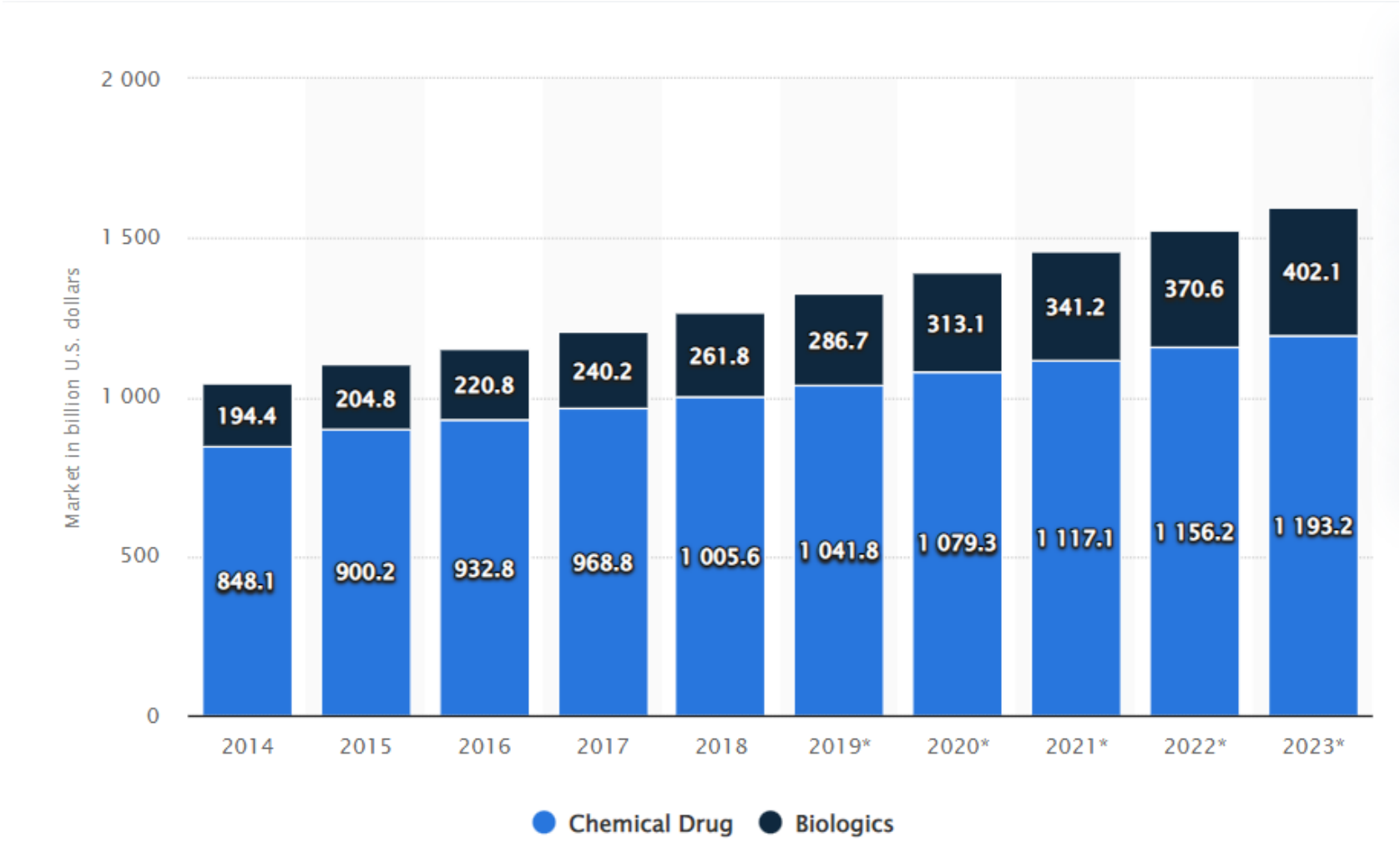
Targeted Anticalin® Protein Therapies to Treat Cancer and Respiratory Diseases

Hitto Kaufmann
PharmGZ March 2nd 2023

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, whether PRS-220 will provide a clinical benefit in the treatment of IPF and PASC-related fibrosis; the receipt of royalty and/or milestone payments provided for in our collaboration agreements; 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 elarekibep (PRS-060/AZD1402), PRS-344/S095012, PRS-220, PRS-352/S095025, PRS-342/BOS-342, PRS-346/SGN-BB228 and PRS-400; our continued progress in the areas of co-stim bispecifics and inhaled therapeutics; the therapeutic potential of our Anticalin platform; the potential addressable market for our product candidates; and the advancement of and funding for our developmental programs generally. 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 or geo-political issues, including the conflict in Ukraine; 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, 2021 and the Company’s subsequent Quarterly Reports on Form 10-Q.

Market Value of Biopharmaceuticals



Source: https://www.statista.com

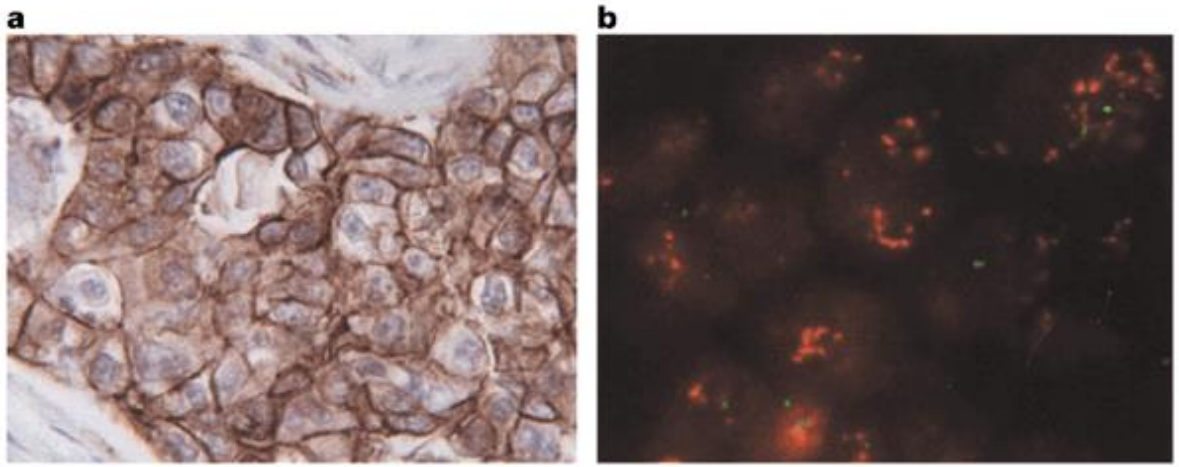
Herceptin®/Trastuzumab

Humanized monoclonal antibody binding the **tyrosine kinase Her2/ErbB2**

25-30% of all breast carcinomas overexpress Her2/ErB2 – poor prognosis

Approved for the European market in 2000

- used as first line therapy to treat metastatic HER2-overexpressing breast cancer in combination with Paclitaxel (Taxol® (BMS))
- used as monotherapy after two unsuccessful chemotherapies



Nature Reviews | Molecular Cell Biology

a) Immunohistochemistry and

b) fluorescence in situ hybridization (FISH) analysis of ErbB2 in human breast cancer. The ErbB2 gene is seen as red fluorescence and the chromosome-17 centromeric a-satellite probe as green fluorescence.

Checkpoint Inhibitor Therapy

mAbs have been developed to block checkpoint inhibitors

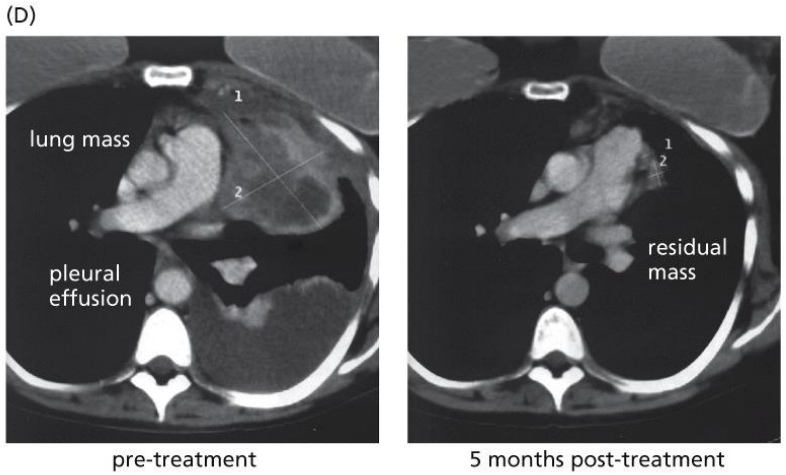
PD-1 inhibitors include:

- **Pembrolizumab (Keytruda)**
- **Nivolumab (Opdivo)**
- **Cemiplimab (Libtayo)**

PD-L1 inhibitors include:

- **Atezolizumab (Tecentriq)**
- **Avelumab (Bavencio)**
- **Durvalumab (Imfinzi)**

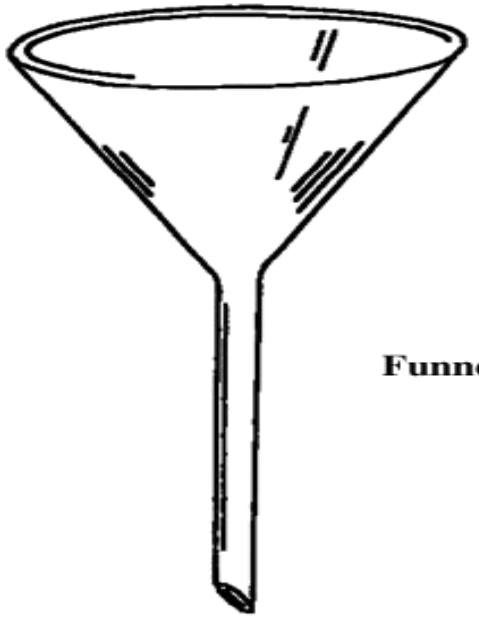
melanoma skin cancer
Hodgkin lymphoma
non small cell lung cancer
cancer of the urinary tract (urothelial cancer)



Driver for growth: Biotechnology - Partnering

biotech companies

- ⇨ new technologies
- ⇨ innovative products
- ⇨ agility

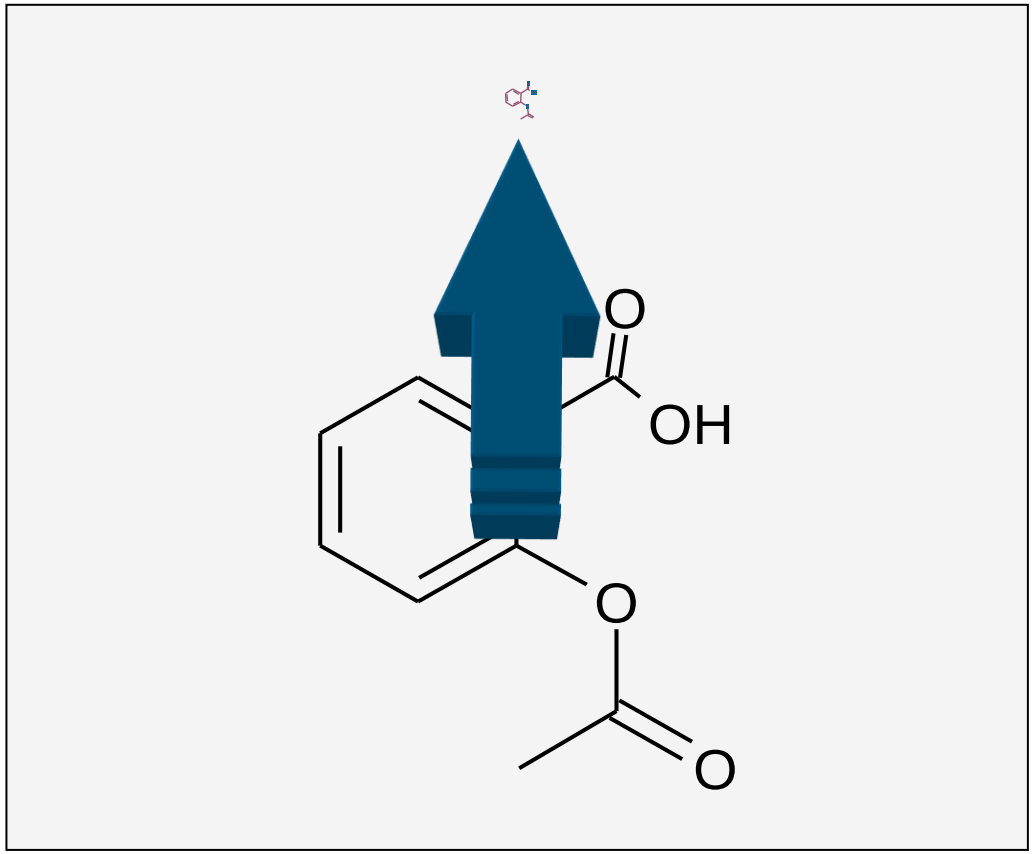


big pharma

- ⇨ expertise and resources in/for launch, registration and marketing
- ⇨ financial resources

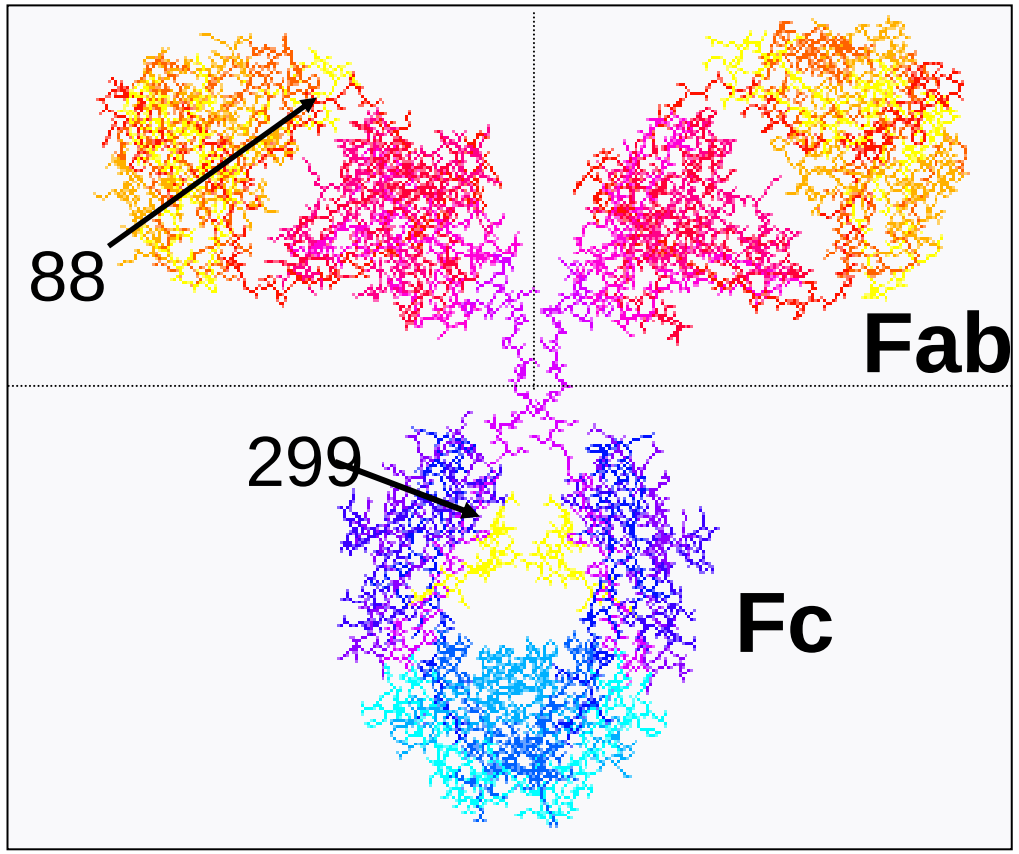
- ⇨ growth potential
- ⇨ increase in flexibility
- ⇨ reduced risk

Comparison small molecules vs therapeutic protein



Acetylsalizylsäure

$C_9H_8O_4$ (Mw = 180)

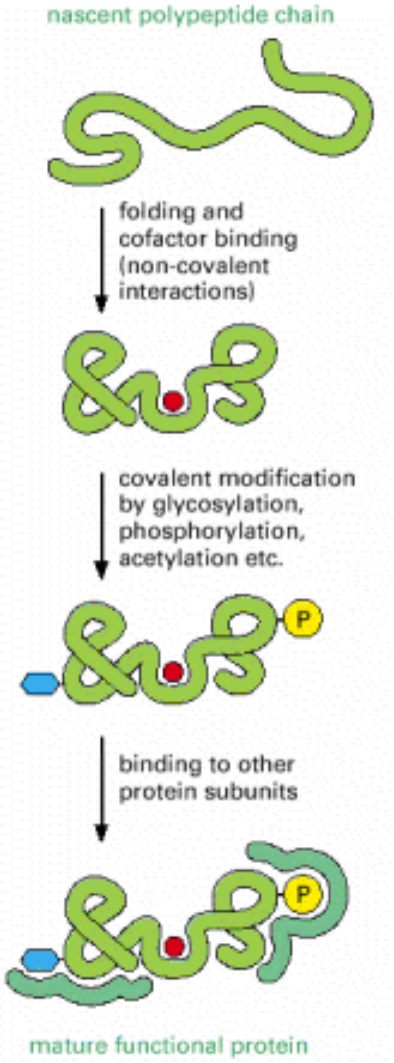


Antikörper

$C_{6466}\ H_{9982}\ N_{1726}\ O_{2024}\ S_{40}$ (Formula from amino acid sequence) (Mw = 146.000)

Creation of a Functional Protein

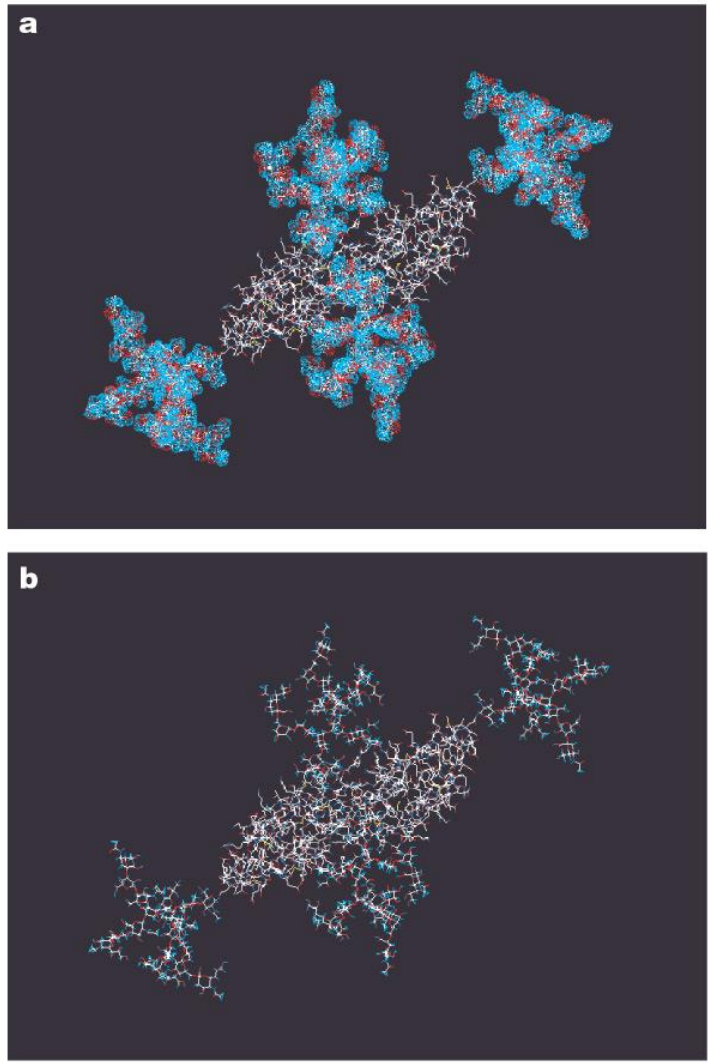
- Translation of an mRNA sequence into an amino acid sequence on the ribosome is not the end of the process of forming a protein
- To be functional as a human therapeutic, the completed polypeptide chain must fold correctly into its three-dimensional conformation, bind any cofactors required, and assemble with its partner protein chains (e.g. antibodies)
- Many proteins also have covalent modifications made to selected amino acids. Most frequent covalent post-translational-modifications (PTM) are protein glycosylation and protein phosphorylation, however, more than 100 different types of covalent modifications are known



PTM - Strong Impact on Protein Properties

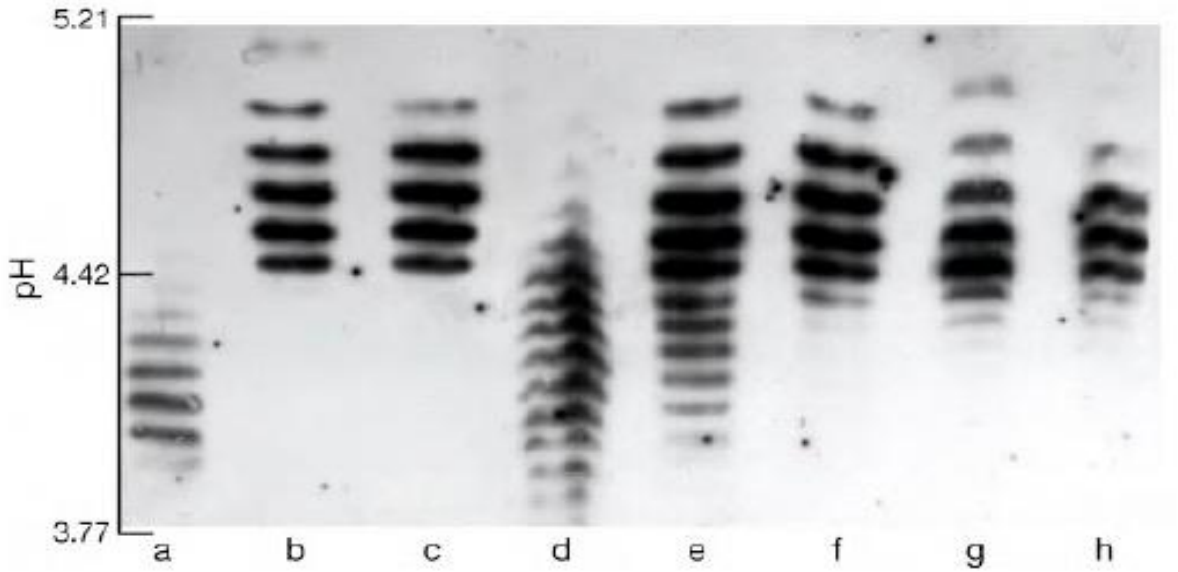
Structure of glycosylated glucocerebrosidase.

Panels show glycosylated glucocerebrosidase with (**a**) and without (**b**) glycans highlighted to illustrate the extent to which glycans influence the hydrodynamic volume and surface properties of glycoproteins



Nature Reviews | Microbiology

A little story about EPO.....

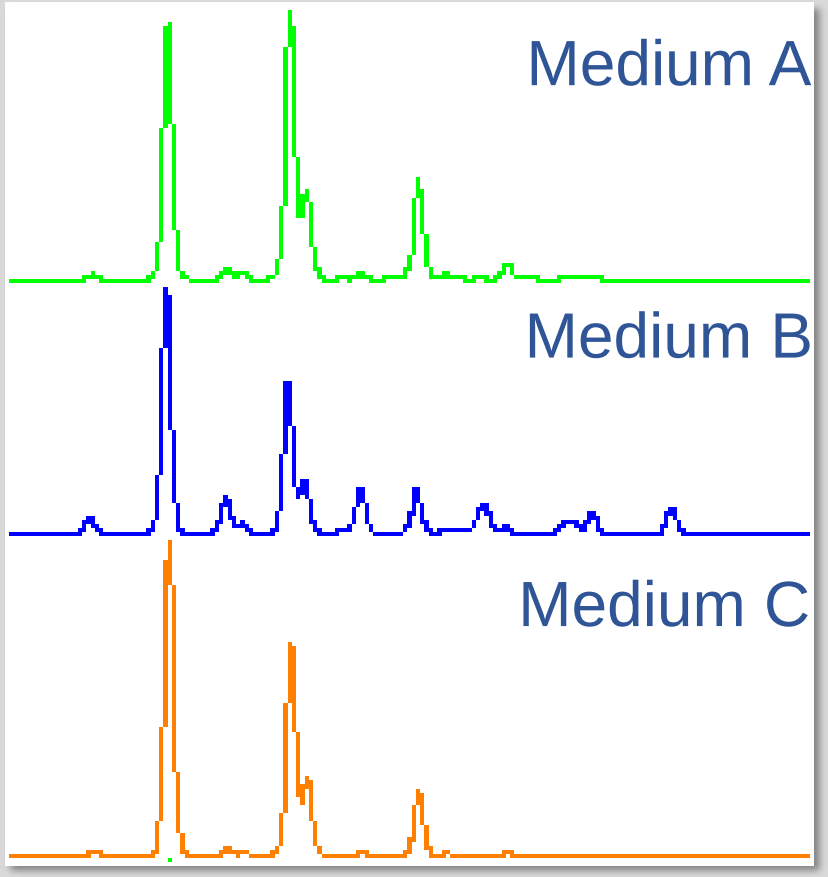


Isoelectric patterns of exogenous and endogenous erythropoietin (EPO)

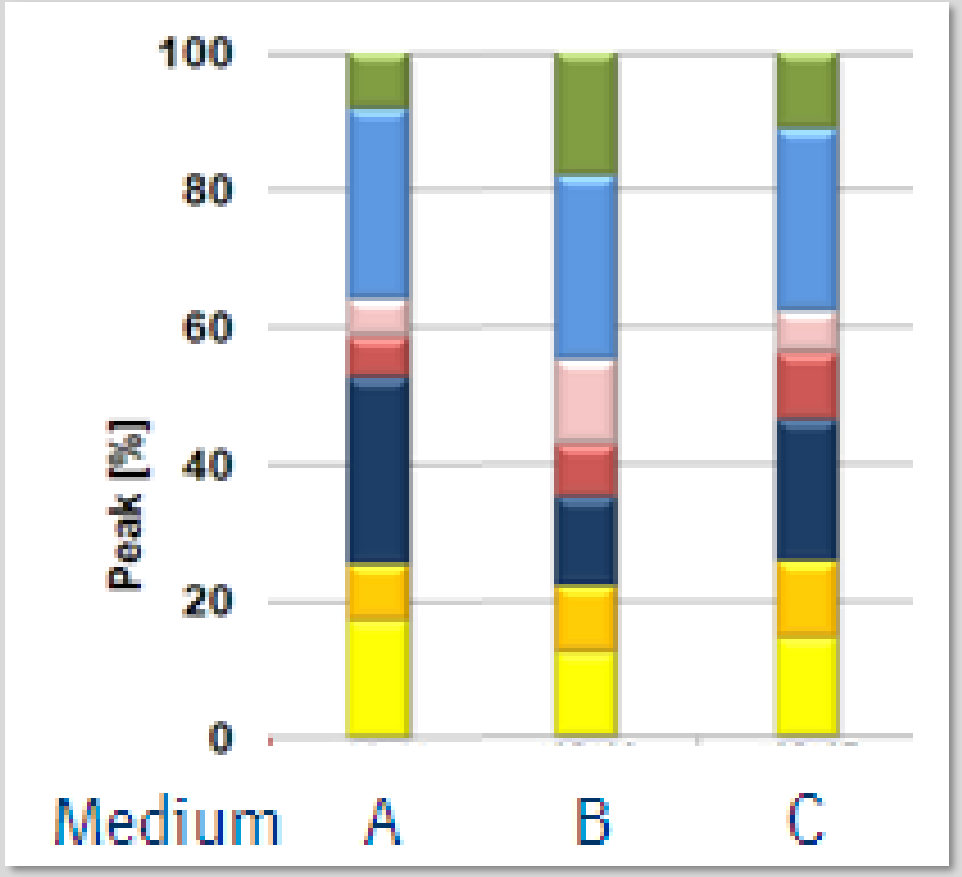
a	purified commercial human urinary EPO (Sigma)
b and c	recombinant human EPO
d	urine from a control subject
e and f	urine from 2 patients treated with recombinant EPO for post-haemorrhagic anemia
g and h	urine from two cyclists from Tour de France 1998

The process defines the product: example media

Glycosylation Profile



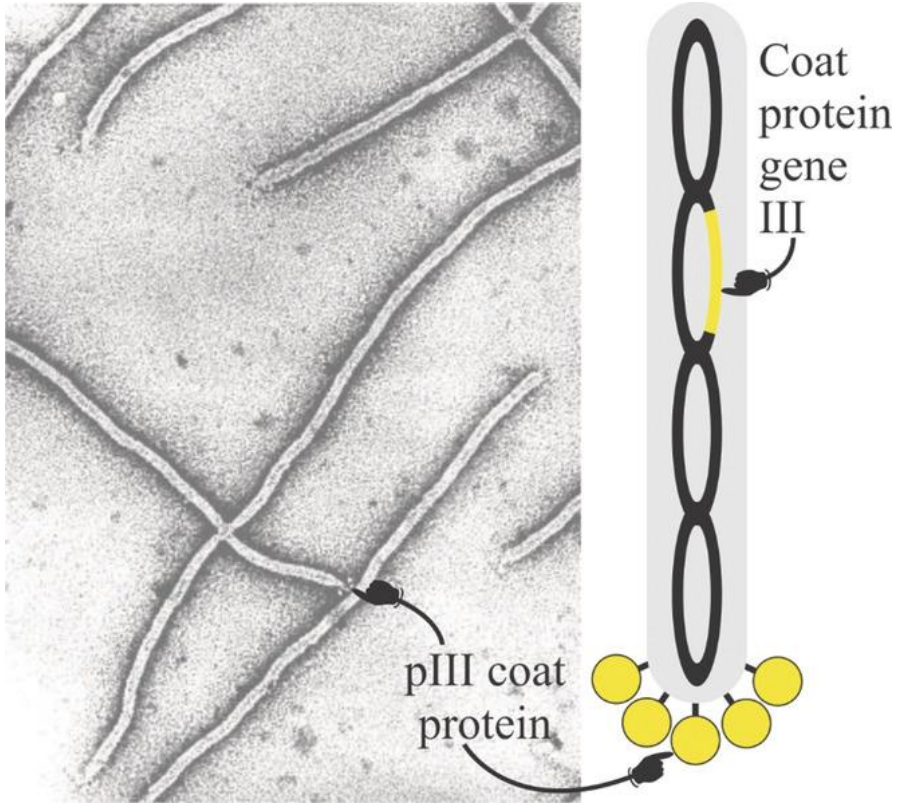
WCX Profile



source: H. Kaufmann, Bioprocess International Conference, Düsseldorf, April 2013: Evolving Strategies for Successful Development of Biosimilar Manufacturing Processes.

Phage Display: Simple Evolution in a Petri Dish

(Nobel Price 2018)



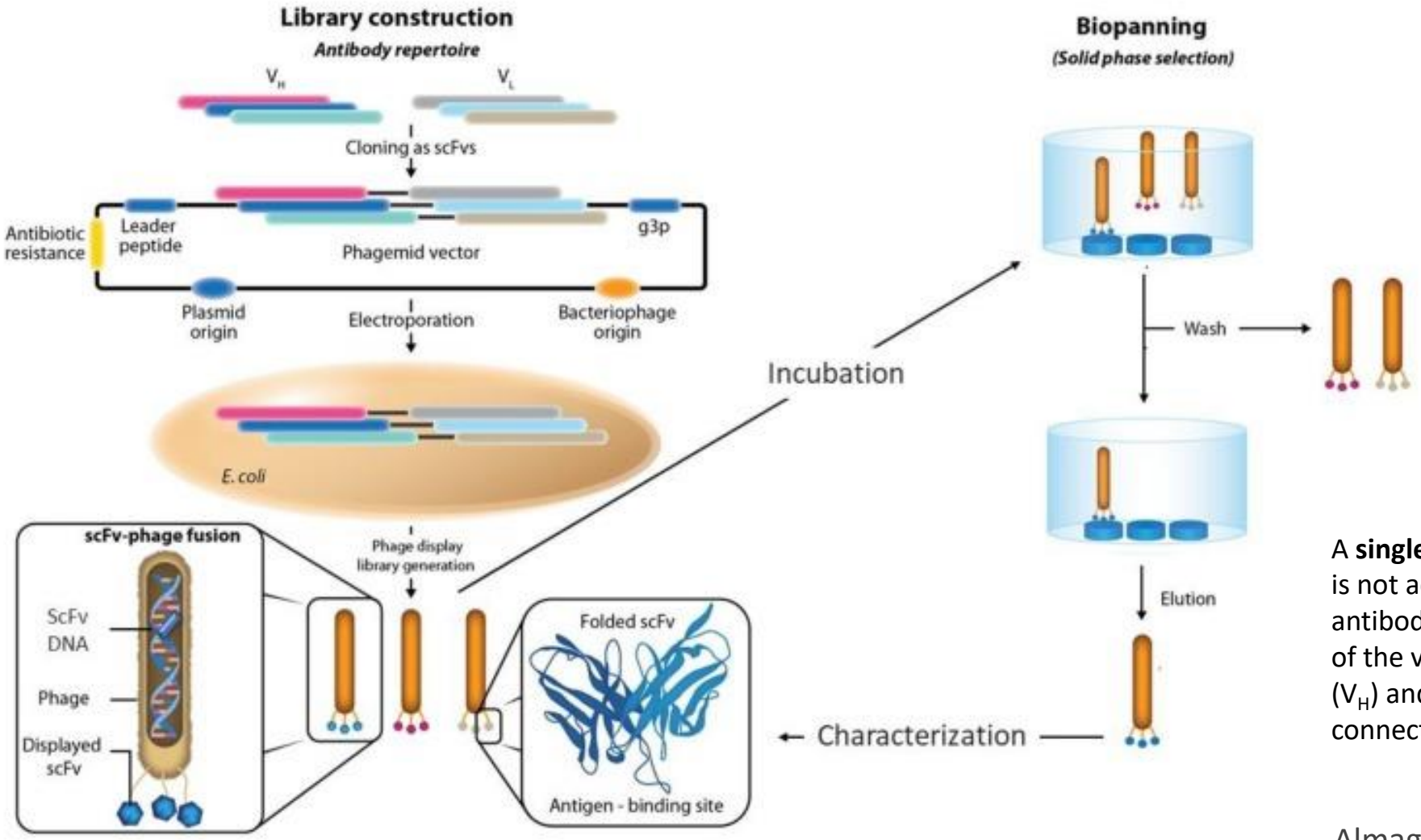
Artificial introduction of the phage chromosome into the bacterial cell via transfection initiates the same infection program as does natural infection

George P. Smith:

'It occurred to me that it might be possible to genetically fuse all or part of a foreign protein to the exposed parts of pIII without greatly impairing pIII's function in the phage infection cycle. If so, the foreign amino acids would be displayed at the tip of the virion, where they would be accessible to macromolecules such as antibodies and receptors'

Angew. Chem. Int. Ed., Volume: 58, Issue: 41, Pages: 14428-14437, First published: 17 September 2019, DOI: (10.1002/anie.201908308)

Phage Display



A **single-chain variable fragment** (**scFv**) is not actually a fragment of an antibody, but instead is a fusion protein of the variable regions of the heavy (V_H) and light chains (V_L) of IgGs connected with a short linker peptide

Almagro et al, Antibodies, 2019

Pieris Pharmaceuticals - Company Overview

Pieris Overview

- Nasdaq-listed (PIRS)
- Operations in Boston (HQ) and Munich (main R&D site)
- ~150 employees

Anticalin Platform

- Anticalin proteins designed to exploit validated biology and engineered for focused activity at disease locus
- Improved activity, reduced side effects, increased convenience

Two Focus Areas

- Oral inhaled antagonists for respiratory disease
- Locally activated immuno-oncology bispecifics

Partnerships

SERVIER AstraZeneca Seagen BOSTON pharmaceuticals Genentech A Member of the Roche Group

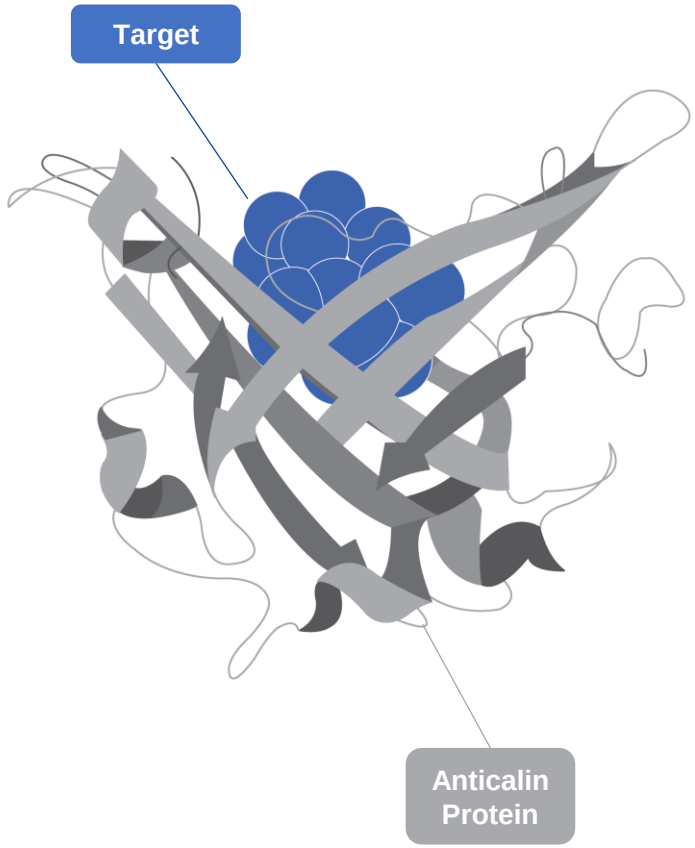
Anticalin® Proteins as Therapeutic Modalities

A Novel Therapeutic Class with Favorable Drug-Like Properties

- **Human –** Derived from lipocalins (human extracellular binding proteins)
- **Small** – Monomeric, monovalent, small size (~18 kDa vs. ~150kDa mAbs)
- **Stable** – Inhalable delivery
- **Simple** – Bi/multispecific constructs
- **Proprietary** – Strong IP position on platform and derived products

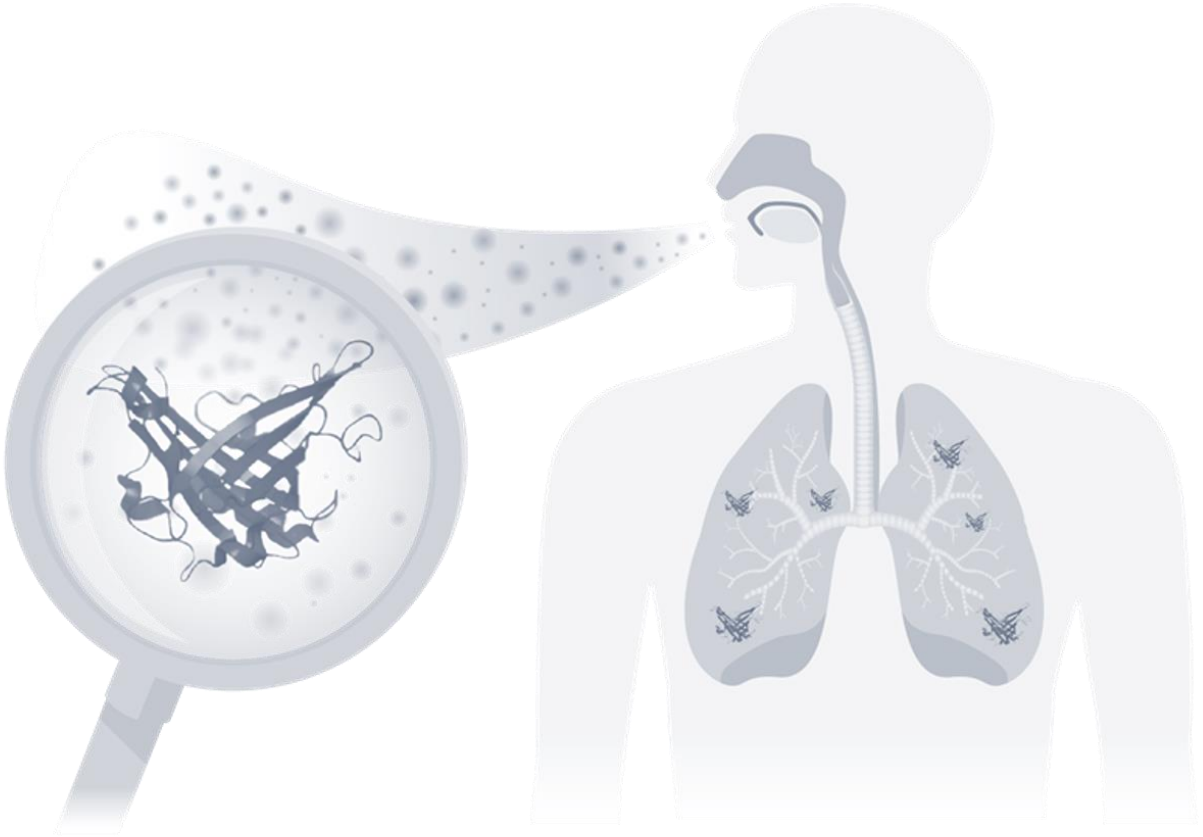
Translational Science Expertise to Deploy Platform in Meaningful Way

- Immunology expertise underpins IO and respiratory focus
- A leader in 4-1BB and costim biology
- Patient stratification efforts for improved stratification and novel targets in, e.g., asthma

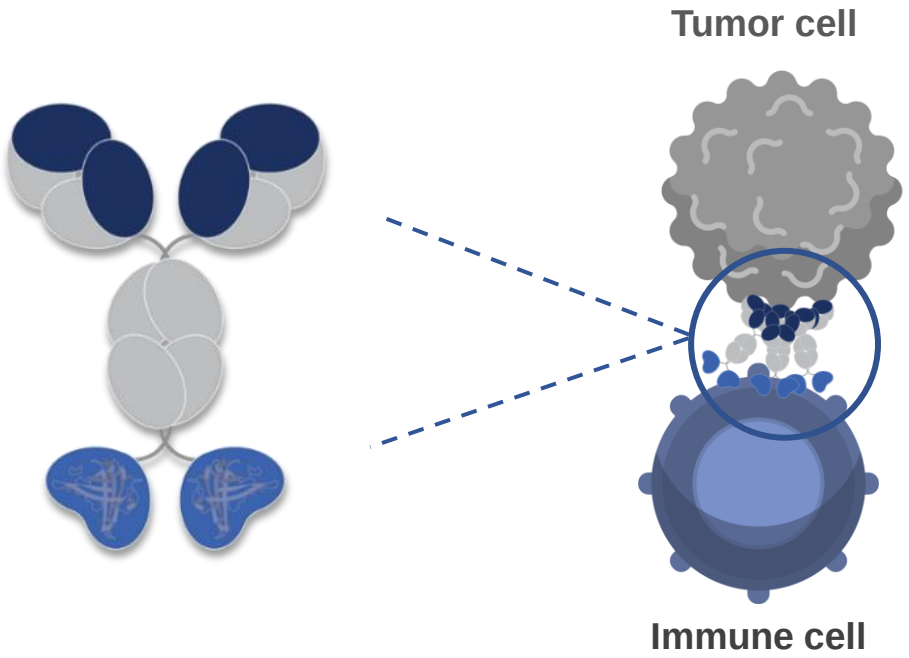


Two-fold Focus of Anticalin Platform Deployment

Inhalable formulations to treat respiratory diseases locally



Bispecifics for local immune agonism to treat cancer

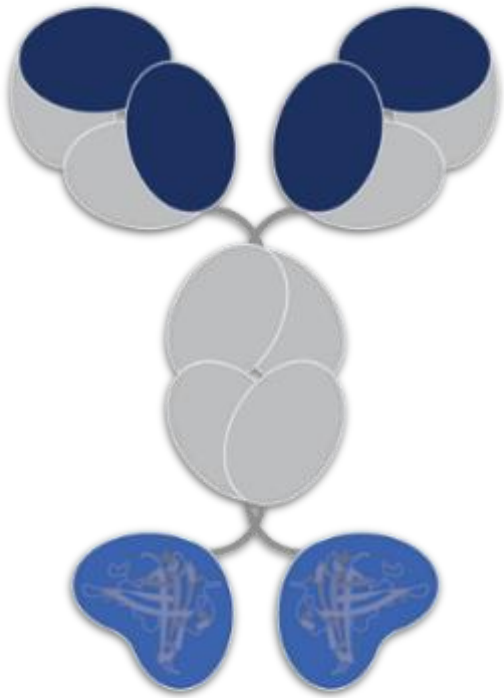


Immuno-Oncology Pipeline

Program	Target	Indication	Discovery	Preclinical	Phase 1	Phase 2	Partner
PRS-344/ S095012	4-1BB/PD-L1	n.d.	~50% co-dev cost share				SERVIER
PRS-346/ SGEN-BB228‡	4-1BB/CD228	n.d.					Seagen
PRS-352/ S095025	OX40/PD-L1	n.d.					SERVIER
PRS-342/ BOS-342	4-1BB/GPC3	n.d.					BOSTON pharmaceuticals

‡ *One additional active bispecific program in collaboration with Seagen, with Pieris retaining a U.S. co-promotion option in one of the programs in the collaboration*

Mabcalin™ proteins– a versatile class of bi-specifics with superior properties



- Design resulted from systematic functional studies
- Validated in clinical studies (additional two programs with anticipated FIH within the next 6 months)
- No mispairing
- Established developability workflow
- Robust high-yield manufacturing already for Phase I demonstrated
- < 130 Euro per gramm COGS achievable for commercial

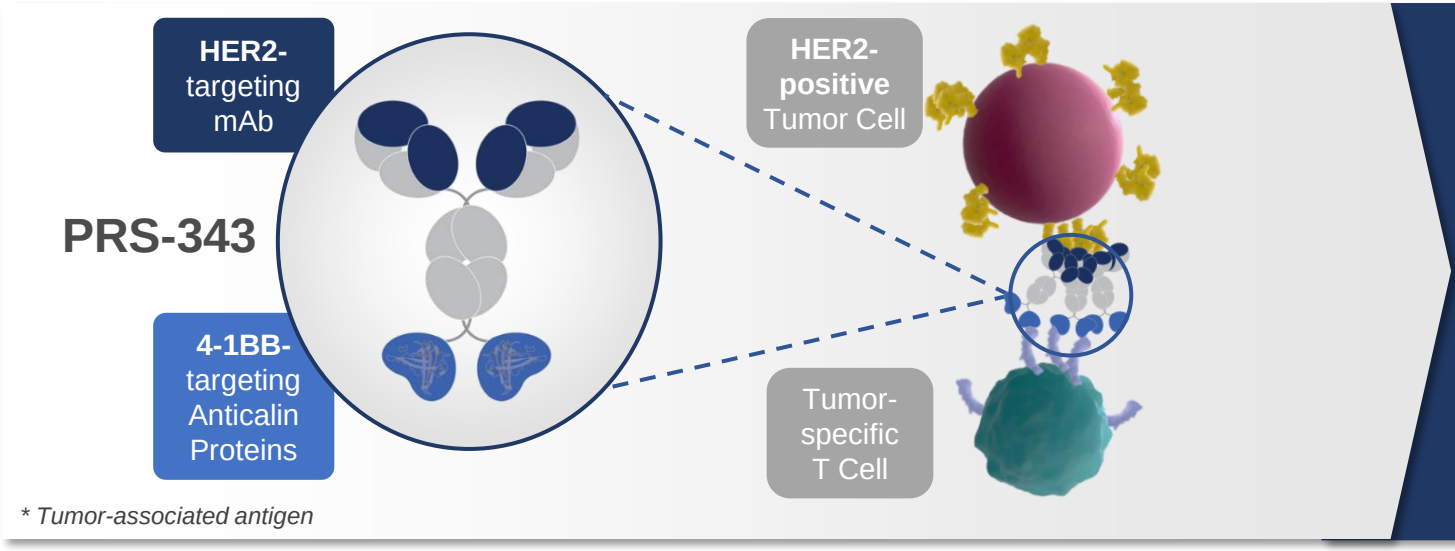
4-1BB Agonism Offers Promise of Strong & Durable Clinical Benefit
Pieris' Bispecifics Drive Desired Effect Locally in the Tumor Microenvironment

Unique Attributes of 4-1BB Agonism on Tumor-specific T cells…

- ✓ Increased T cell proliferation & enhanced cytotoxicity
- ✓ Central memory formation[1]
- ✓ Enhanced mitochondrial function & metabolic fitness[2]
- ✓ Enhanced anti-tumor activity via both innate & adaptive immunity[3]

…Offer Important Anti-Tumor Benefits

- ➢ Turn cold tumors hot
- ➢ Increased number of cytotoxic T cells
- ➢ Potent and durable anti-tumor response
- ➢ Survival of T cells in immunosuppressive TME



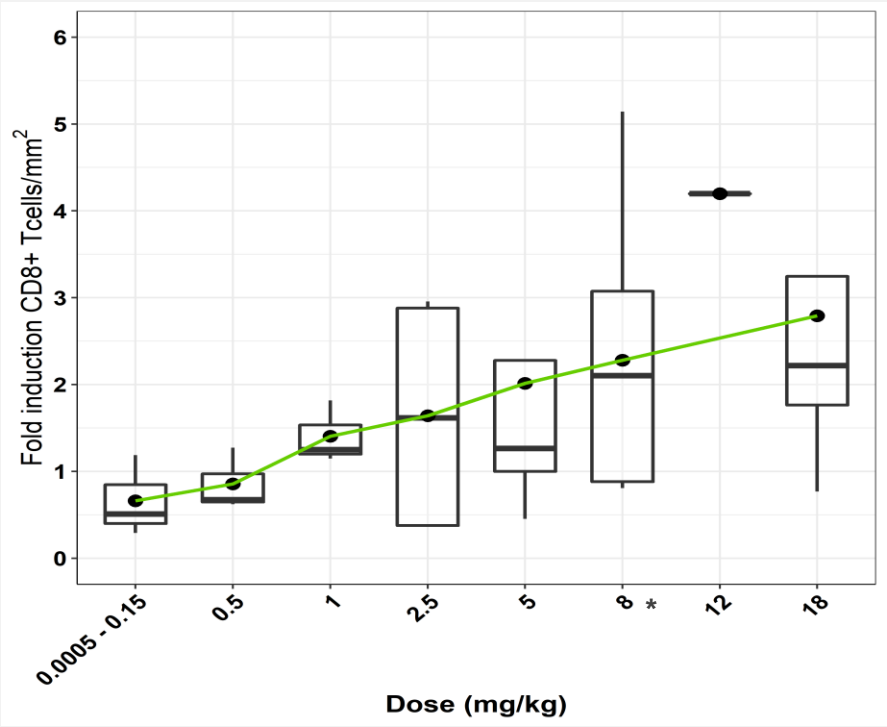
** Tumor-associated antigen*

Tumor-localized MoA of Pieris' 4-1BB-based bispecifics enables full immune activation while avoiding systemic toxicities

1. *Bartkowiak and Curran, In Preparation.*
2. *Teijeira and Melero, CIR. 2018.*
3. *Bartkowiak and Curran, Front Oncol 2015*

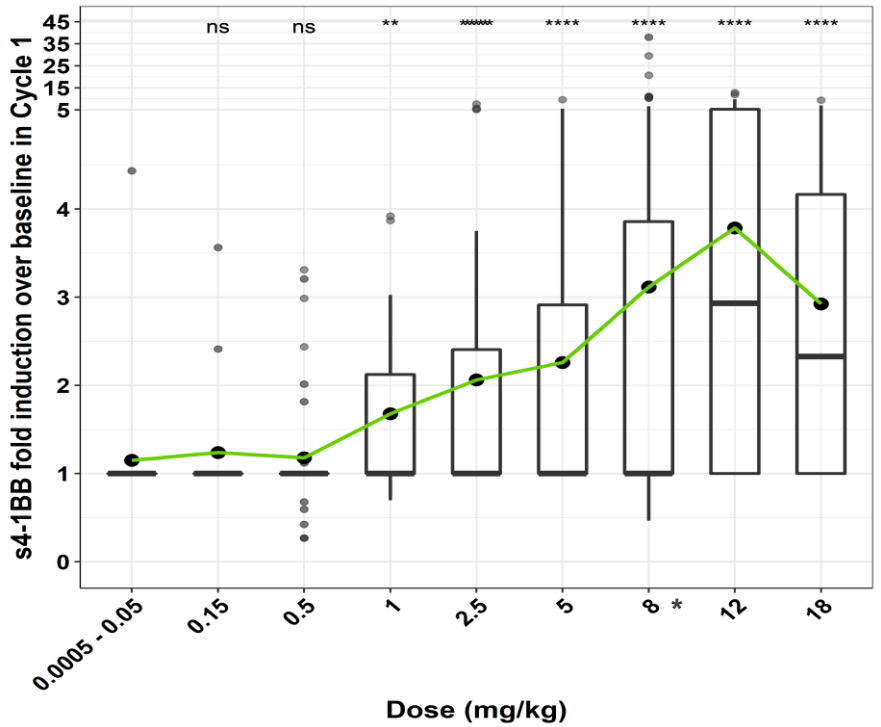
PRS-343 Shows Dose Dependent Activity Across Key Pharmacodynamic Parameters

Tumor (CD8+)



Connects group averages — Median

Serum (s4-1BB)

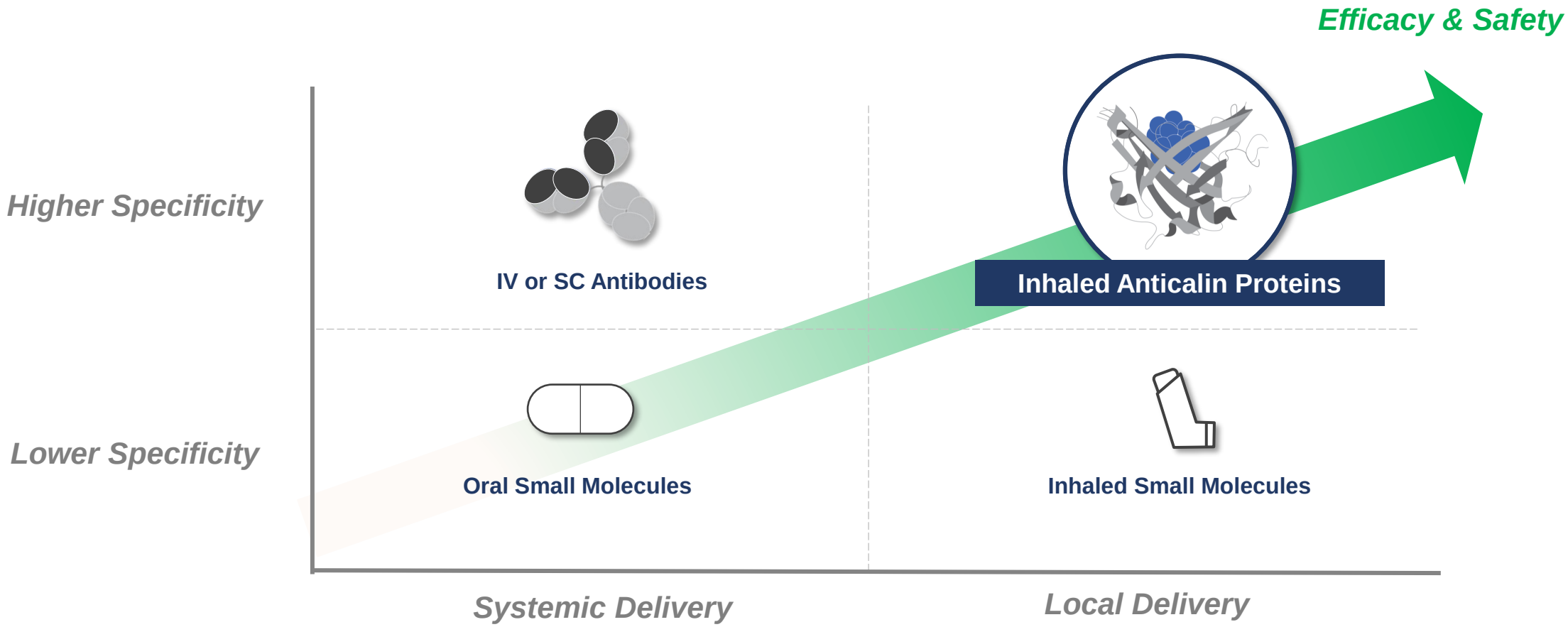


Mann-Whitney U test

- CD8+ T cells and soluble 4-1BB increase in a dose-dependent manner
- 4-1BB specific target engagement observed in both tumor and blood
- Demonstrates activity of PRS-343's 4-1BB arm

* Dose at 8 mg/kg incorporates patients treated at Q1W, Q2W or Q3W

Combined Potential Advantages of Higher Specificity with Local Delivery



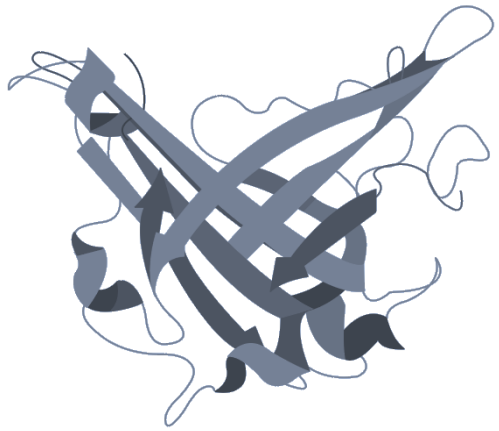
Respiratory Pipeline

Program	Target	Indication	Discovery	Preclinical	Phase 1	Phase 2	Partner
Elarekibep* (PRS-060/AZD1402*)	IL4Rα	Asthma	Phase 2a fully sponsored by AZ; co-dev option				AstraZeneca
PRS-220	CTGF	IPF, PF-ILD, PASC-PF#	>50% grant-funded‡				
AstraZeneca Programs**	n.d.	n.d.					AstraZeneca
PRS-400	Jagged-1	n.d.					
Genentech (GENE1)	n.d.	n.d.					Genentech A Member of the Roche Group

#IPF - Idiopathic Pulmonary Fibrosis, PF-ILD - Progressive Fibrosing Interstitial Lung Diseases, PASC-PF - Post-Acute sequelae of SARS-CoV-2 infection (PASC) Pulmonary Fibrosis (PF)
‡~$17 million grant from the Bavarian government to evaluate PRS-220 in PASC-PF covers more than half of early-stage and phase 1 development costs of PRS-220
**Pieris has separate co-development and U.S. co-commercialization options on elarekibep*
***Pieris has separate co-development and U.S. co-commercialization options for the two additional programs partnered with AstraZeneca*

PRS-060/AZD1402: Inhaled IL-4Rα Antagonist

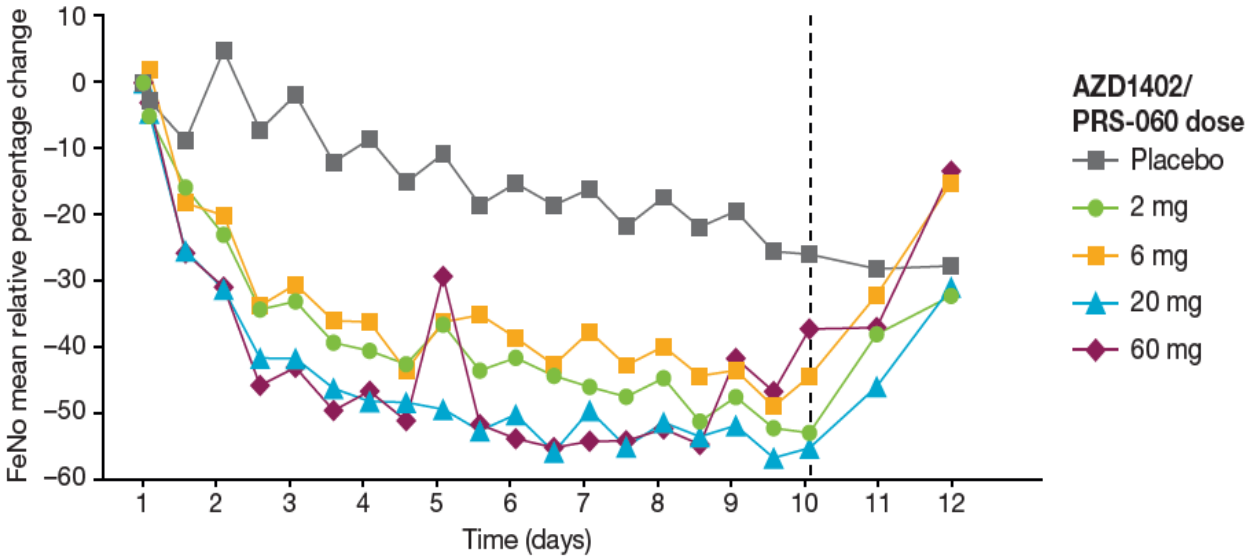
Candidate	PRS-060/AZD1402
Function/MoA	Inhibiting IL4-Rα (disrupts IL-4 & IL-13 signaling)
Indications	Moderate-to-severe asthma
Development	Phase 2a in moderate asthmatics
Commercial Rights	Co-development and U.S. co-commercialization options, including gross margin share



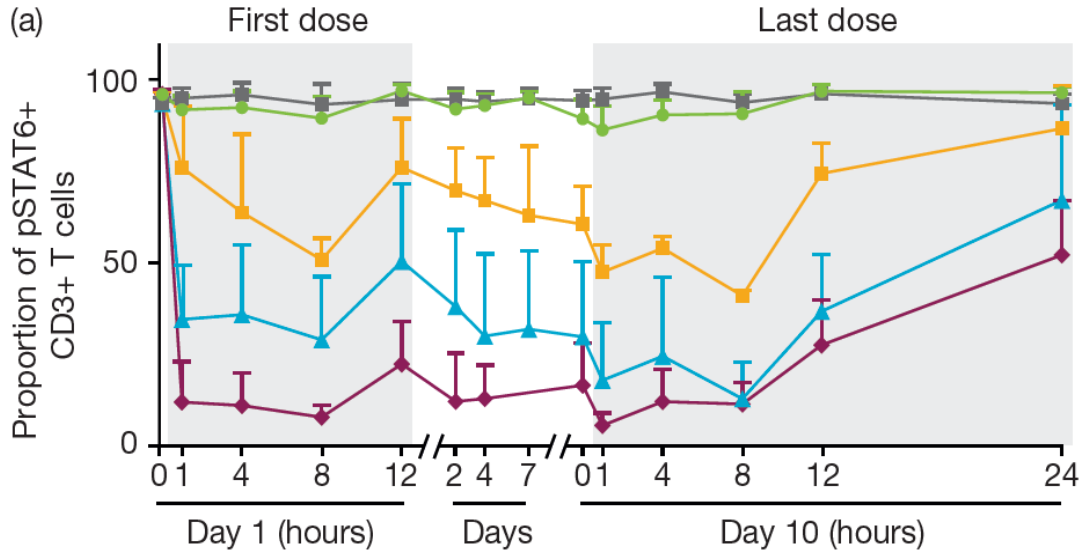
PRS-060/AZD1402

PRS-060 Has Demonstrated Local Target Engagement and Biomarker Activity – Supporting the Inhaled Approach

Inhaled PRS-060 Demonstrated Significant FeNO Reduction at all Dose Levels



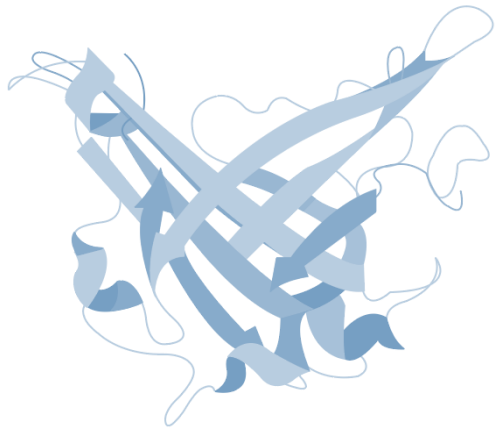
Inhaled PRS-060 Lowered systemic pSTAT6 levels in a dose-dependent manner



- No systemic target engagement and minimal systemic exposure was observed at the 2mg dose while still achieving strong FeNO reduction – suggests that local target engagement is sufficient to reduce FeNO and airway inflammation
- PRS-060 enables pharmacological versatility, given low-dose (2mg) FeNO reduction with no observed systemic activity (pSTAT6) versus high-dose FeNO reduction with systemic activity

PRS-220: Inhaled CTGF Antagonist

Candidate	PRS-220
Function/MoA	Inhibiting CTGF/CCN2
Indications	IPF, PF-ILD and PASC-PF*
Development	Phase 1 in healthy volunteers
Commercial Rights	Fully proprietary

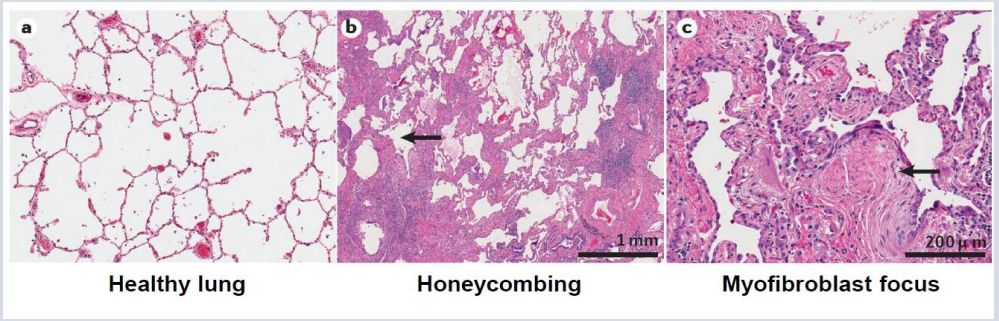


PRS-220

*IPF - Idiopathic Pulmonary Fibrosis
*PF-ILD - Progressive Fibrosing Interstitial Lung Diseases
*PASC-PF - Post-Acute sequelae of SARS-CoV-2 infection (PASC) Pulmonary Fibrosis (PF)

IPF: High Unmet Medical Need and Significant Commercial Opportunity

PF – a chronic lung disease:
ultimately fatal lung disease of unknown cause characterized by progressive scarring of the interstitial lung tissue



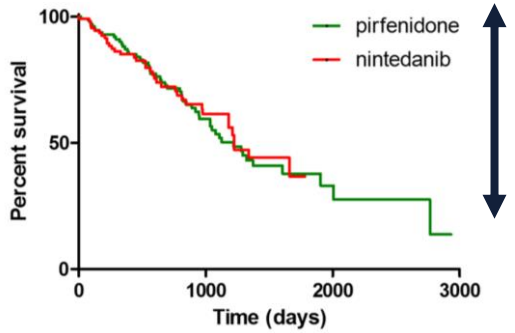
Martinez, Nature Rev Dis Primer, 2017

3 to 5 years

median survival from the time of diagnosis
Hopkins, European Respiratory Journal, 2016

2

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



medical need

Adapted from Cameli, Frontiers in Molecular Biosciences, 2020

>$3B

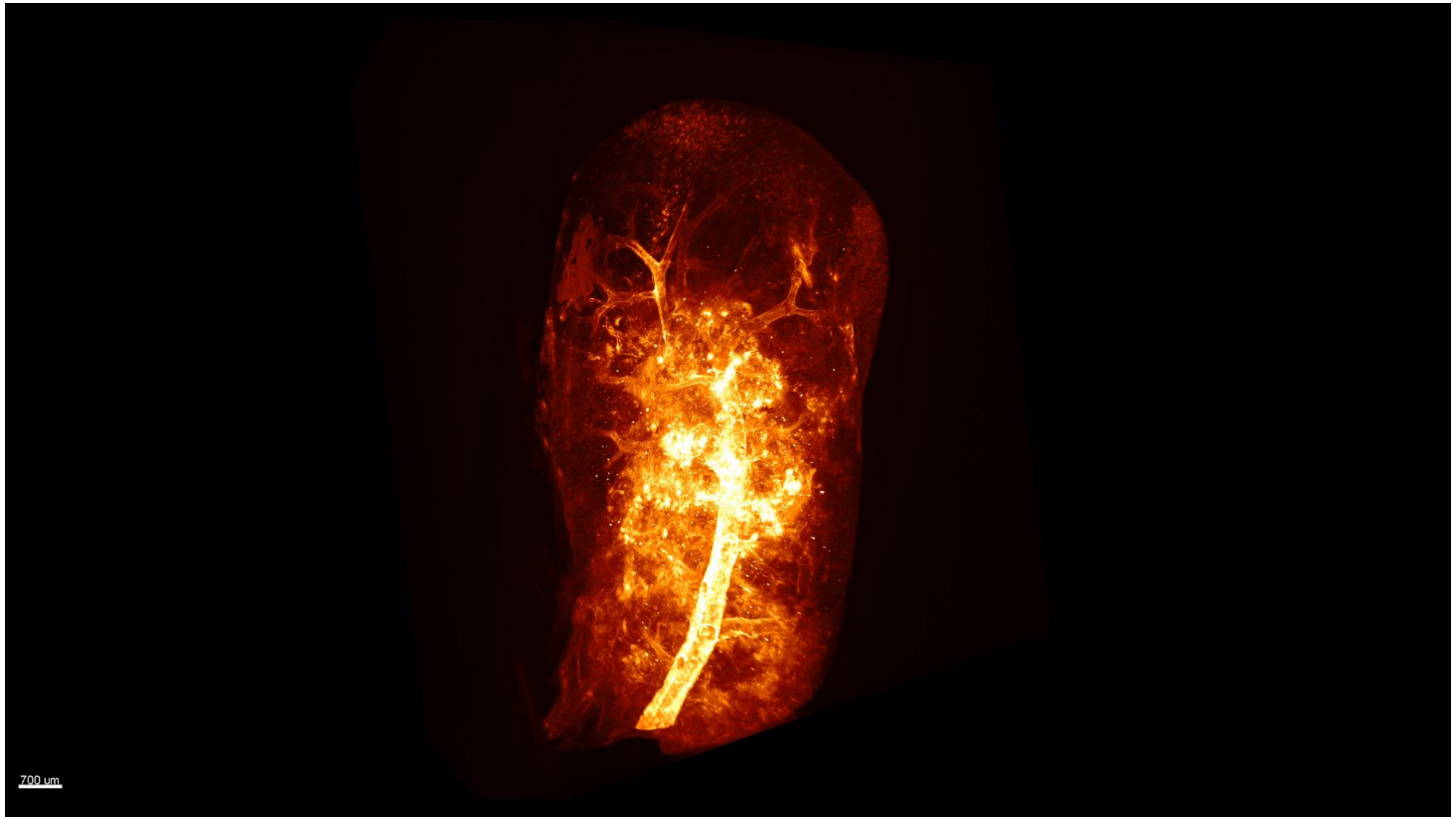
current market in sales

Significant need for well-tolerated and effective therapies

Favorable Tissue Distribution of PRS-220 in Fibrotic Mouse Lungs

Lung biodistribution study of PRS-220 delivered to fibrotic lungs of mice

Light sheet imaging of Alexa-647-labeled PRS-220 2 h after delivery to lungs of bleomycin-challenged mice (d21)



Glow scale = fluorescently labeled PRS-220 (imaged at 630±15 nm)
Grey = tissue autofluorescence (imaged at 560±20 nm)

PRS-220 penetrates into small airways and lung interstitium

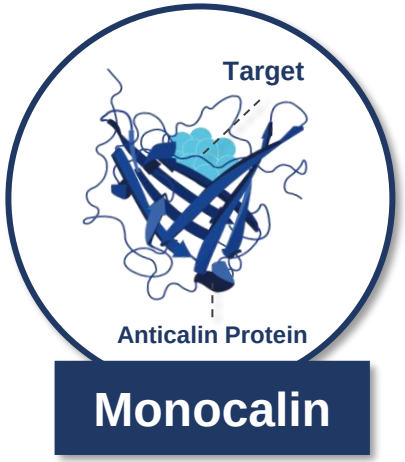
Inhaled Delivery of PRS-220: A Novel Approach to Modulate CTGF Biology with Best-in-Class Potential

Potential key points of differentiation of inhaled PRS-220 compared to systemically delivered CTGF antagonists:

More Efficient Target Saturation	• Avoidance of systemic CTGF sink (in blood) • Significantly higher affinity with superior binding profile
Superior Lung Biodistribution	• Local delivery to the site of the disease in the lung via inhalation • Increased concentration
Increased Convenience	• Inhalation at home compared to regular visits to infusion centers for i.v. administrations

PRS-400: An Inhaled JAG1 Antagonist

Candidate	PRS-400
Target	Jagged-1 (JAG1)
Function/MoA	Reducing mucus hypersecretion by blocking Jagged1/Notch signaling to reduce goblet cell metaplasia, hyperplasia and mucus plugging
Indications	Respiratory Diseases: COPD, CF, PCD, CRS, Bronchiectasis and Asthma*
Development	Lead Optimization
Commercial Rights	Fully proprietary



*__COPD__ - Chronic Obstructive Pulmonary Disease; __CF__ - Cystic Fibrosis; __PCD__ - Primary Ciliary Dyskinesia; __CRS__ - Chronic Rhinosinusitis

Organisation of the airway lining

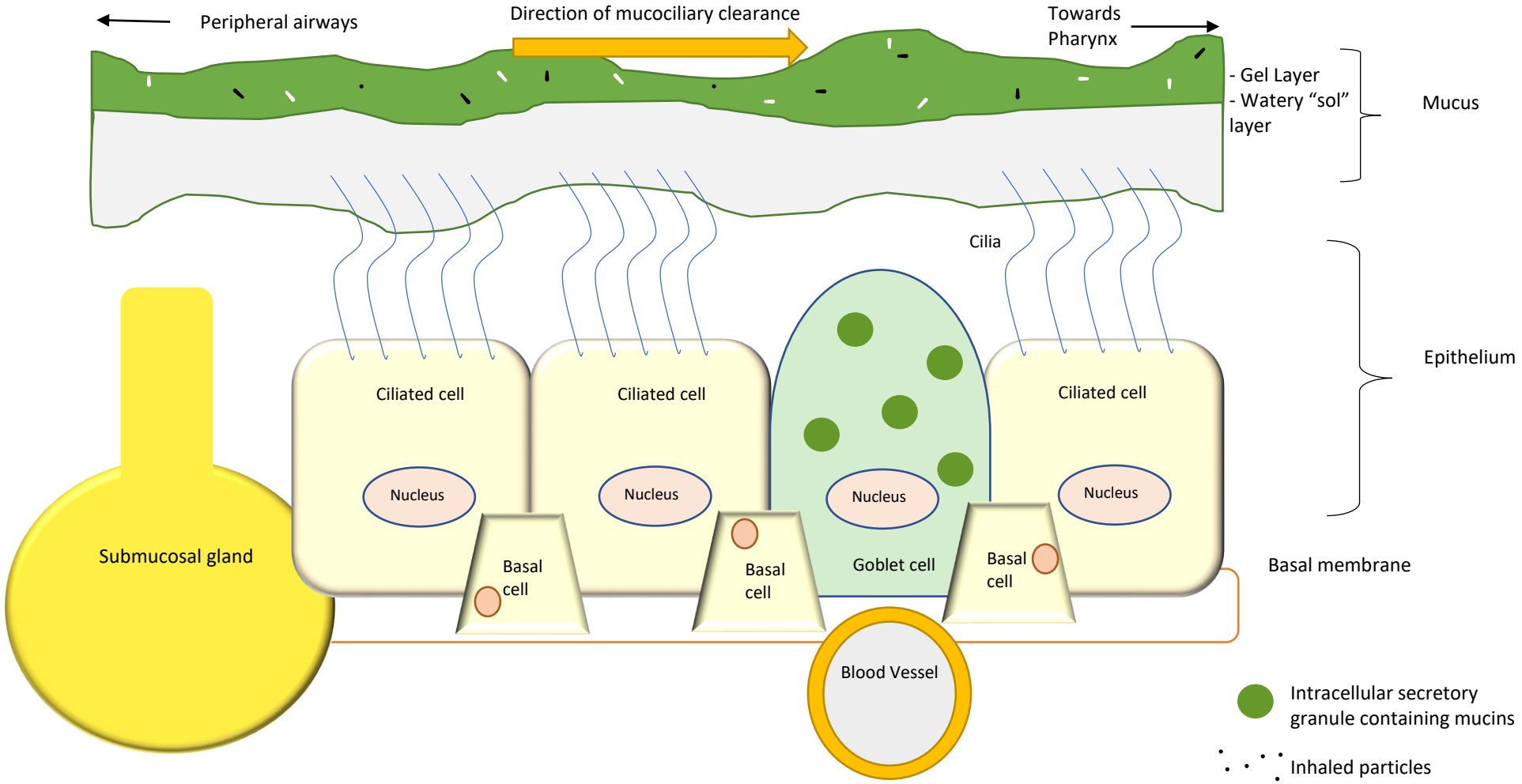
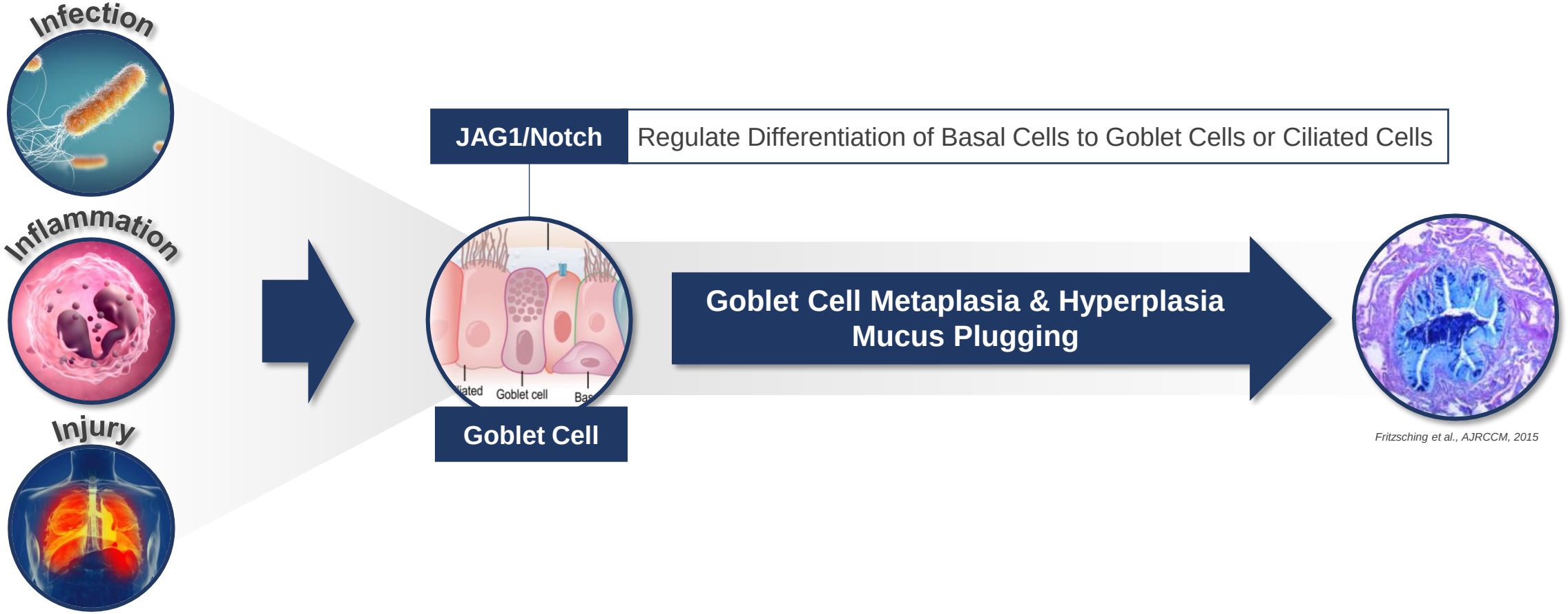


Figure 2. Adapted from Fig1 of *Novel Therapies to Inhibit Mucus Synthesis and Secretion in Airway Hypersecretory Diseases*. Emily V.S. Ha Duncan F. Rogers. *2015*

PRS-400 (anti-JAG1) Designed to Disrupt Master Regulator of Mucus Production

Reversing Goblet Cell Metaplasia (GCM), Hyperplasia (GCH) and Mucus Plugging

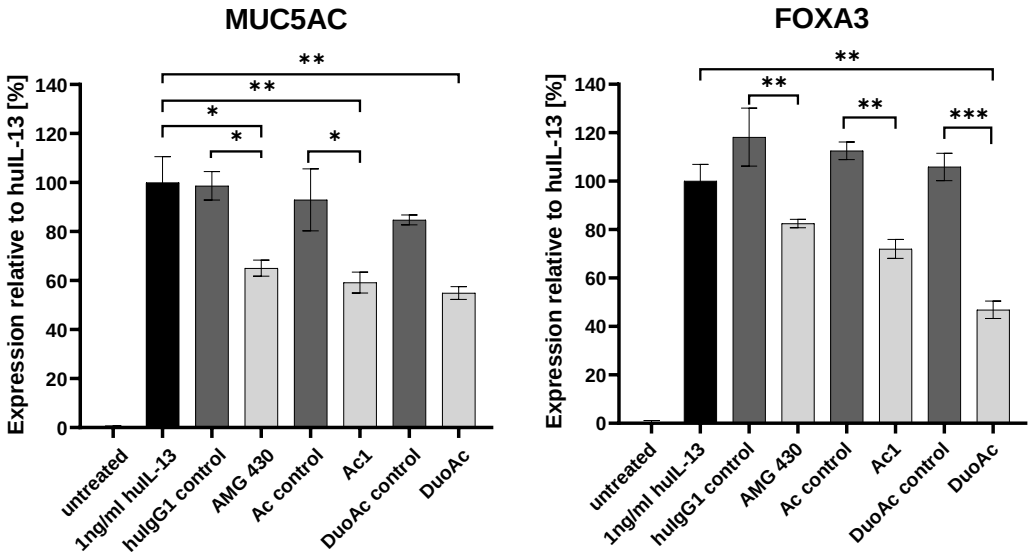


Fritzsching et al., AJRCCM, 2015

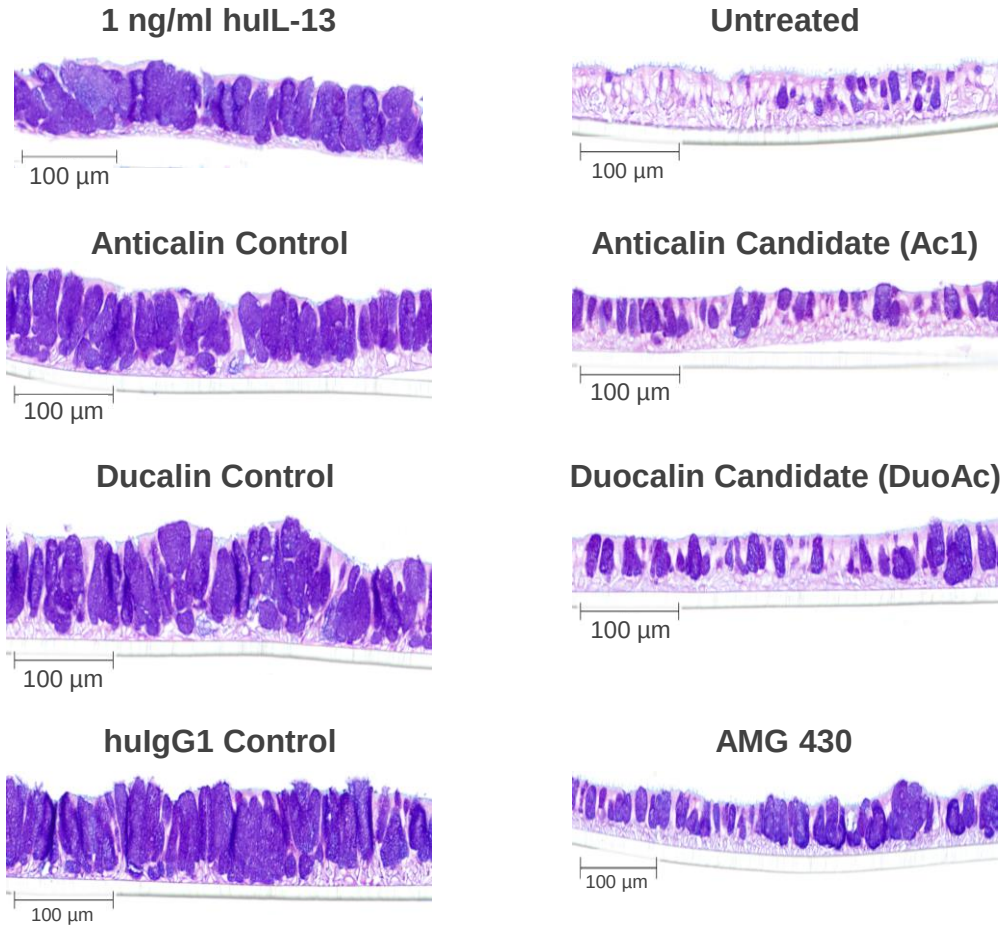
PRS-400 is designed to block Jag1/Notch signaling, reversing, independent of stimulus, GCM, GCH and mucus plugging, as well as increasing number of ciliated cells

PRS-400 Candidates Reduce Mucin Expression and Goblet Cells in ALI Model

ALI IL-13 ex-vivo Model

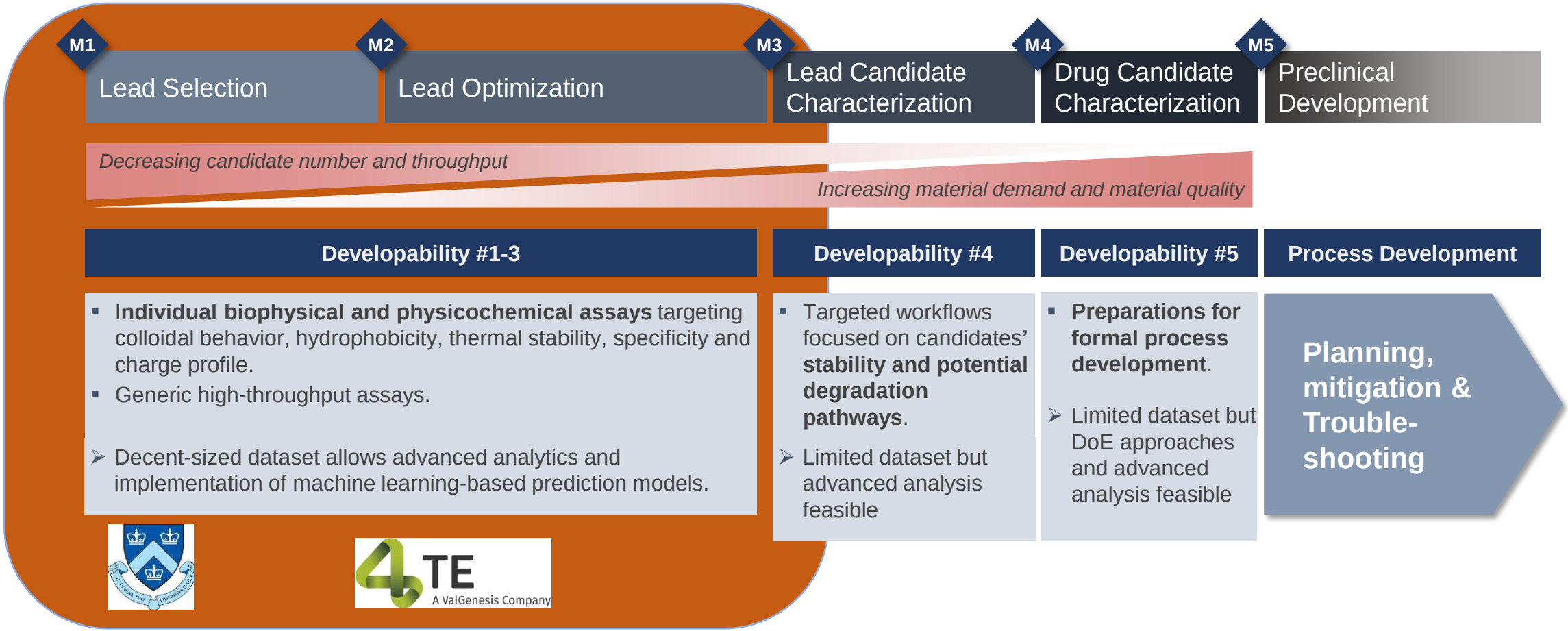


- Treatment with PRS-400 candidates show similar decrease in mucin expression (MUC5AC) and expression of goblet cell marker FOXA3 as anti-JAG1 antibody benchmark (AMG 430)
- Treatment with PRS-400 candidates show decrease in goblet cells



Machine-Learning-guided Developability Assessment

Unique Multi-tiered developability assessment from naïve screening to final lead selection



Critical Variables and Developability Score

Dev. Attribute	Method	Description	Variable	Max/Min
Aggregation Propensity	SEC-HPLC	Monomer content and retention time after 1st capture step	Main peak (%)	Max
			RT scaffold diff (%)	Min
	DLS/SLS	Diffusion rate and colloidal behavior	Pd (%)	Min
			Intensity Range 1 (%)	Max
			Mw-S diff. to calc. Mw (kDa)	Min
Charge Variants	cIEF	Charge variants	Acidic peak(s) (%)	Min
			Basic peak(s) (%)	Min
			Main peak pI diff. to calc. pI	Min
Immunogenicity	Epibase™ (in silico)	T-cell epitope identification	Global score	Min
Protein-Protein Interaction	Heparin-HPLC	Predictor for non-specific clearance	RT (min)	Min
	off-target Luminex	Multiplex assay to test binding to panel of non-related proteins	CBR sum	Min
	off-target FACS	FACS off-target binding on at least 2 target negative cell lines	S/B	Min
Thermal Stability	TSF	Fluorescent dye-based determination of Tm	Tm (°C)	Max
	DLS	Onset temperature of unfolding	Ton (°C)	Max
Hydrophobicity	HIC-HPLC	Hydrophobicity assessment	RT (min)	Min
PTM	Sequence analysis (in silico)	PTM motifs for deamidation, isomerization, fragmentation, oxidation, glycosylation and integrin binding	PTM motif sum all	Min
			PTM motif sum var	Min

Normali-zation of assay data to score between 0 and 10 based on data distribution and min/max target

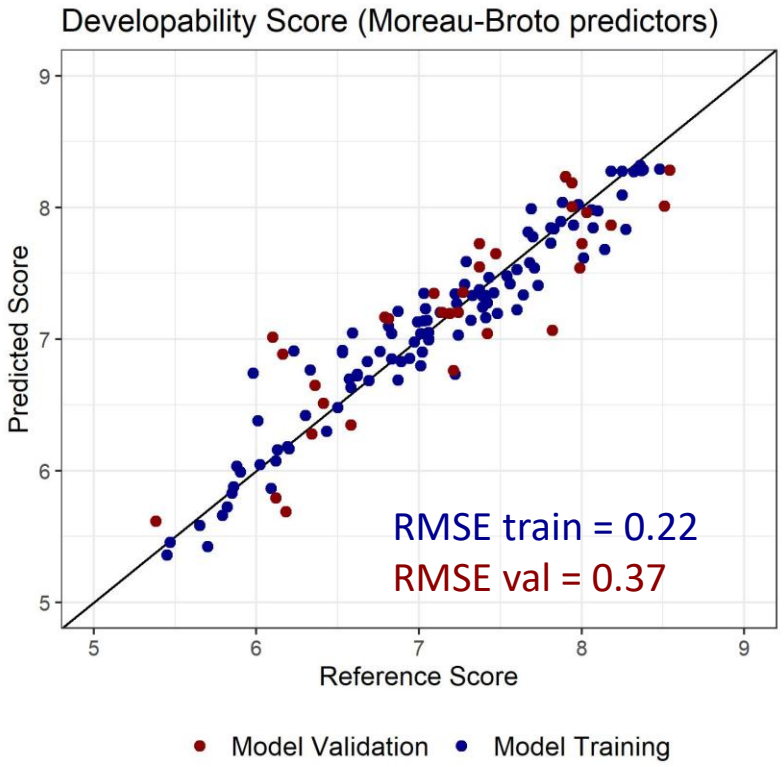
Developability score

- Weighted average of variables
- Weighted average of dev. attributes

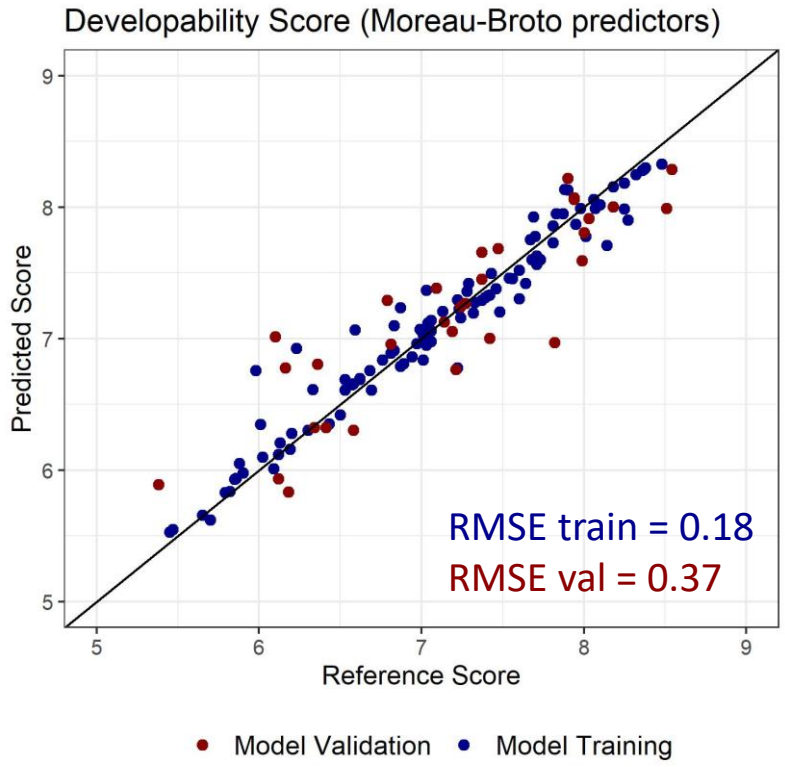
In silico Developability prediction

Developability prediction of an external validation set using machine learning statistical models based on sequence-based descriptors

Partial Least Squares (PLS)



Support Vector Machines (SVM)



- **1520** sequence-based **descriptors** extracted from public libraries (protr).
- Descriptors based on amino acid sequence-based parameters such as **residue volume** or **accessible surface area.**
- **Variable selection** process filtering to **240** descriptors.

protr: Nan Xiao et al., (2015), Bioinformatics 31 (11), 1857-1859.

Conclusion and outlook

- Anticalin proteins are based on small scaffolds and are being developed as two novel drug classes
- Clinical data suggest that local interventions will provide attractive treatment options for various respiratory diseases
- Drug development will undergo a major transformation towards *in silico* prediction of drug-like properties

Our Mission

Purpose

Improving lives

Vision

Innovating today for tomorrow's cures

Mission

Develop life-changing therapeutic proteins for patients suffering from cancer and respiratory diseases through the innovative application of novel science and cutting-edge technologies

Passion | *Integrity* | *Excellence* | *Responsibility* | *Innovation* | *Spirit of collaboration*

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