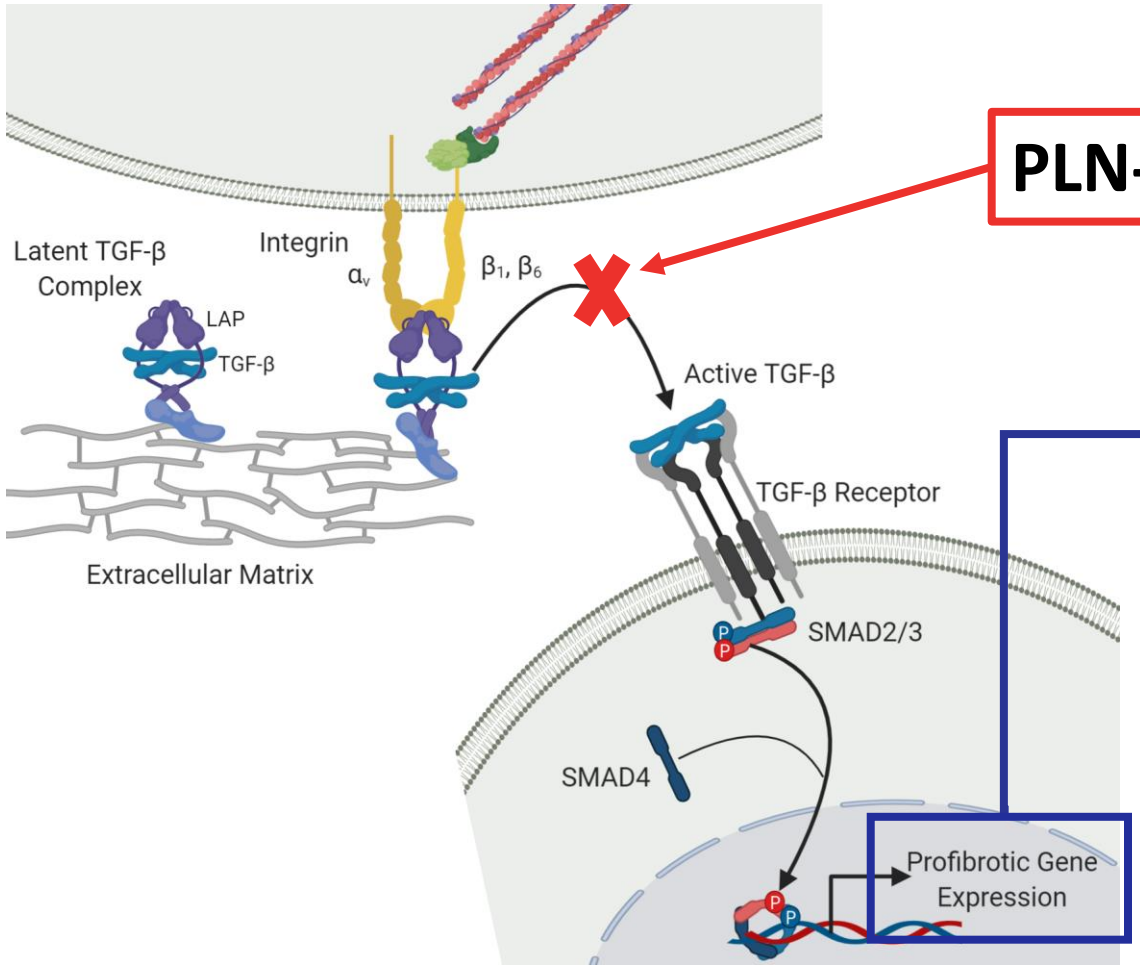
PLN-74809 Provides Profound Antifibrotic Activity through Upstream Inhibition of TGF-β Activation



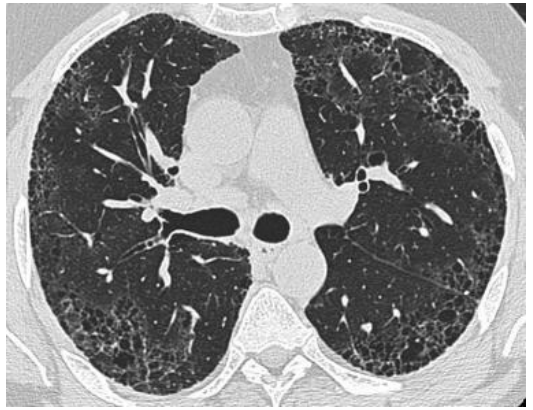
PLN-74809

Pamrevlumab

GLPG 1690

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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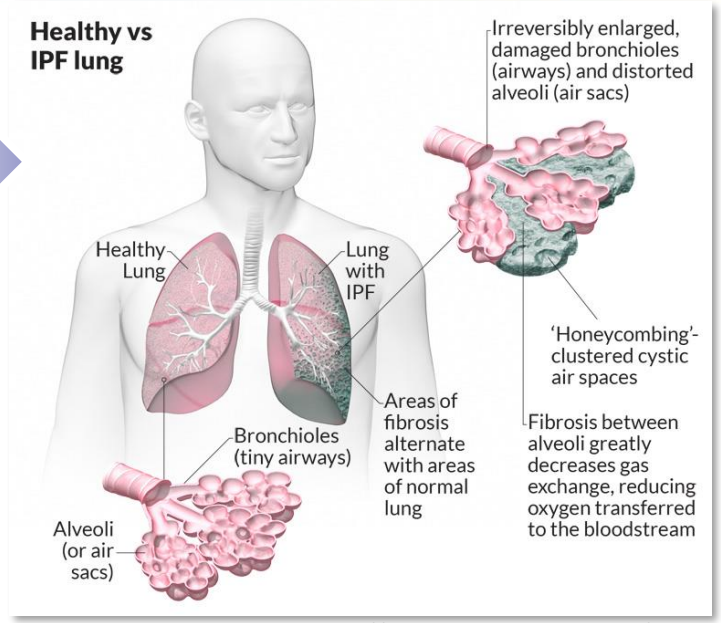
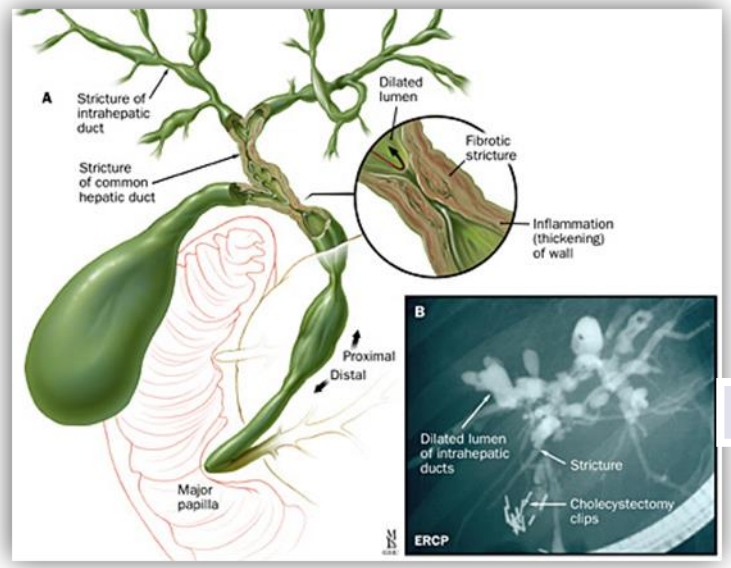
Fibrosis, the Silent Killer

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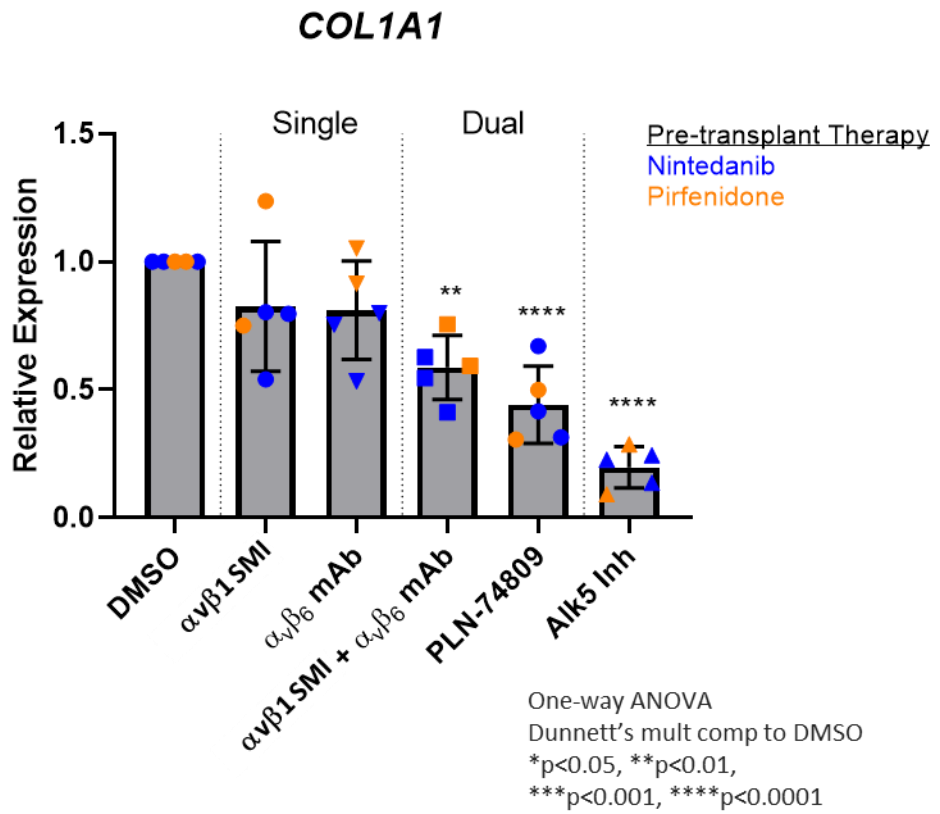
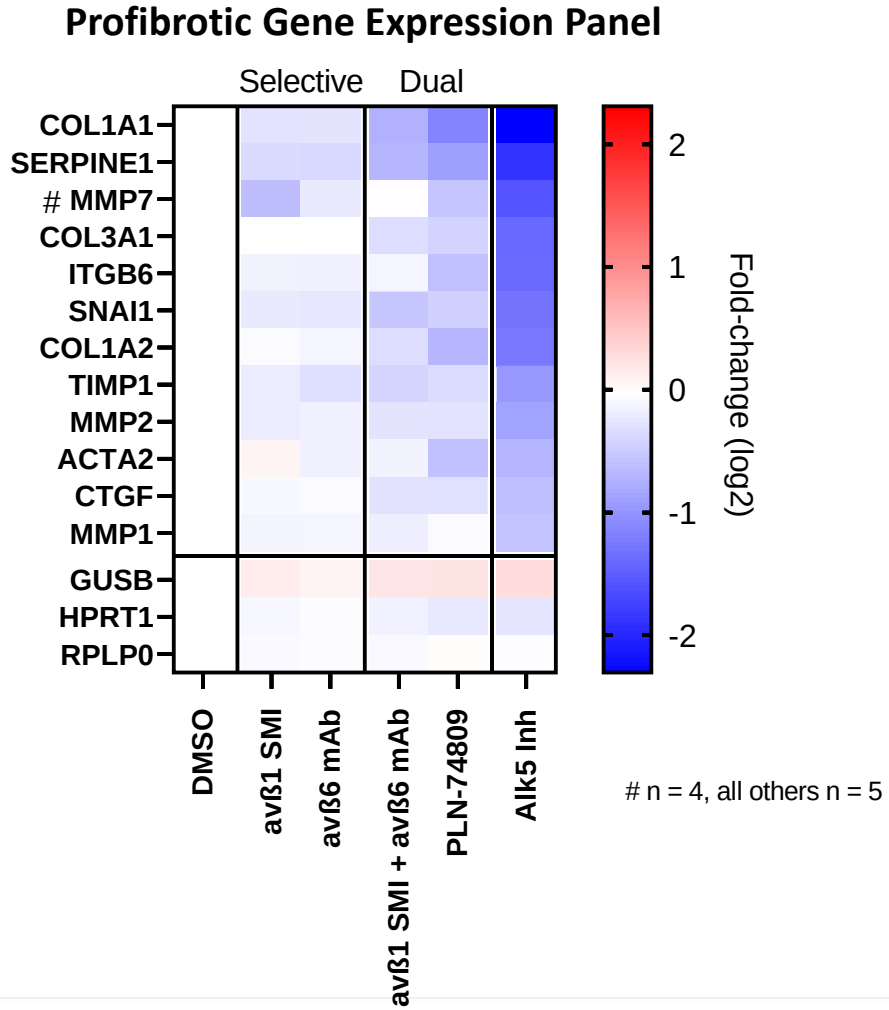
Dual $\alpha_v\beta_6/\alpha_v\beta_1$ Inhibition Blocks COL1A1 Gene Expression More than Single Inhibition in Human IPF Tissue

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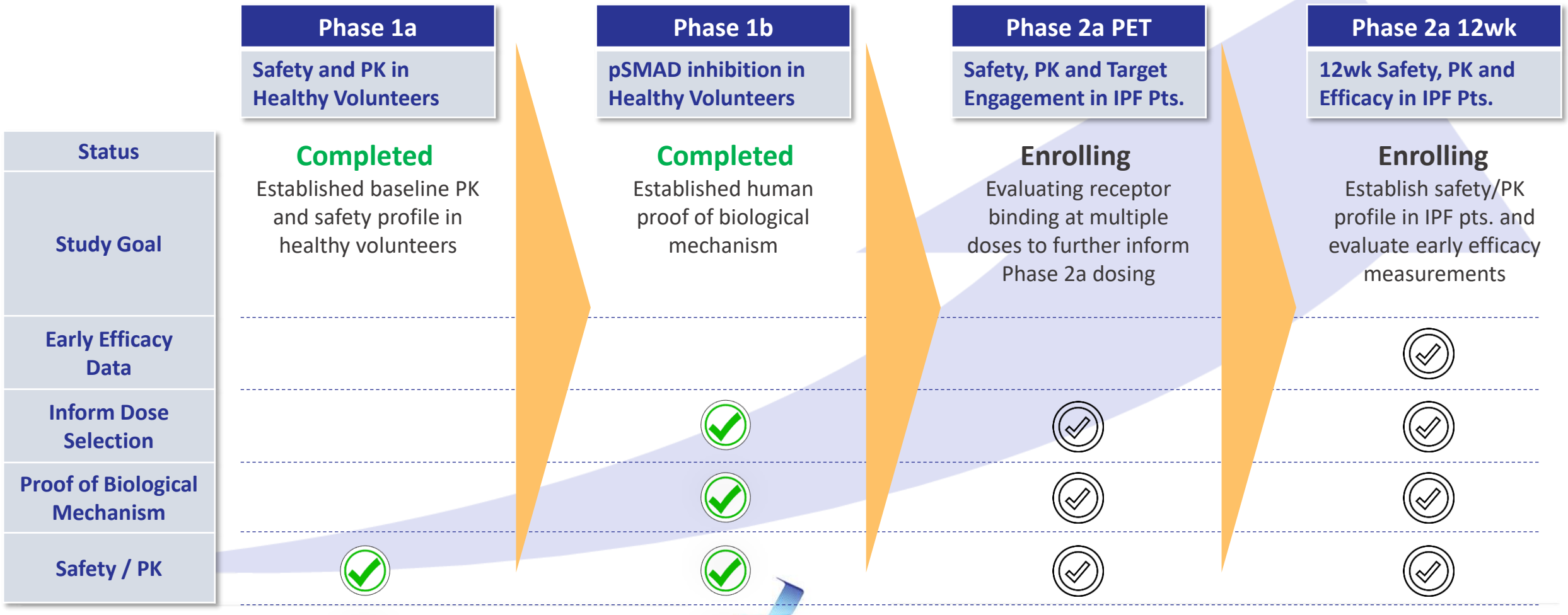
PLN-74809 – Rational Clinical Development in IPF
Step-by-Step De-risking

Maximize Phase 2b POS Through Intelligent Early Trial Design



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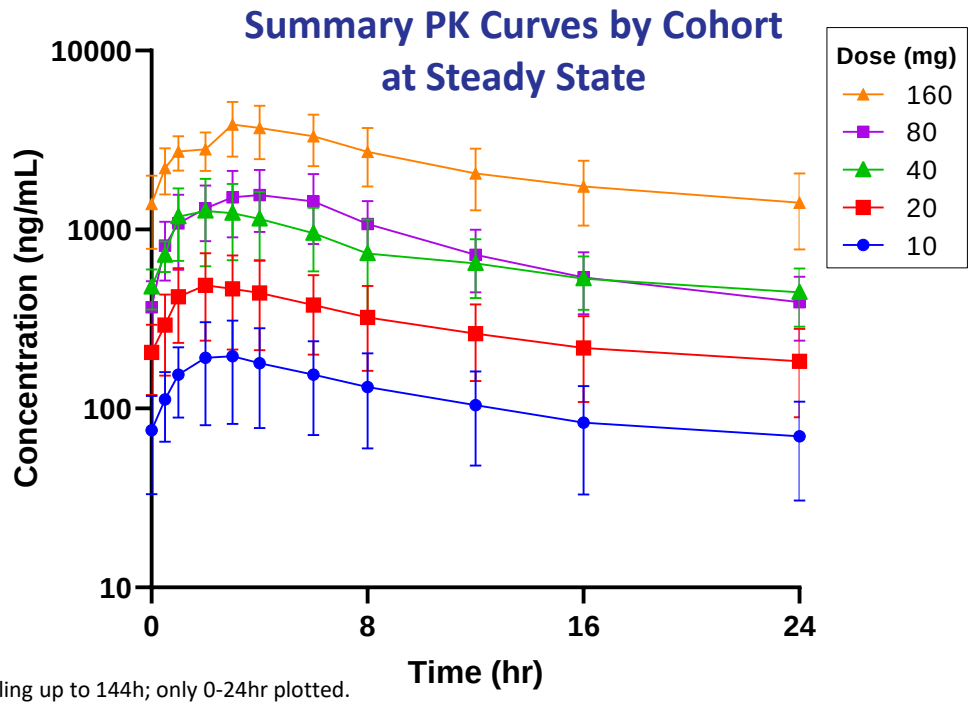
PLN-74809 – Extended Phase 1a Data Summary

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

- Drug generally well tolerated
- Mostly mild AEs, no severe AEs observed
- No dose relationship for TEAEs

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	--	--	--	--	--

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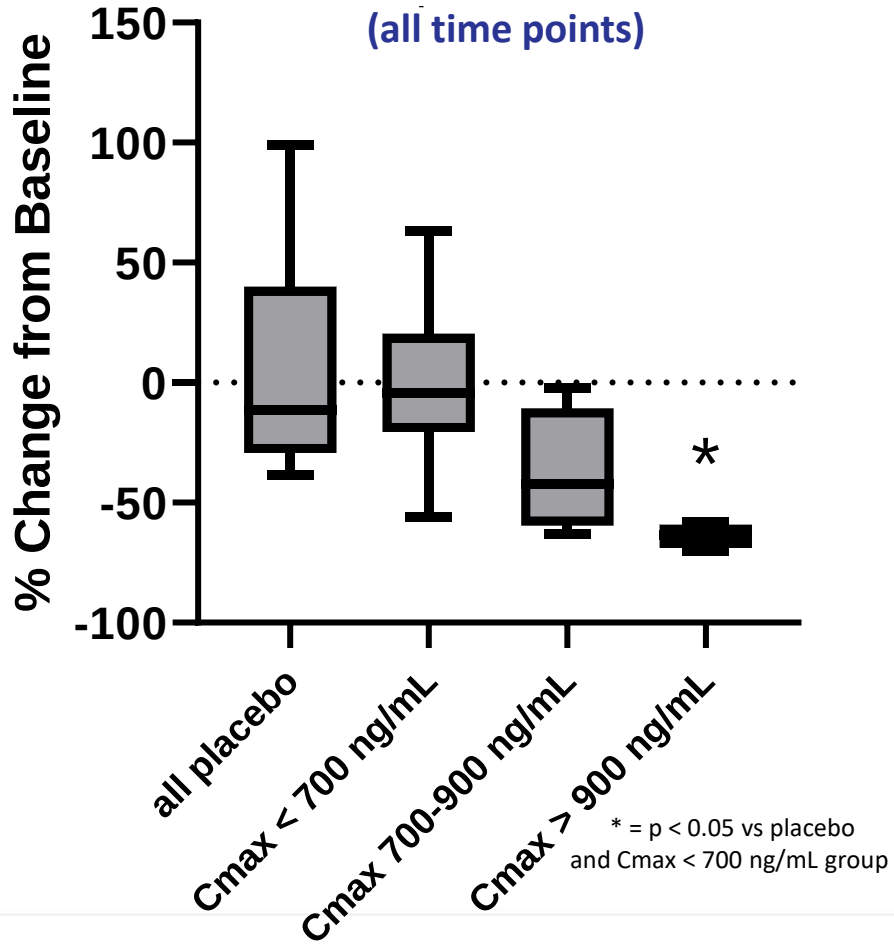
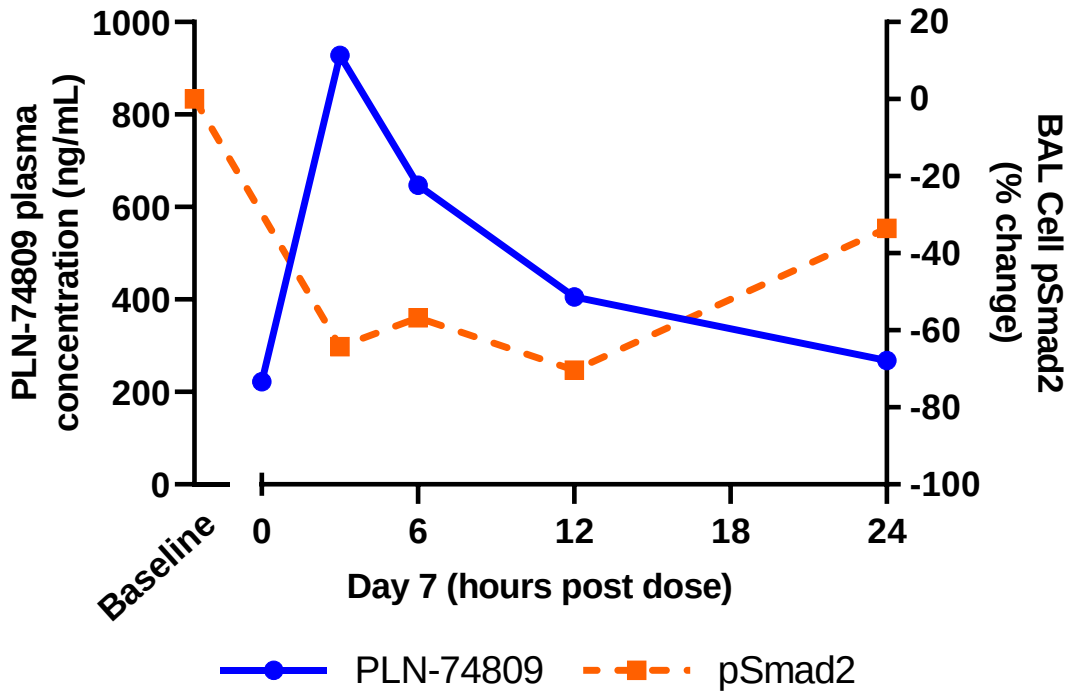
PLN-74809 – Phase 1b Proof of Biological Mechanism

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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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

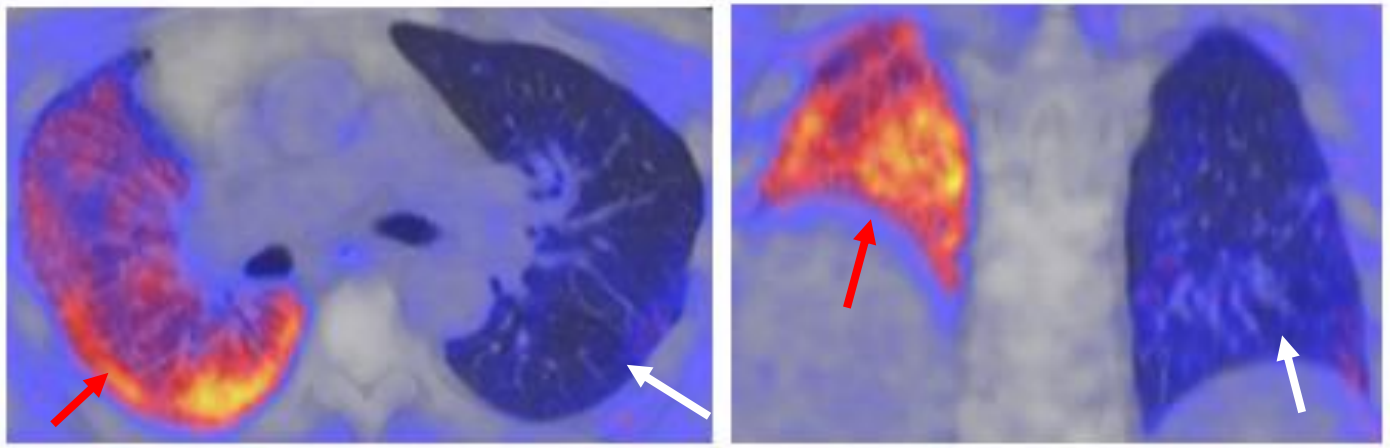
Trial Design

- Single-site open-label trial at Stanford University
- Adults with IPF diagnosis (n=12) and FVC ≥ 50% of predicted
- Patients receive single oral dose of PLN-74809 with PET scans prior to dosing and at T_{max} post dose
- Multiple dose cohorts will be explored

Primary and Secondary Endpoints

- Evaluation of $\alpha_v\beta_6$ receptor occupancy by PLN-74809 assessed by change in PET tracer uptake following a single oral dose
- Assessment of safety and tolerability of PLN-74809 in IPF patients

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



Red arrows: IPF lung
White arrows: transplant lung

Stanford University

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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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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Rationale for Treatment of ARDS in COVID-19

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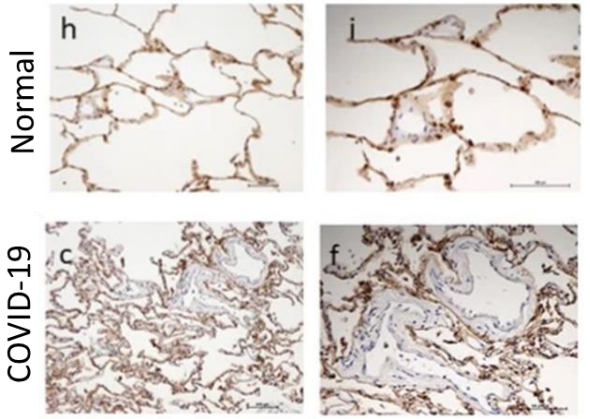
Acute Respiratory Distress Syndrome (ARDS) in COVID-19

- 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

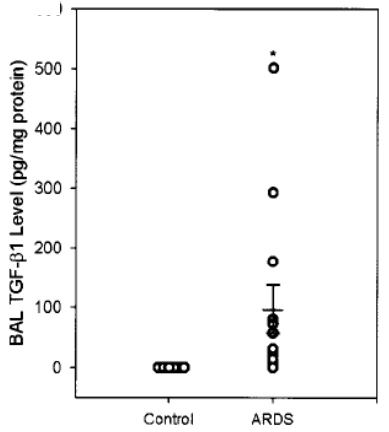
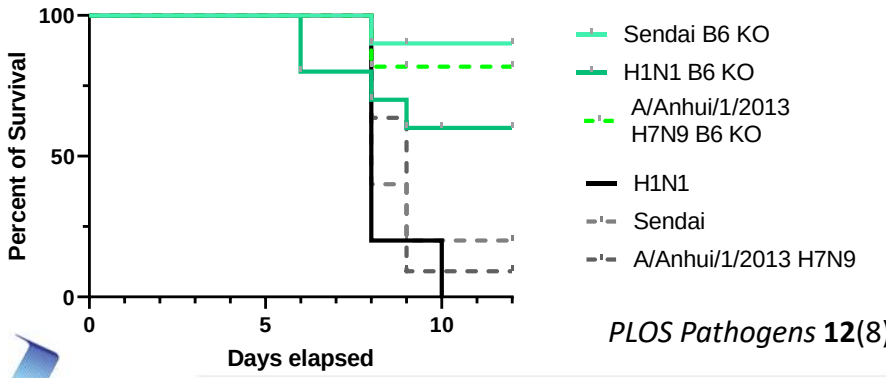


Figure 3. Active TGF-β1 levels in BAL samples in ARDS cases (n = 13) and controls (n = 7) standardized to BAL fluid protein. Mean and SEM are shown. *Significantly greater than control ($P < 0.0001$).

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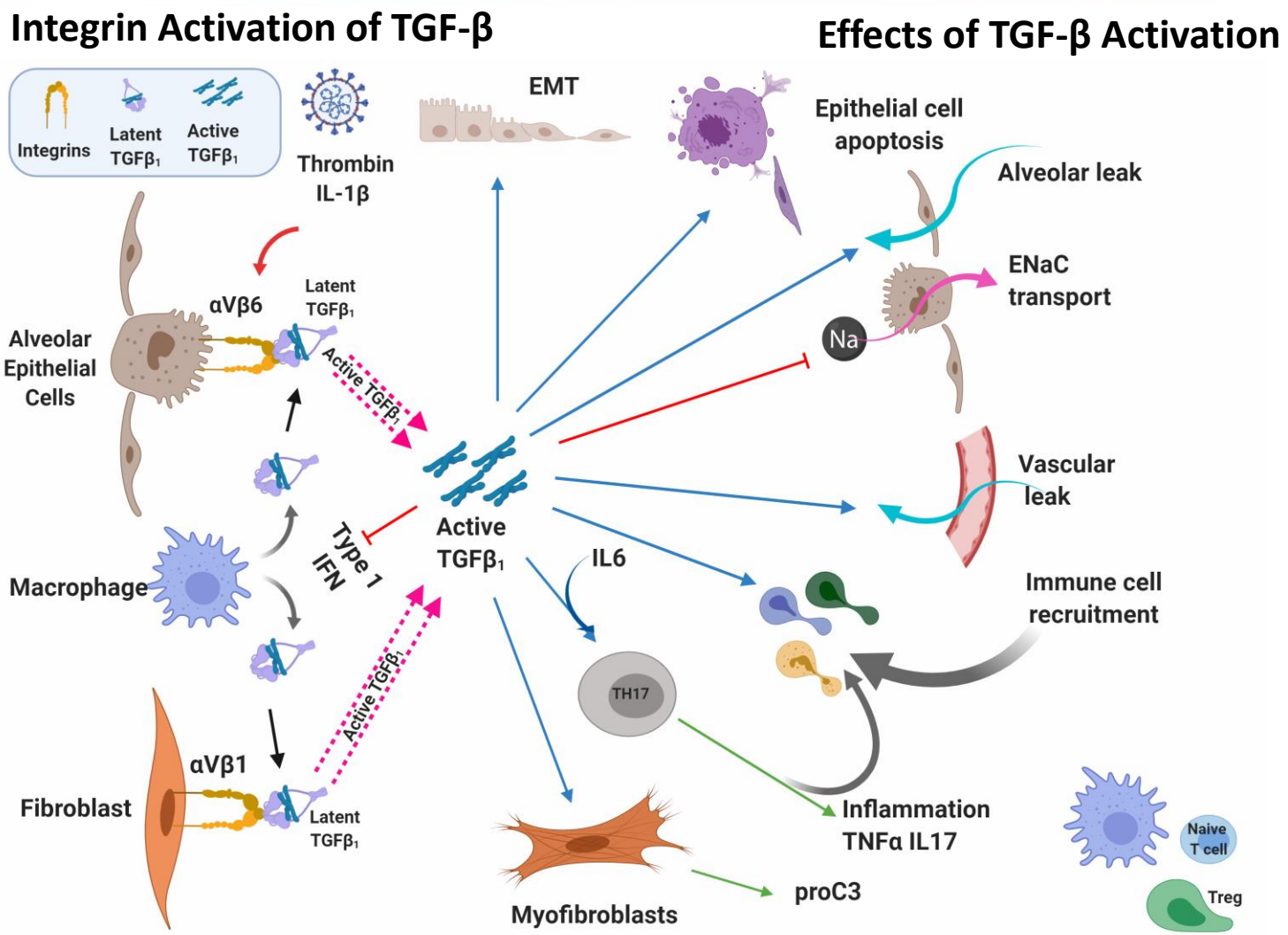
$\alpha_V\beta_6$ Activated TGF-β May Contribute to ARDS in COVID-19

- 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 safely blocks TGF-β activation and may prevent progression from pneumonia to ARDS



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Pliant's Integrin-Based Oncology Program

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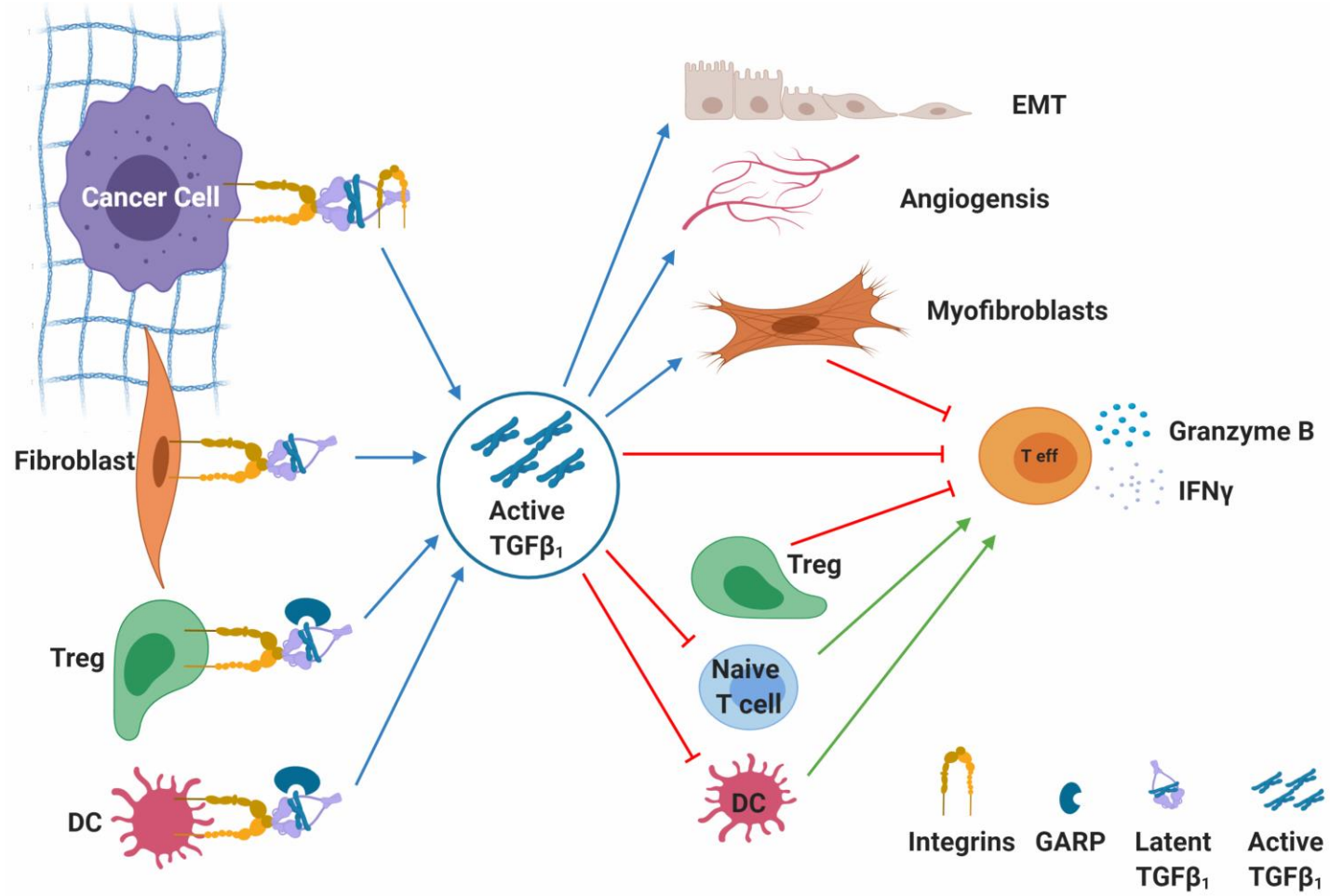
Activated TGF-β Contributes to Immune Exclusion & Evasion, Tumor Metastasis and Angiogenesis

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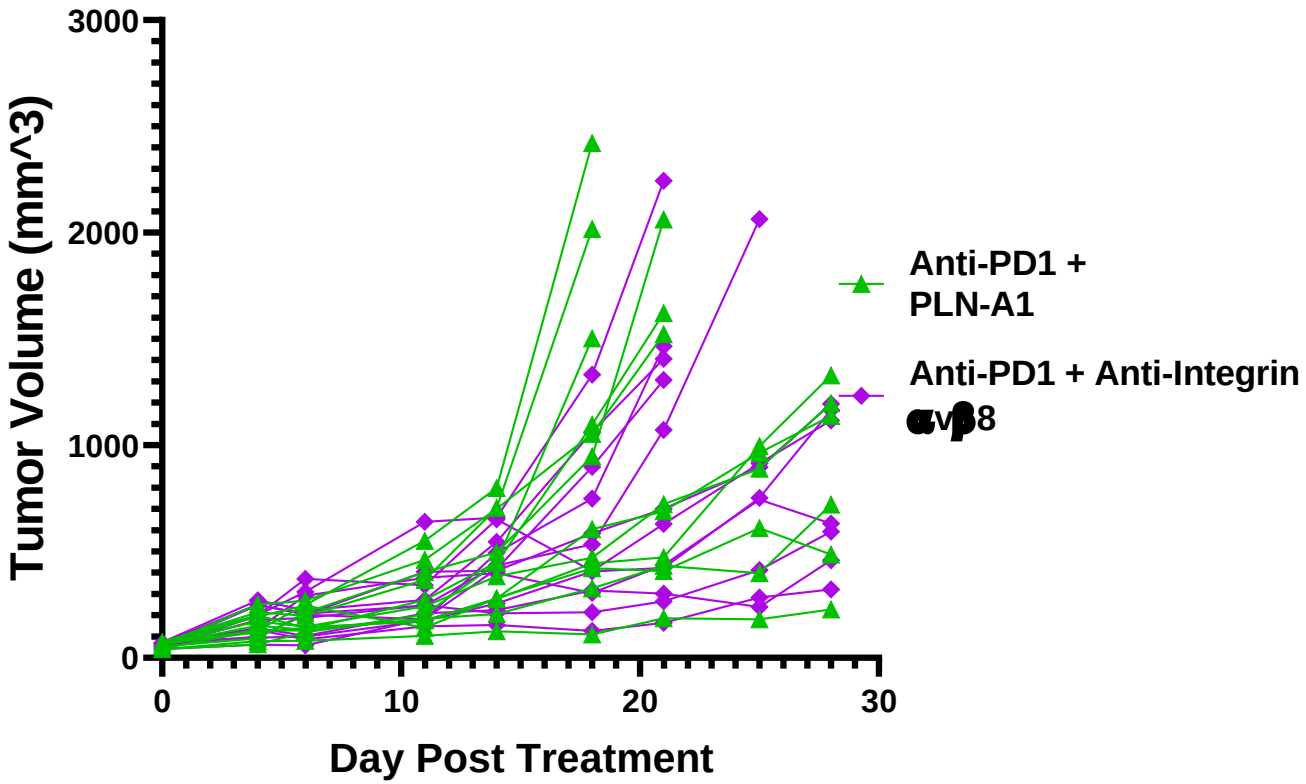
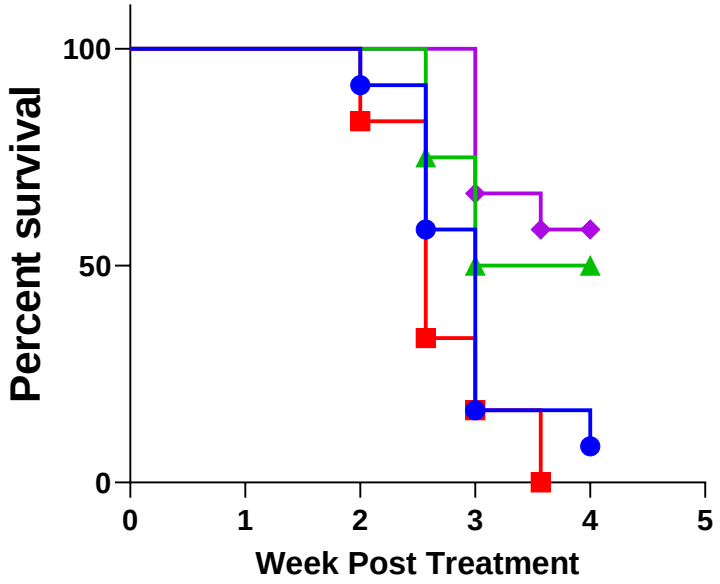
PLN-A1 Reduced Tumor Burden and Increased Survival in Preclinical Models

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 αvβ8	***	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

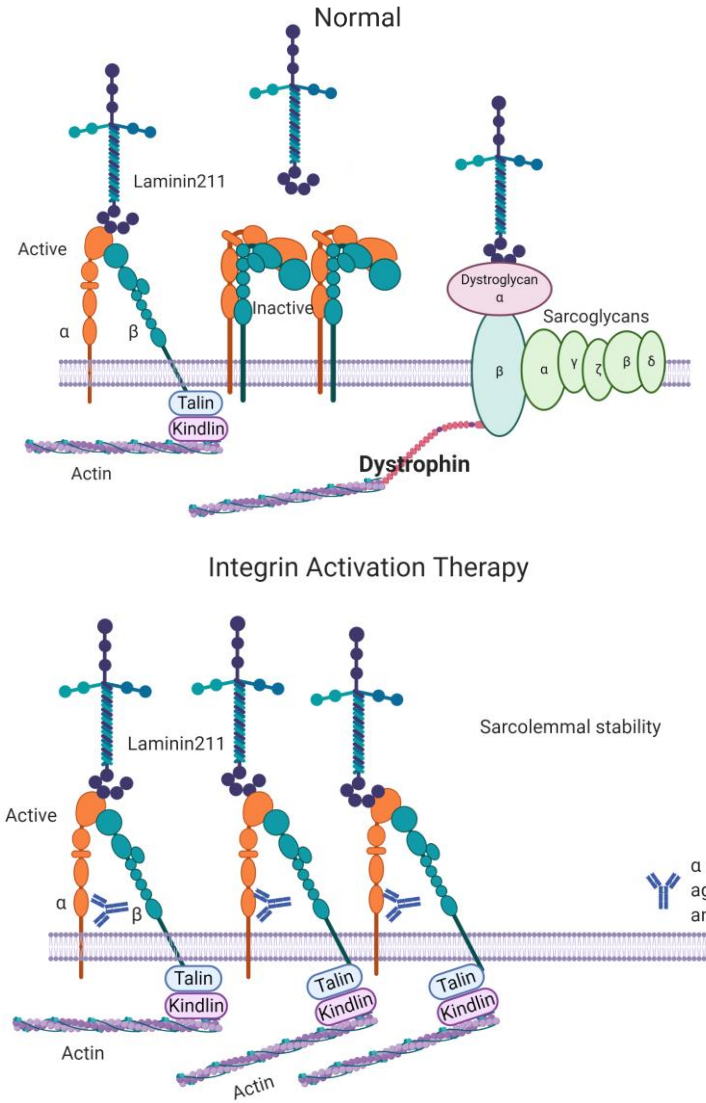
- Integrin target is upregulated as a **compensatory mechanism** in **different types of muscular dystrophy**
- Acts as a **substitute for dystrophin**, helping to stabilize the muscle membrane, decreasing muscle damage
- **Mutations in the target result in human congenital myopathy**

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,…)



PLIANT

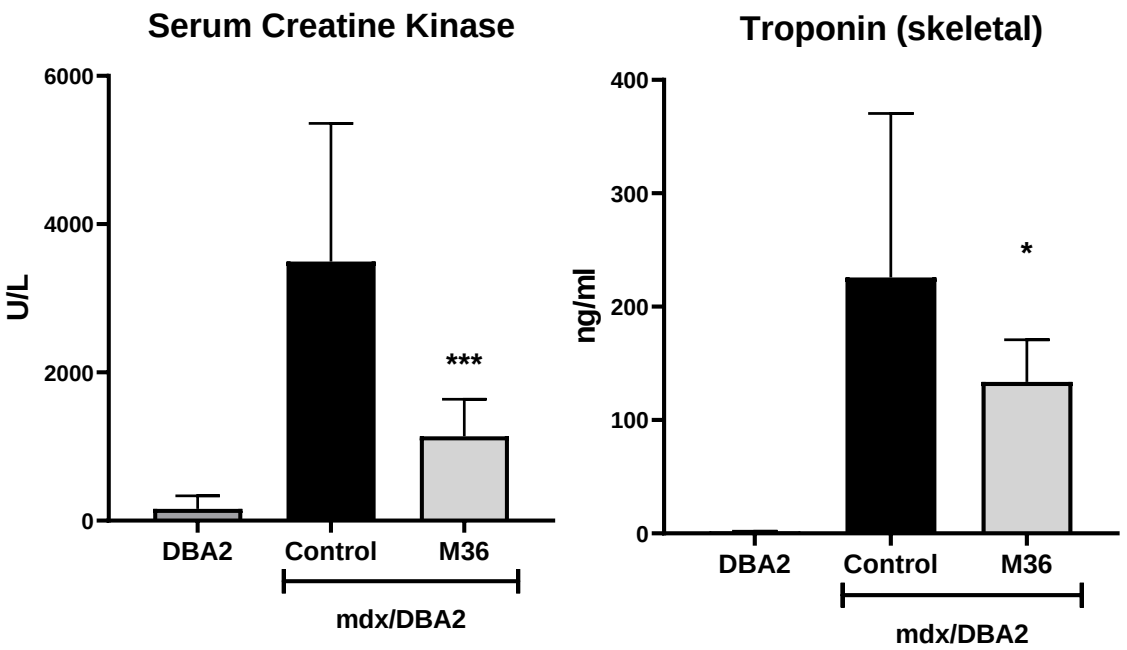
Pliant's mAb Improved Muscle Membrane Integrity and Diaphragm Function in Mouse DMD Model

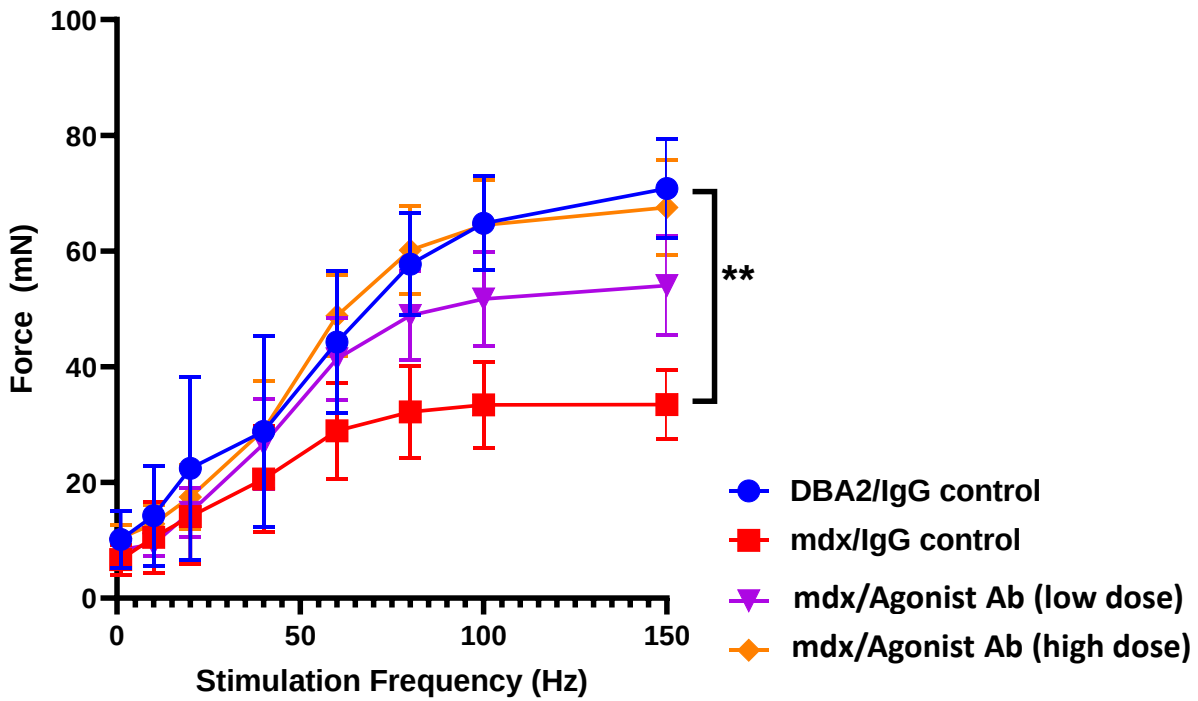
Antibody treatment protected against muscle damage

- 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



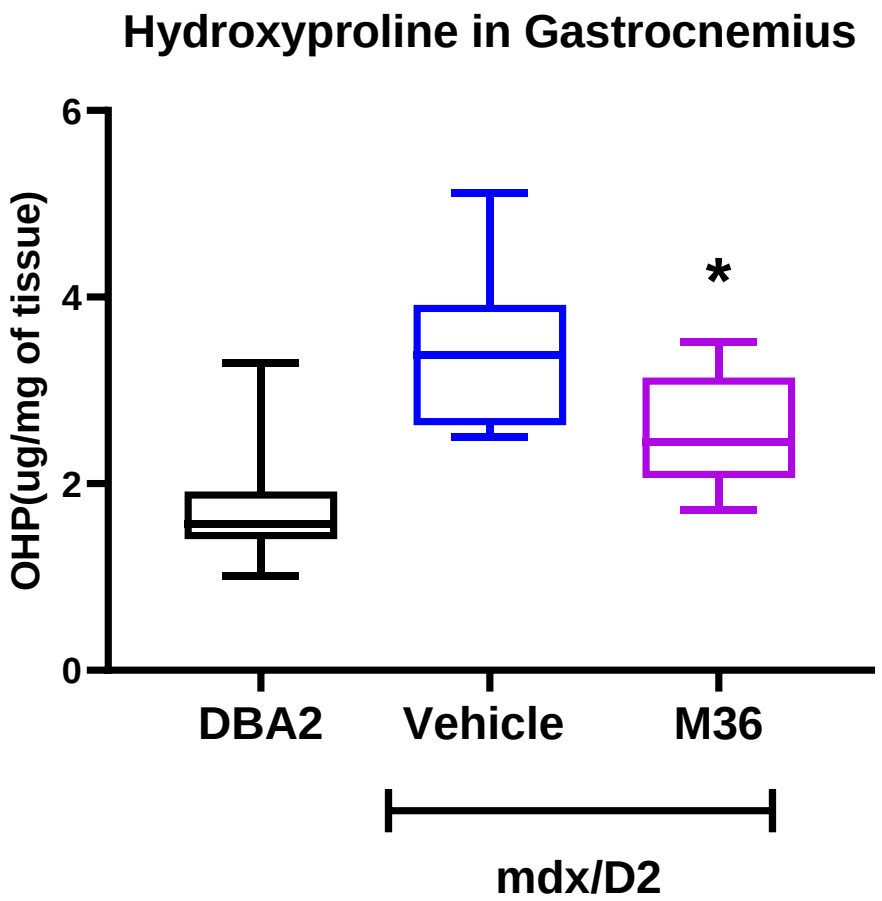


Mean +/- SD n=10/group

PLIANT

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

PLIANT

PLIANT

THERAPEUTICS