# UNITED STATES
# SECURITIES AND EXCHANGE COMMISSION
**Washington, D.C. 20549**

# FORM 8-K

**CURRENT REPORT**
**Pursuant to Section 13 OR 15(d) of the Securities Exchange Act of 1934**

**Date of Report (Date of earliest event reported): August 27, 2021**

# PIERIS PHARMACEUTICALS, INC.
**(Exact name of registrant as specified in its charter)**

| **Nevada** | **001-37471** | **30-0784346** |
|---|---|---|
| **(State or other jurisdiction of Incorporation)** | **(Commission File Number)** | **(IRS Employer Identification No.)** |

**255 State Street, 9th Floor** **02109**
**Boston, MA**
**(Address of principal executive offices)** **(Zip Code)**

**Registrant's telephone number, including area code: 857-246-8998**
**N/A**
**(Former name or former address, if changed since last report.)**

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

| **Title of each class** | **Trading Symbol(s)** | **Name of each exchange on which registered** |
|---|---|---|
| **Common Stock, $0.001 par value per share** | **PIRS** | **The Nasdaq Capital Market** |

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (17 CFR §230.405) or Rule 12b-2 of the Securities Exchange Act of 1934 (17 CFR §240.12b-2).

Emerging Growth Company ☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

**Item 7.01: Regulation FD Disclosure.**

Attached hereto as Exhibit 99.1 and incorporated by reference herein is the August 2021 PRS-220 IPF Summit Presentation.

The information set forth under this "Item 7.01. Regulation FD Disclosure," including Exhibit 99.1 attached hereto, shall not be deemed "filed" for any purpose, and shall not be deemed incorporated by reference into any filing under the Securities Act of 1933, as amended, or the Securities Exchange Act of 1934, as amended, regardless of any general incorporation language in any such filing except as shall be expressly set forth by specific reference in such filing.

**Item 9.01 Financial Statements and Exhibits**
(d) Exhibits.

99.1 PRS-220 IPF Summit Presentation, Dated August 2021.

**SIGNATURE**

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

PIERIS PHARMACEUTICALS, INC.

Dated: August 30, 2021

/s/ Tom Bures

Tom Bures

Vice President, Finance

# Inhaled Biologics:

## The Application of Anticalin® Proteins in the Treatment of IPF

**August 27th, 2021**

*IPF Summit 2021 – Dr. Vanessa Neiens*

-pieris-

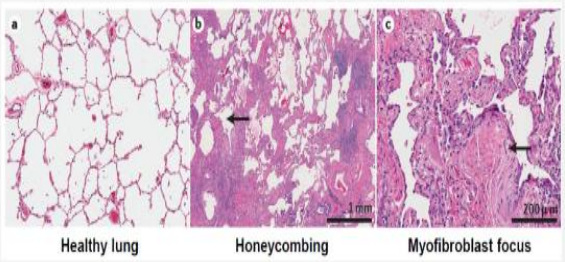
# Forward Looking Statements

This presentation contains forward-looking statements as that term is defined in Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended. Statements in this presentation that are not purely historical are forward-looking statements. Such forward-looking statements include, among other things, the timing for initiation of clinical trials of PRS-220, whether PRS-220 will provide a clinical benefit in the treatment of IPF and PASC-related fibrosis, whether the combination of cinrebafusp alfa with other therapies could address a high medical need in HER2 gastric cancer patients who do not respond to traditional HER2-targeted therapies; whether the effects of the combination of cinrebafusp alfa with other therapies seen in preclinical studies will be observed in clinical trials; whether data from patients enrolled to date will be sufficient to inform the recommended phase 2 dose for the Company's planned proof of concept study of cinrebafusp alfa in gastric cancer; the expected timing and potential outcomes of the reporting by the Company of key clinical data from its programs, references to novel technologies and methods and our business and product development plans, including the Company's cash resources, the advancement of our proprietary and co-development programs into and through the clinic and the expected timing for reporting data, making IND filings or achieving other milestones related to our programs, including PRS060/AZD1402, cinrebafusp alfa, PRS-344, and PRS-352 and the expected timing of the initiation of the next stage of cinrebafusp alfa's development in gastric cancer. Actual results could differ from those projected in any forward-looking statements due to numerous factors. Such factors include, among others, our ability to raise the additional funding we will need to continue to pursue our business and product development plans; the inherent uncertainties associated with developing new products or technologies and operating as a development stage company; our ability to develop, complete clinical trials for, obtain approvals for and commercialize any of our product candidates, including our ability to recruit and enroll patients in our studies; our ability to address the requests of the U.S. Food and Drug Administration; competition in the industry in which we operate; delays or disruptions due to COVID-19; and market conditions. These forward-looking statements are made as of the date of this presentation, and we assume no obligation to update the forward-looking statements, or to update the reasons why actual results could differ from those projected in the forward-looking statements, except as required by law. Investors should consult all of the information set forth herein and should also refer to the risk factor disclosure set forth in the reports and other documents we file with the Securities and Exchange Commission available at www.sec.gov, including without limitation the Company's Annual Report on Form 10-K for the fiscal year ended December 31, 2020 and the Company's Quarterly Reports on Form 10-Q.

# Idiopathic Pulmonary Fibrosis (IPF) is a Life-threatening Disease with the Need for Effective Therapies

## IPF – a chronic lung disease:

ultimately fatal lung disease of unknown cause characterized by progressive scarring of the interstitial lung tissue.




*Martinez, Nature Reviews Disease Primer, 2017*

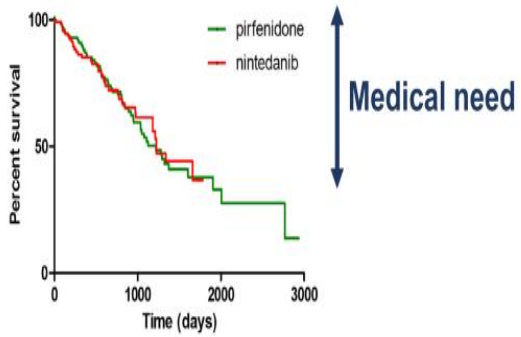
**2 to 5 years**

**median survival from the time of diagnosis**

*Meltzer, Orphanet Journal of Rare Diseases, 2008*

**2**

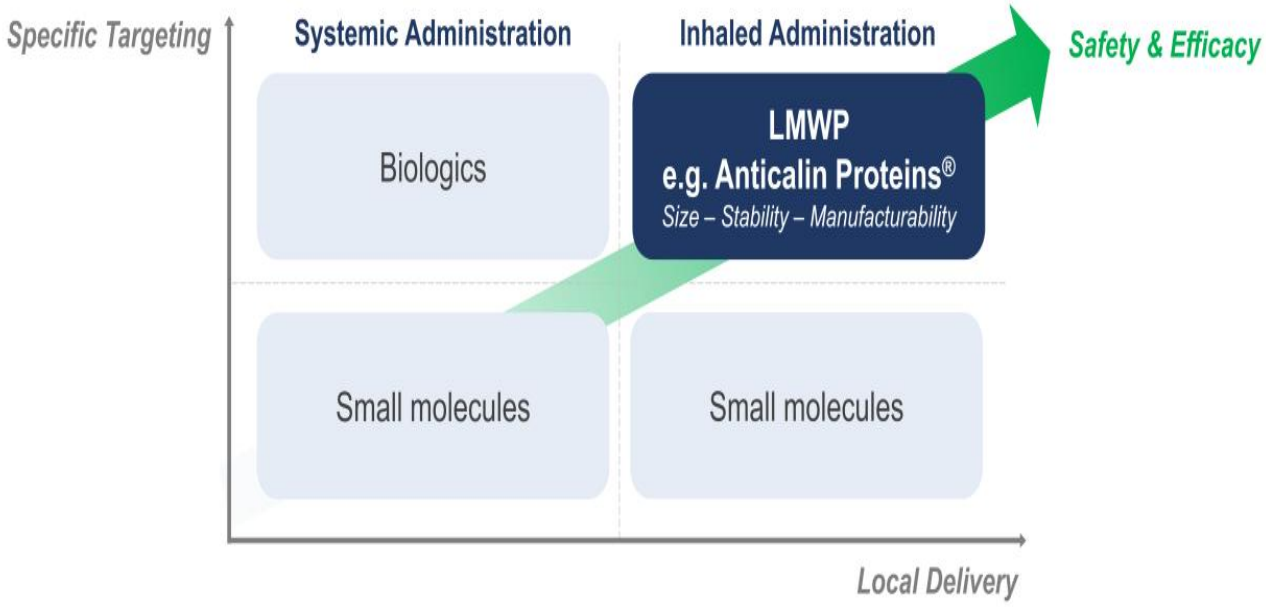
**approved therapies nintedanib & pirfenidone providing modest benefit with significant side effects**




*Adapted from Cameli, Frontiers in Molecular Biosciences, 2020*

**High medical need for well-tolerated and effective therapies**

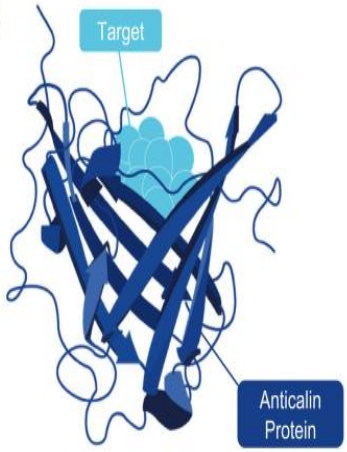
# Inhaled Low Molecular Weight Proteins (LMWP) are a Promising Strategy for IPF treatment



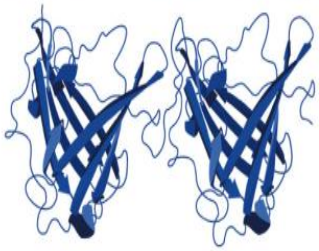

| Pieris Strategy | Local & specific targeting of profibrotic pathways in the lung via inhaled delivery of Anticalin proteins |
|---|---|

# Anticalin® Proteins are a Novel Therapeutic Class of Inhaled Low Molecular Weight Proteins

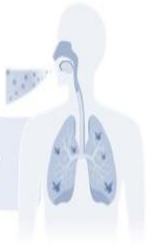
- **Human** – Scaffold derived from human lipocalins (extracellular binding proteins)
- **Specific** – High potency and selectivity for targets
- **Small** – Monomeric, monovalent, small size (~18 kDa vs ~150 kDa mAbs)
- **Stable** – High melting temperatures & insensitivity to mechanical stress
- **Formulable** – Nebulization & dry powder inhalation
- **Proprietary** – Broad IP position on platform and derived products
- **Validated** – Strong industrial partners and clinically tested
- **Innovative** – Modularity to build multispecific constructs




Innovative "Duocalin®" concept



**Favorable drug-like properties for lung delivery**

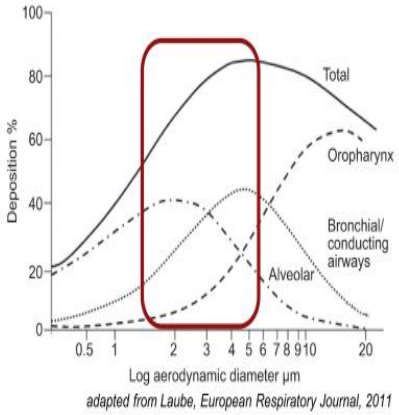


-pieris-

# Favorable Biophysical Properties of Anticalin Proteins Allow for Inhaled Delivery

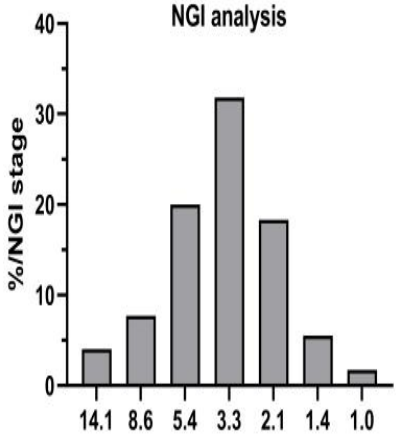
## Nebulization of Anticalin proteins using a vibrating mesh nebulizer:

**Particles < 5 µm (fine particle fraction) have greatest potential for deposition in the lung**




*adapted from Laube, European Respiratory Journal, 2011*

**Mass median aerodynamic diameter (MMAD) of Anticalin proteins upon nebulization is < 5 µm**




*Exemplary data of Monocalin*

| | Monocalin | Duocalin |
|---|---|---|
| MMAD | 4.4 µm | 4.9 µm |
| GSD | 2.0 | 1.8 |
| FPF | 58.2 % | 49.7 % |

MMAD: mass median aerodynamic diameter
GSD: geometric standard deviation
FPF: fine particle fraction
NGI: next generation impactor

- Aerodynamic properties suitable for effective lung deposition
- Anticalin proteins also suitable for dry-powder inhalation

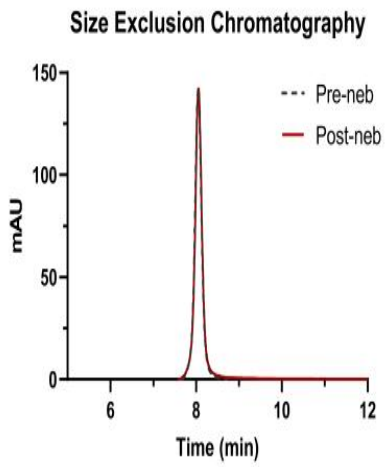
# Favorable Biophysical Properties of Anticalin Proteins Allow for Inhaled Delivery

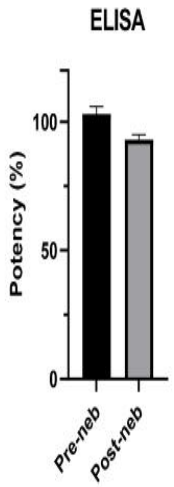
## Nebulization of Anticalin proteins using a vibrating mesh nebulizer:

**Key for successful development of inhaled proteins is to avoid:**

- Degradation
- Aggregation
- Denaturation
- Deamidation
- Oxidation

**High resistance of Anticalin proteins to stresses during aerosolization confirmed by post nebulization integrity testing**



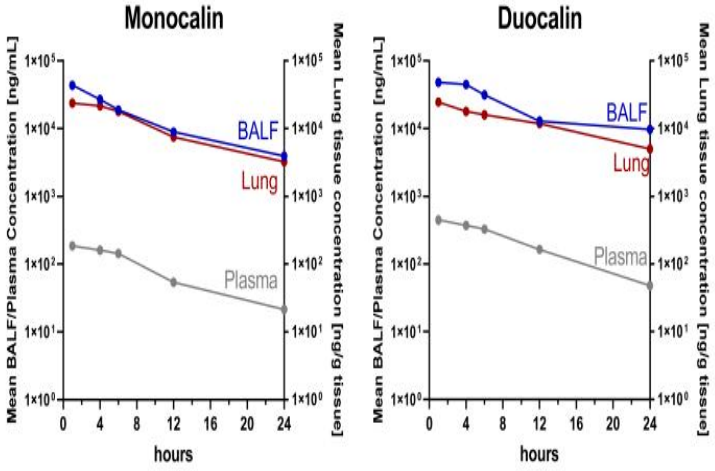




*Exemplary data from post nebulization integrity testing*

**Anticalin proteins retain stability and molecular integrity upon nebulization**

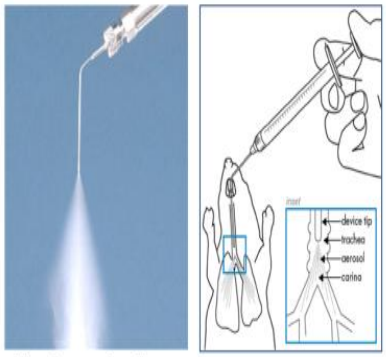
# Anticalin Proteins are Suitable for Once or Twice Daily Inhaled Administration

## Lung PK study following single intratracheal dose in mice




| | T1/2 (h) | | | Plasma exposure compared to lung (%)* |
|---|---|---|---|---|
| | BALF | Lung | Plasma | |
| Monocalin | 7.4 | 7.2 | 6.7 | 0.75 |
| Duocalin | 9.5 | 10.9 | 6.5 | 1.66 |

* Expsoure was set to 100% for compartment of administration




*MicroSprayer Aerolizer*

- Favorable PK profile for lung delivery
- <5% systemic availability
- ~100-fold split in lung:plasma concentrations

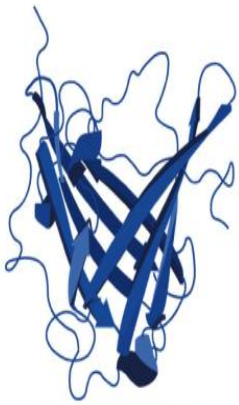
# Conclusion – Part 1

## Anticalin proteins -
## A novel class of inhaled biologics opening up new paths for innovative therapies

- Well suited for lung delivery based on favorable biophysical properties and small size
- Pharmacokinetic profile allows for once or twice daily inhaled dosing
- Possibility to generate bispecifics to increase biologic impact of future therapies
- Proof of concept for lung delivery and local target engagement by PRS-060/AZD1402, an inhaled IL-4Rα antagonist for the treatment of moderate to severe asthma (currently in Ph2a with our collaboration partner, AstraZeneca)

# PRS-220: A First-in-Class Inhaled CTGF Antagonist

| | |
|---|---|
| Candidate | PRS-220 |
| Function/MoA | Inhibiting CTGF/CCN2 |
| Indications | IPF and PASC-PF* |
| Development | Entering phase 1 in 2022 |
| Commercial Rights | Fully proprietary |



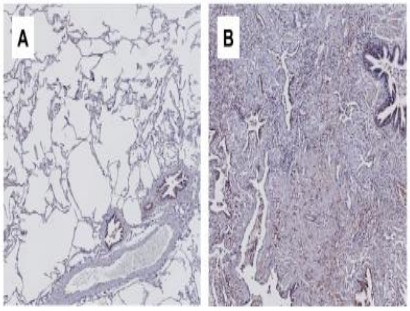
PRS-220

*Idiopathic Pulmonary Fibrosis and Post-Acute sequelae of SARS-CoV-2 infection (PASC) Pulmonary Fibrosis

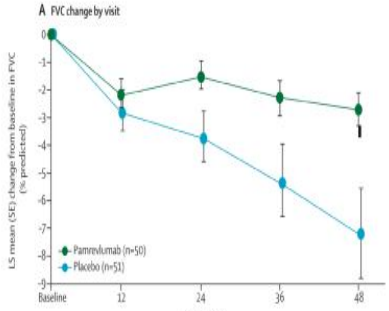
# CTGF is a Clinically Validated Intervention for IPF

## Connective Tissue Growth Factor (CTGF/CCN2): A driver of fibrotic remodeling

- Secreted, matricellular protein
- Highly expressed in lung tissue of IPF patients
- Affecting multiple processes & signaling pathways important in IPF pathophysiology
- Systemically delivered CTGF targeting mAb Pamrevlumab reduced the lung function decline in Ph2b clinical trial in IPF patients




CTGF immunohistochemistry of A) human control and B) IPF lung tissues (collaboration with Prof. Dr. Janette Burgess).




| | | | | |
|---|---|---|---|---|
| Pamrevlumab | -2·2 (0·6) | -1·5 (0·5) | -2·3 (0·7) | -2·7 (0·6) |
| Placebo | -2·8 (0·8) | -3·8 (0·9) | -5·3 (1·3) | -7·2 (1·7) |
| Absolute difference | 0·6 (0·9) | 2·3 (1·1) | 3·0 (1·5) | 4·5 (1·8) |
| 95% CI | (-1·3 to 2·5) | (0·1 to 4·4) | (0·1 to 6·0) | (0·9 to 8·0) |
| Relative difference | 22·2% | 59·8% | 57·0% | 62·4% |
| p value | 0·51 | 0·042 | 0·044 | 0·014 |

**Change in FVC from baseline in Pamrevlumab Ph2 clinical trial.**
*(Richeldi, Lancet Respiratory Medicine, 2020)*

# Inhaled Delivery of PRS-220 - a Novel Approach to Modulate CTGF Biology

## Key points of differentiation when compared to systemically delivered CTGF antagonists

**Local**

Better drug delivery to the site of the disease in the lung via inhalation

**Potent**

Better target saturation due to avoidance of systemic CTGF sink

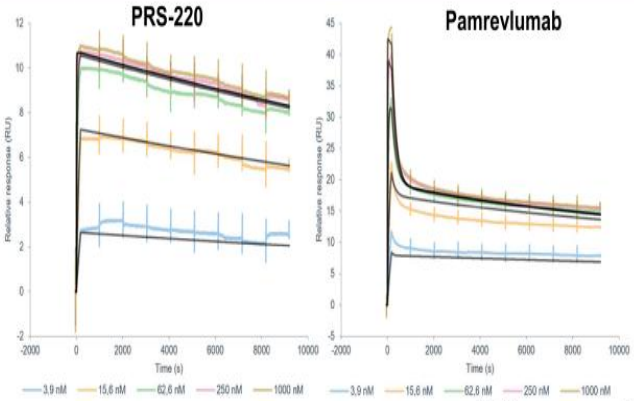
**Non-invasive**

Better convenience for patients (inhalation vs. i.v. administration)

# Superior Target Binding Properties of PRS-220 to Pamrevlumab

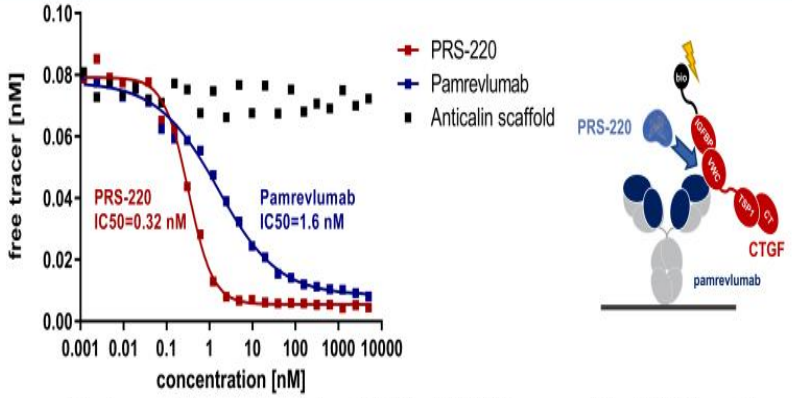
## Analysis of PRS-220 binding behavior

**PRS-220 shows prolonged target engangement through slower dissociation rate**




*SPR measurements on CTGF protein*

**PRS-220 binds to the clinically active epitope of CTGF with superior potency**



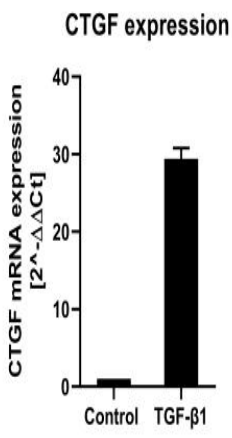

*Displacement of pamrevlumab from CTGF by PRS-220 in a competition ELISA-based format*

*Pamrevlumab was generated inhouse from patent signatures*

# PRS-220 Binds the Endogenously Expressed Target *in Vitro*

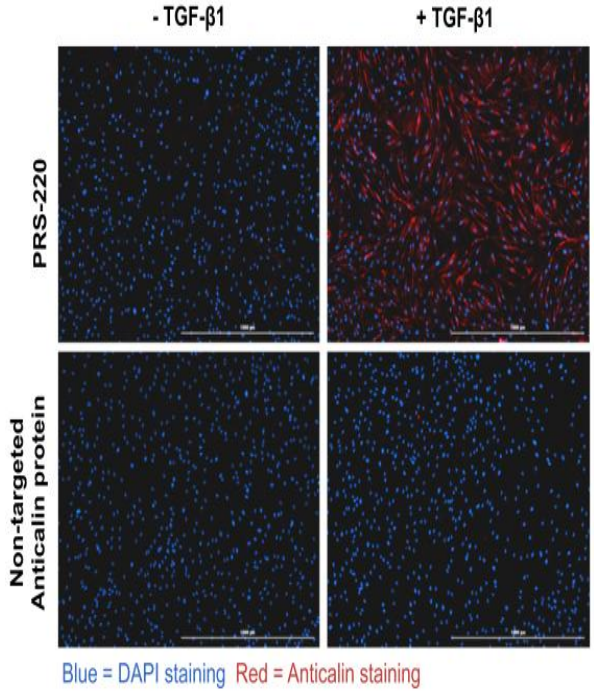
## *In vitro* target binding of PRS-220 to CTGF expressed on TGF-β1 activated NHLF

**TGF-β1 stimulation enhances CTGF expression of primary human lung fibroblasts**




*RT-qPCR analysis*

**PRS-220 binds to CTGF expressed on activated fibroblasts**




Blue = DAPI staining Red = Anticalin staining

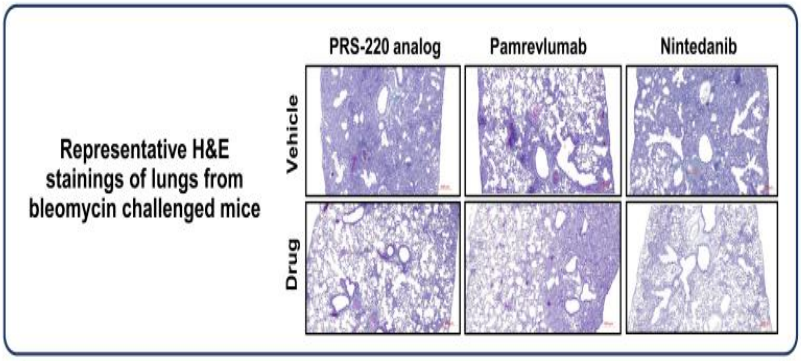
*Immunofluorescence staining of Anticalin Protein*

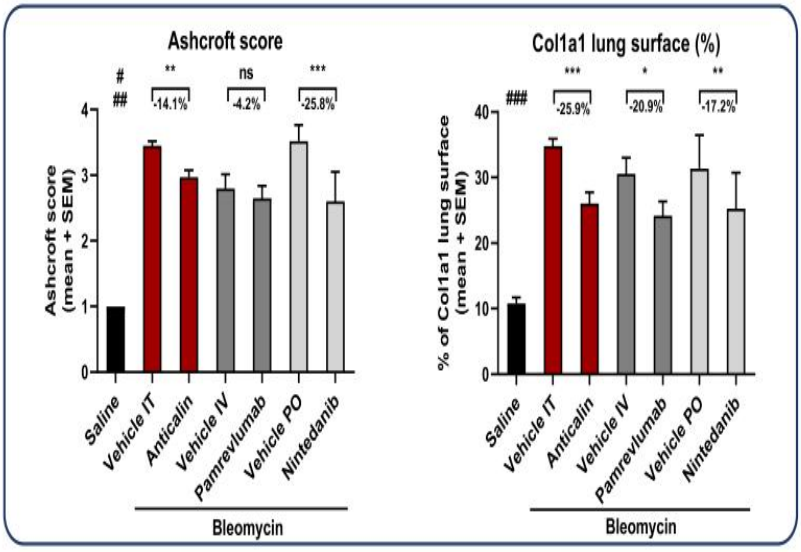
# PRS-220 Analog Delivered to the Lung Mediates Superior Anti-Fibrotic Effect *in Vivo*

## *In vivo* potency of PRS-220 analog in the bleomycin mouse model


*Treatment:*
*Anticalin*: 5 mg/kg IT QD, start D0*
*Pamrevlumab**: 10 mg/kg IV QAD, start D-1*
*Nintedanib: 60 mg/kg PO BID, start D0*

** Analog of PRS-220 targeting murine CTGF with higher affinity (KD = 0.039 nM)*
*** Pamrevlumab, generated inhouse from patent signatures*

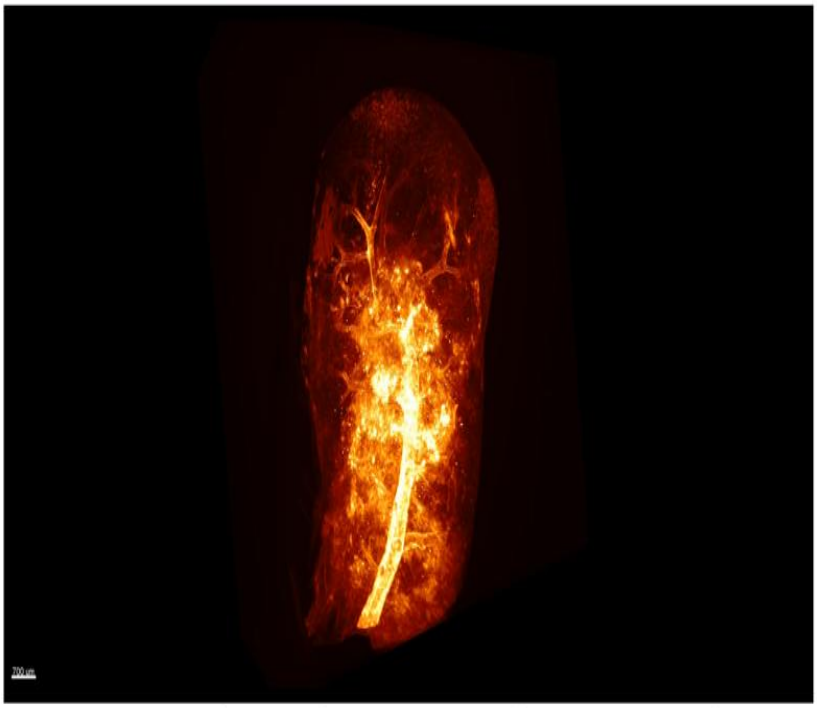


# Efficient Exposure of PRS-220 in Fibrotic Mouse Lungs

## Pilot lung biodistribution study of PRS-220 intratracheally delivered to fibrotic lungs of mice

**Alexa-647-labeled PRS-220 delivered intratracheally to bleomycin-challenged mice & imaged after 2 h by Light Sheet imaging**



*Glow scale = fluorescently labeled PRS-220, grey = tissue autofluorescence*

**PRS-220 shows a favorable tissue distribution profile & penetrates into small airways and lung interstitium**

# Conclusion – Part 2

- PRS-220 is an inhaled CTGF antagonist for the treatment of IPF and PASC-PF.
- PRS-220 shows best-in class potential based on:
  - strong target engagement
  - excellent stability and aerosol behavior upon nebulization
  - significant attenuation of lung fibrosis *in vivo* by targeting CTGF locally in the lung
  - favorable preclinical PK and lung biodistribution

**PRS-220's preclinical profile supports proceeding to clinical development, with a planned start of Phase 1 studies in 2022.**

# Presentation at European Respiratory Society Congress 2021


**Abstract: Development of PRS-220, a potential best-in-class, inhaled CTGF/CCN2 inhibitor for the treatment of IPF**

**Session:** Poster Session - Developments in biomarkers and treatment strategies for chronic lung diseases

**Time:** September 5th 2021, 1:15-2:15 pm (CET)

# Acknowledgements


## The PIERIS team:

Marina Pavlidou
Gabriele Matschiner
Thomas Jaquin
Eva-Maria Hansbauer
Cornelia Wurzenberger
Claudia Wurzenberger
Stefan Grüner
Janet Peper-Gabriel
Rachida Siham Bel Aiba
Alexander Hahn
Mareike Maurer
Kristina Heinig
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Theresia Mosebach
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Patrick Zägel
Josefine Morgenstern
Adam Cichy
Antonio Konitsiotis
Mary Fitzgerald
Josef Prassler
Jimmie Hofman
Shane Olwill

... and the extended team!

## & our advisors, supporters & collaborators!

***For further questions feel free to reach out via e-mail:***

***neiens@pieris.com***

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Bavarian Ministry of Economic Affairs,
Regional Development and Energy

**FUNDING:** This work is partially funded by a grant from the Bavarian Ministry of Economic Affairs, Regional Development and Energy within the framework of the Bavarian Therapy Strategy to combat the COVID-19 pandemic ("BayTherapie2020").


-pieris-

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NASDAQ: PIRS


BACK-UP

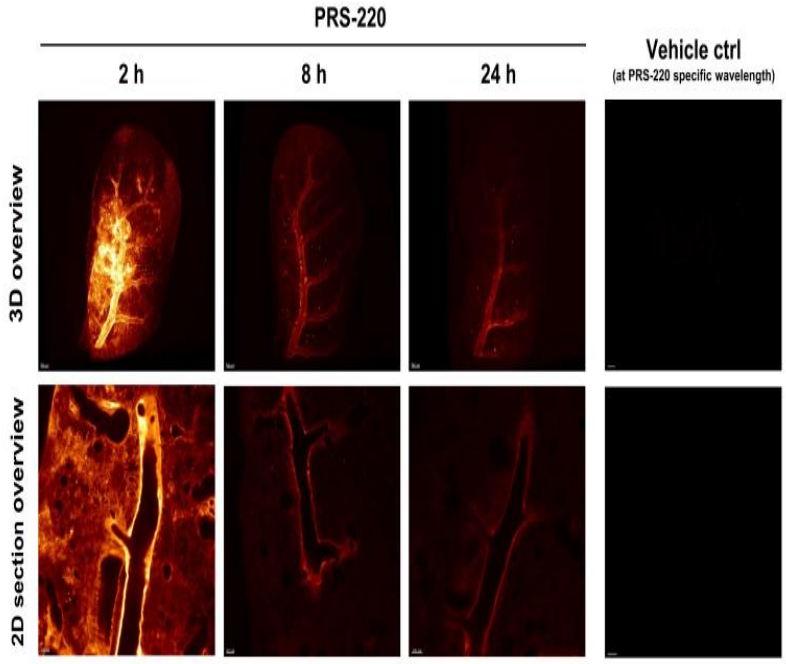
# Efficient tissue distribution of PRS-220 in fibrotic lungs of mice

## Pilot lung biodistribution study of PRS-220 intratracheally delivered to fibrotic lungs of mice

**Aim:** Does PRS-220 distribute into areas of the fibrotic lung relevant for effective treatment?

**Experimental procedure:**


*Treatment:*
*Alexa647-labeled PRS-220: 100 µg/mouse*
*single intratracheal administration*
*Analysis:*
*Investigation of drug distribution using Light sheet imaging of whole left lung*




*Glow scale = Fluorescently labeled PRS-220*

**PRS-220 shows a favorable tissue distribution profile & penetrates into small airways and lung interstitium**