



Integrating Innovative AI and Human-Relevant Models: Transforming Respiratory Drug Development

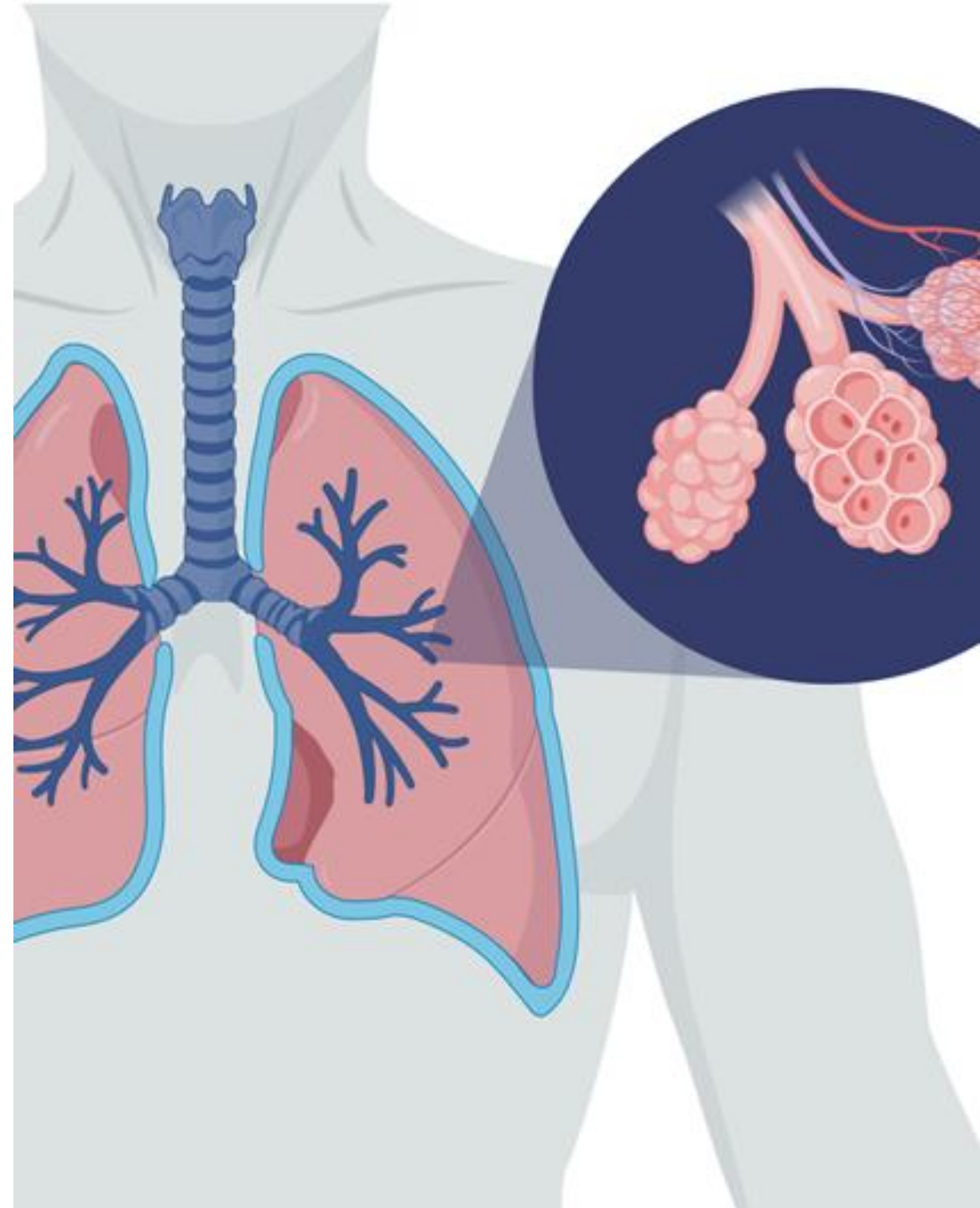
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London

DDL Conference 2025, Edinburgh, Scotland

12th Dec 2025



Why do we need a new approach?

In the last 22 years:

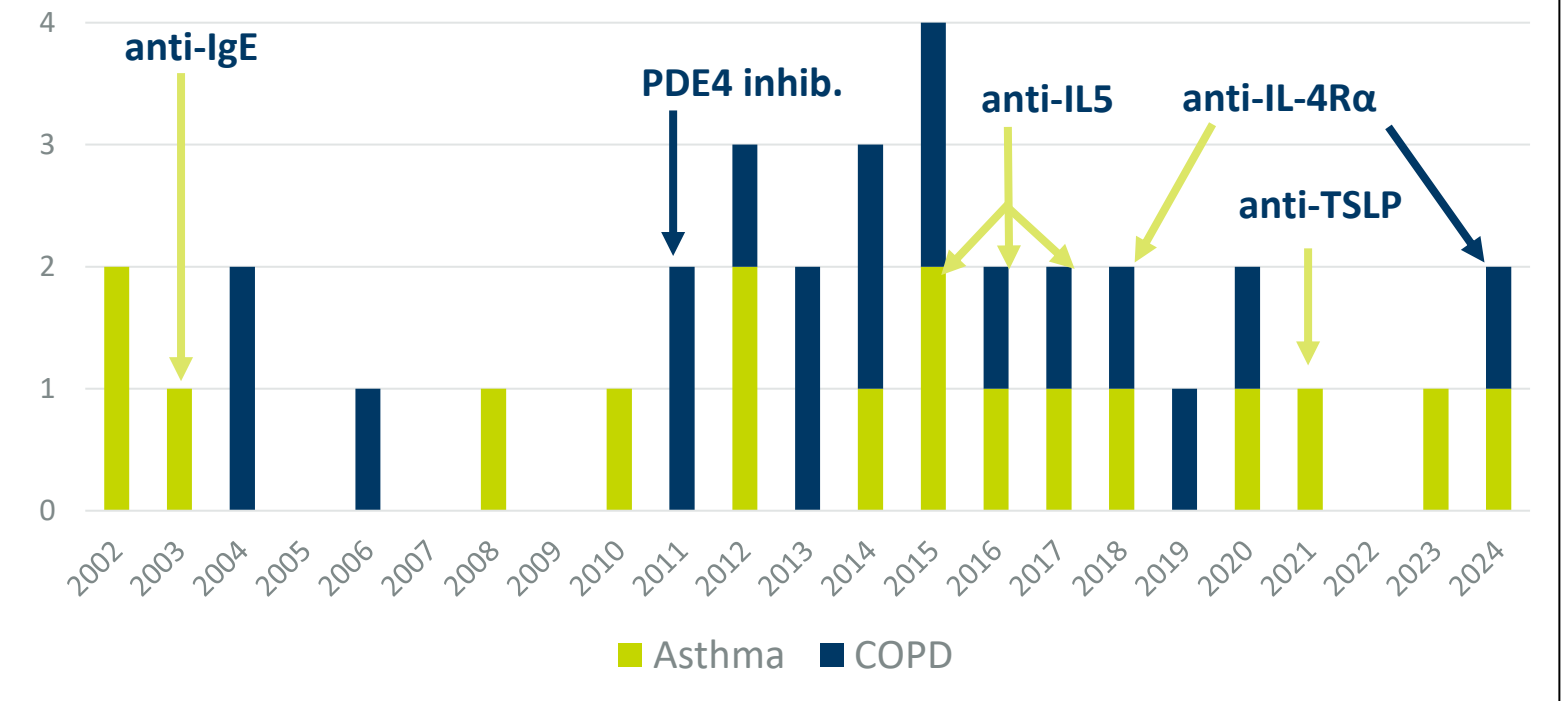
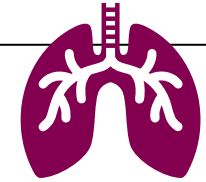
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novel
mechanisms
in asthma

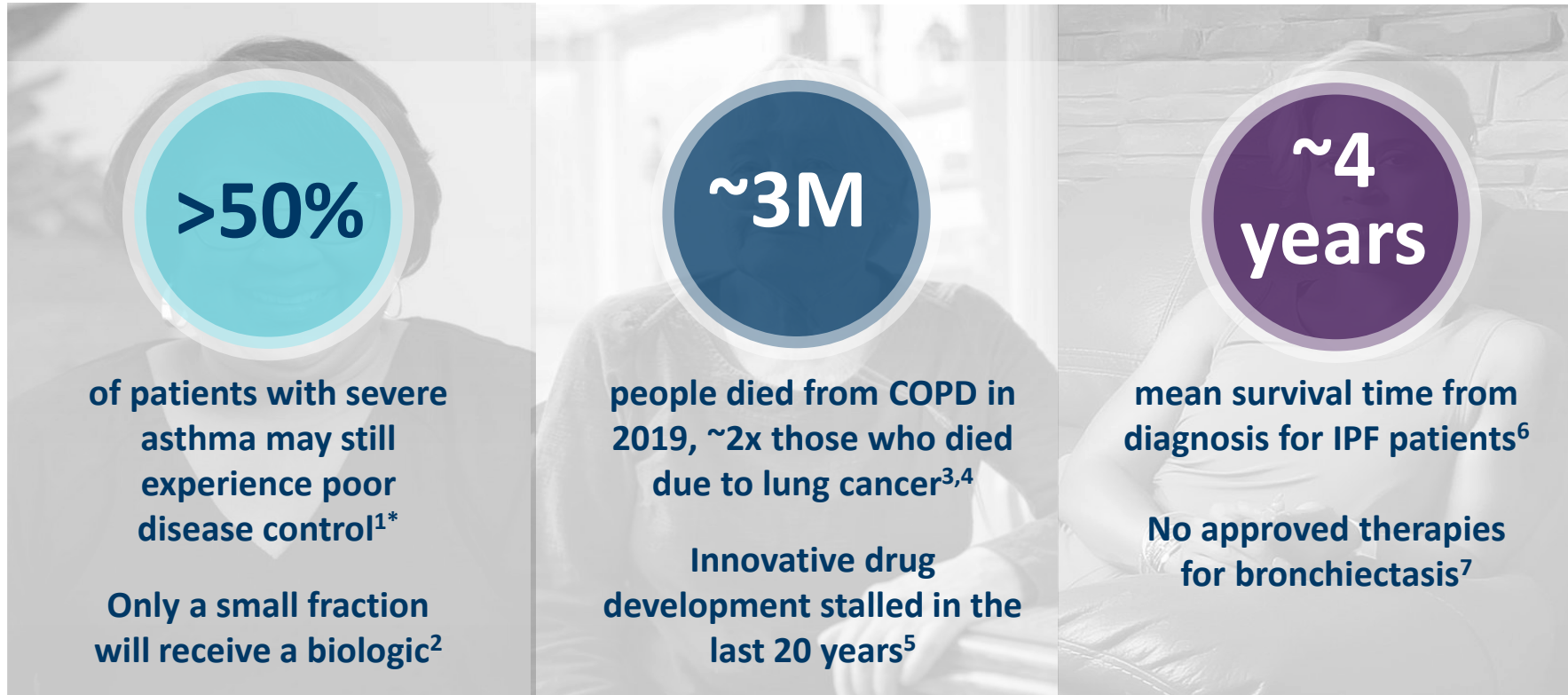
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in COPD

FDA Asthma/COPD drug approvals



Moving beyond symptom control to disease modification, remission and, one day, cure



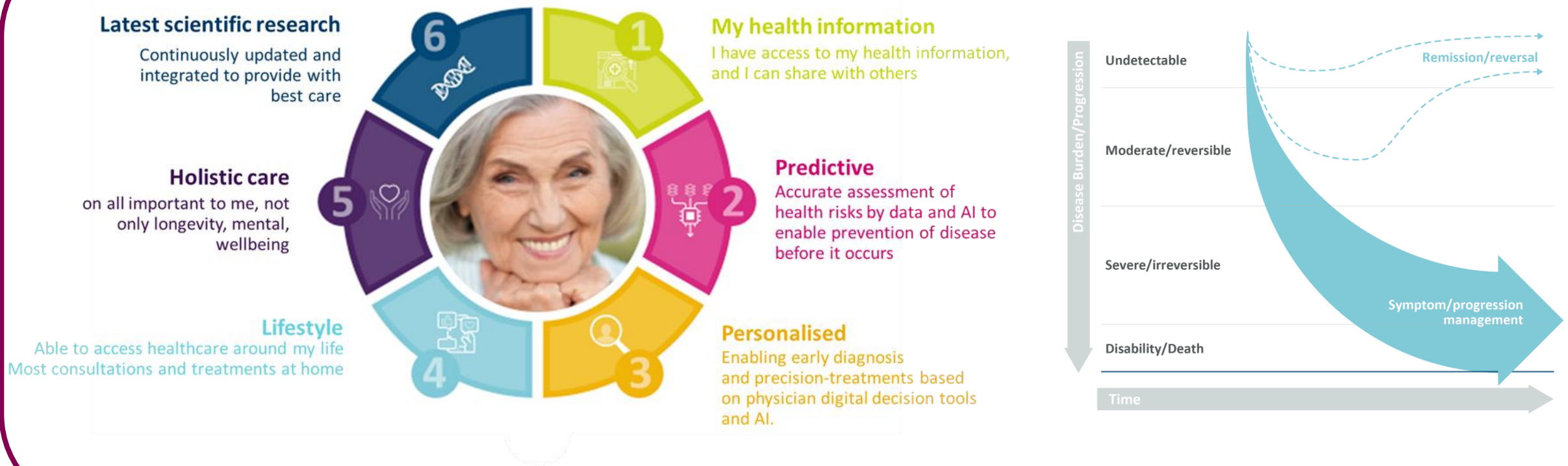
- COPD and IPF impose large global health and societal burdens; therapeutic progress remains slow.
- Complexity of lung biology and limited translation from traditional models are core constraints.

1. Menzies-Gow A, et al. A Renewed Charter: Key Principles to Improve Patient Care in Severe Asthma. *Advances in therapy*. 2022 Dec;39(12):5307-26. 2. AstraZeneca Data on file 2023. Severe asthma bio-penetration. REF-175768 3. World Health Organization. COPD Factsheet. Available at: <https://www.who.int/news-room/fact-sheets/detail/chronic-obstructive-pulmonary-disease-copd> [Accessed January 2023] 4. World Health Organization. Cancer Factsheet. Available at: <https://www.who.int/news-room/fact-sheets/detail/cancer> [Accessed January 2023] 5. Expert Panel Working Group of the National Heart, Lung, and Blood Institute (NHLBI) administered and coordinated National Asthma Education and Prevention Program Coordinating Committee (NAEPCC). 2020 Focused Updates to the Asthma Management Guidelines: A Report from the National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group. *J Allergy Clin Immunol*. 2020; 146 (6): 1217-1270. Doi: 10.1016/j.jaci.2020.10.003. Erratum in: *J Allergy Clin Immunol*. 2021; 147 (4): 1528-1530. 6. Kaur A, et al. Genetics in Idiopathic Pulmonary Fibrosis Pathogenesis, Prognosis, and Treatment. *Front Med (Lausanne)*. 2017; 4: 154. 7. Metersky M, Chalmers J. Bronchiectasis insanity: Doing the same thing over and over again and expecting different results?. *F1000Research*. 2019;8. 8. AstraZeneca Data on file 2023. Bio-penetration. REF-168341. 9.

*Based on patient population with multiple overlapping endotypes. **Based on US market data from 2018.

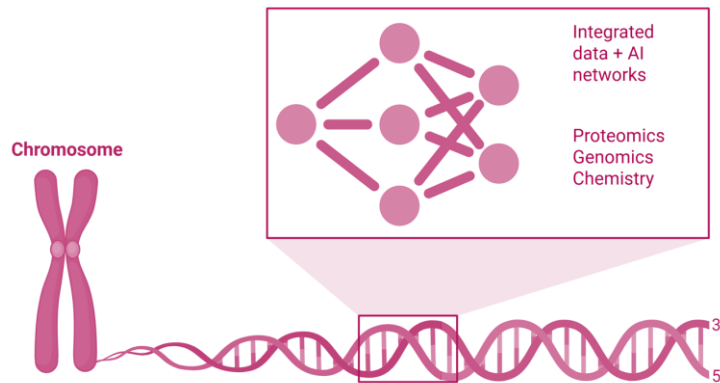


Shifting in focus from late management of disease to prevention



Why Change Now? The Opportunity

- Mechanistic insight is improving; human-relevant preclinical platforms now exist.
- AI/simulation/modelling can enhance predictivity and decision-making earlier.



- Need for better translation to the emergence of new tools (omics, imaging, organotypic models, computational pipelines).

Lung-on-chip (mechano-transduction, barrier, infection)

Human airway/bronchial organoids and ALI cultures (type-2 inflammation, mucins, CFTR)

Human precision-cut lung slices (PCLS) and ex vivo explants

Immune co-culture platforms (TSLP, IL-33, IL-25) relevant to asthma/COPD

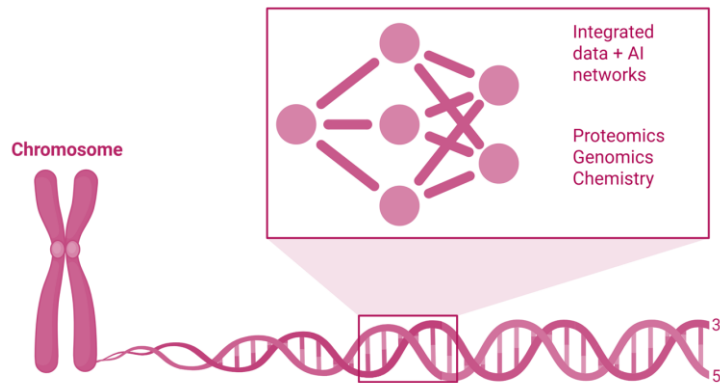
Human iPSC-derived alveolar type II cells, airway smooth muscle, and vascular endothelium

Spatial and single-cell multi-omics on human lung tissues and organoids informing mechanisms and biomarkers



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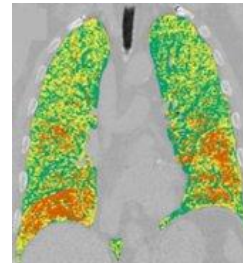


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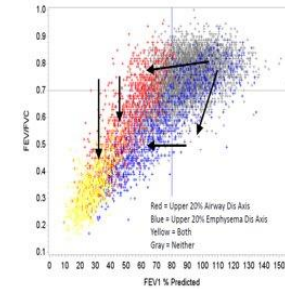
Large multi-omics cohorts



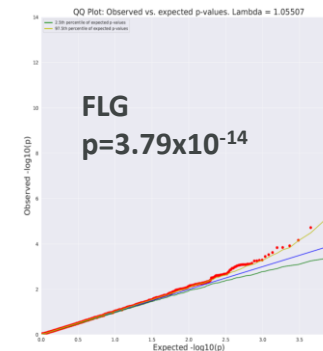
Transformative endpoints



Patient trajectories



Genetic analysis



Healthcare



Are we finally ready to close the loop between data and Healthcare?

Clinical innovation | Multi-omic BMs | AI Algorithms



Core Objectives – How is it achieved?



Better Science

Enable smarter efficient
use of assays, their
development and
deployment



3Rs

Reduce, refine, replace
animal models

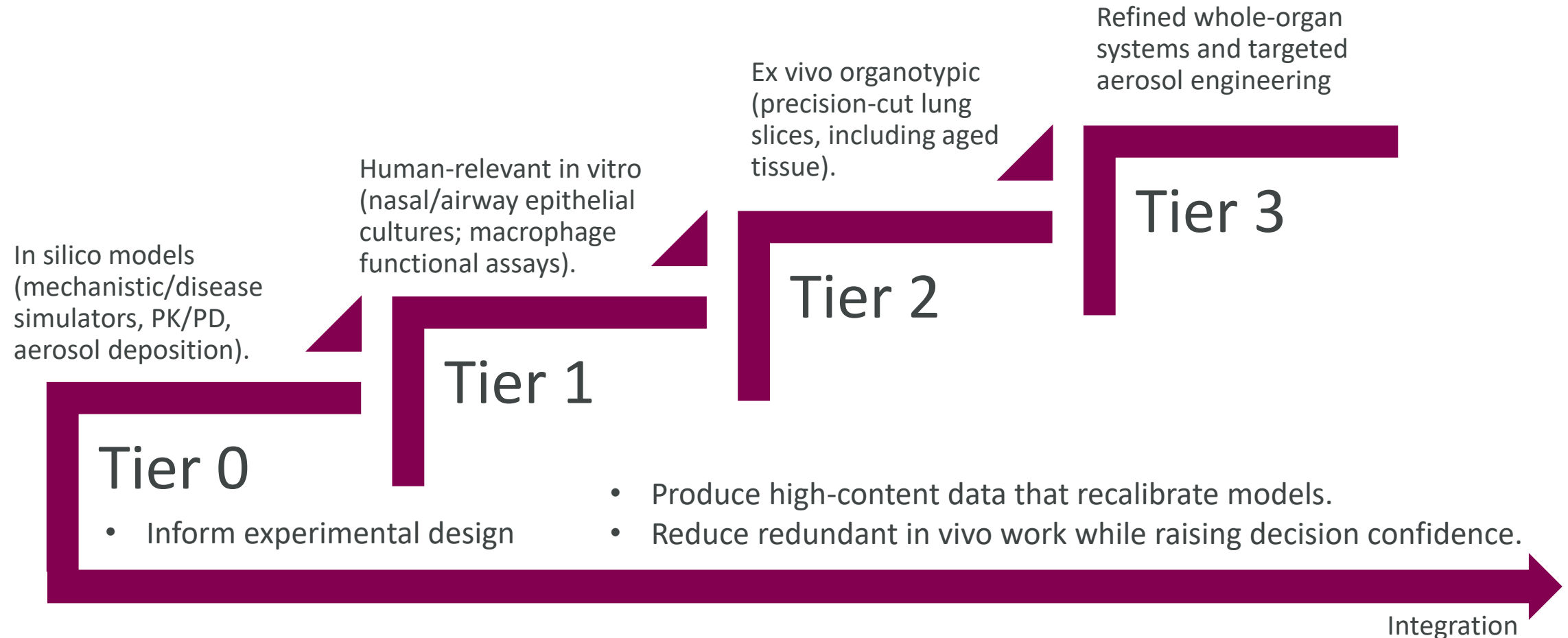


AI/ Data

Capitalise on
AI/simulation/
modelling/data tools to
improve outcomes.



Data Flow is iterative: Driving integrated systems



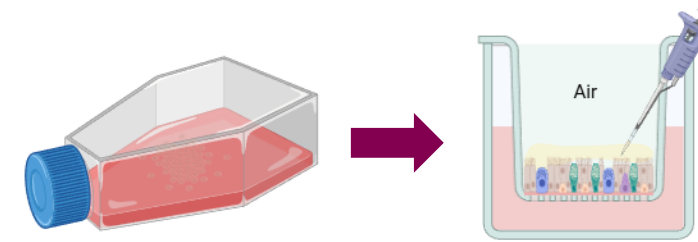
The session ahead

Mike Pasteur et al.

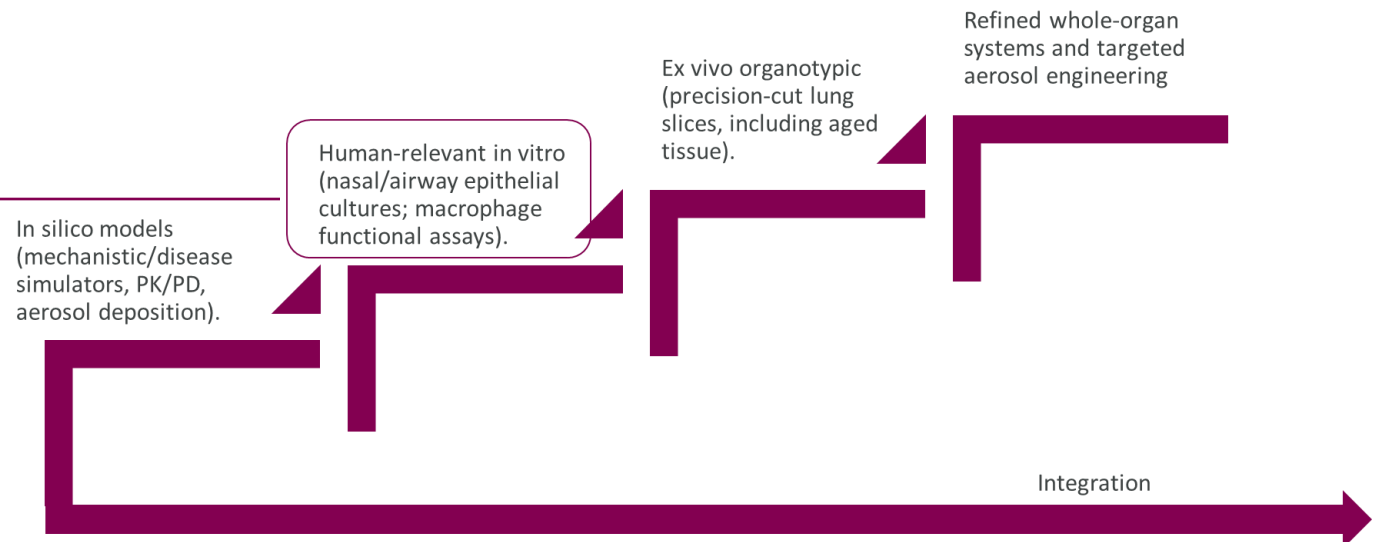
Inter-individual variability in human primary nasal cells to evaluate new nasally inhaled treatments.

Human relevant models are:

- Used to screen compound penetration, epithelial irritation, and anti-inflammatory profiles
- Address reproducible permeability & inflammation readouts
- Identify diverse donor phenotypes, including age ranges
- Provide early ranking of inhaled candidates



air-liquid interface (ALI) Culture



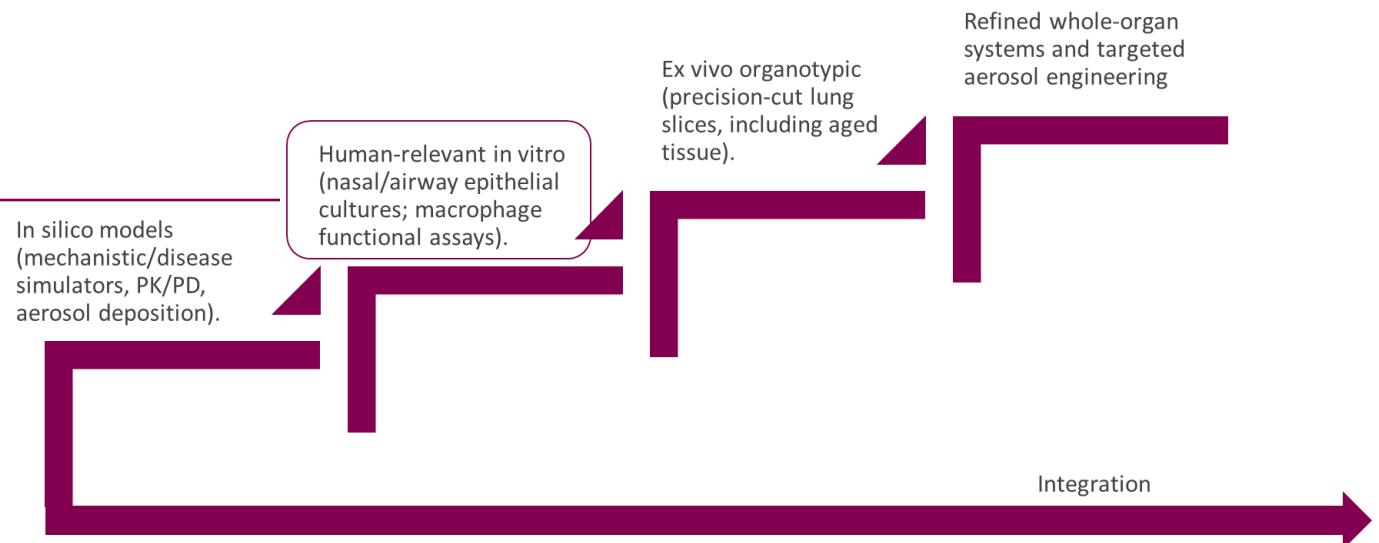
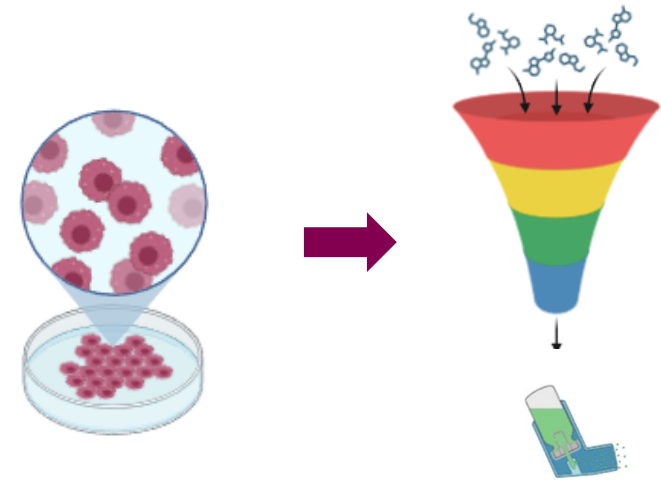
The session ahead

Victoria Hutter et al.

Advances in in vitro endpoints for inhaled drug delivery safety assessment

Human relevant Safety modelling:

- Provides mechanistic insight into innate function
- Flags efficacy and safety liabilities
- Robustly differentiates and supports categorisation of response of test compounds

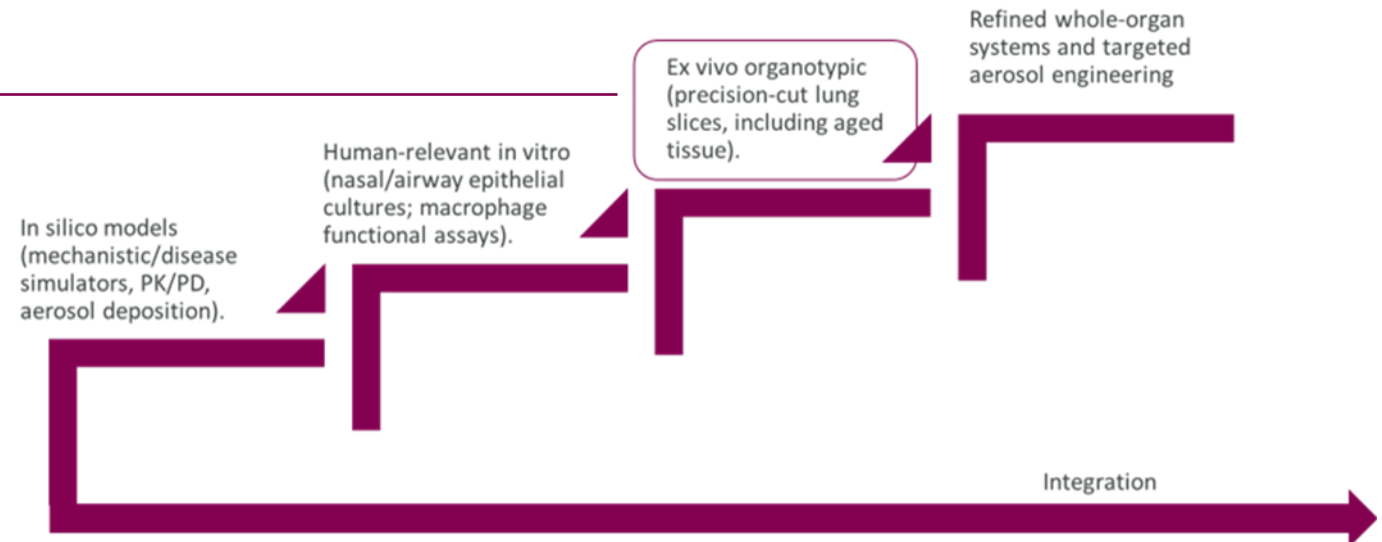
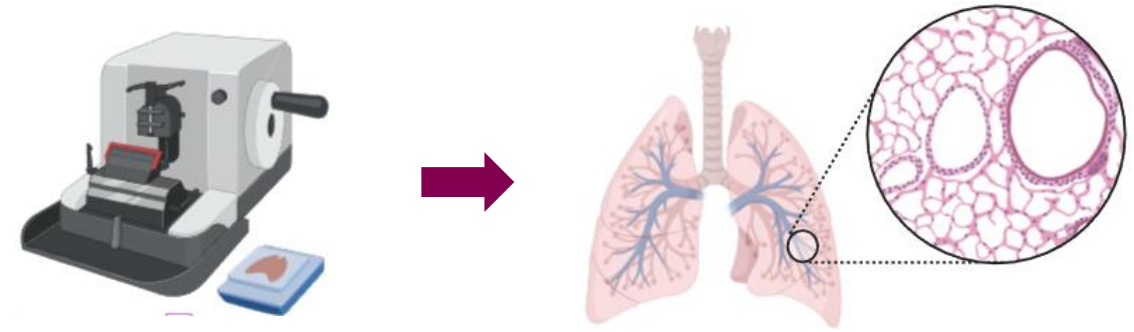


The session ahead

Sally Yunsun Kim et al.

Precision-cut lung slices as a platform to investigate cytotoxicity and efficacy of novel therapeutics

- Preserves structure and cell diversity
- Fibrogenic and bronchodilation responses
- Chronic disease relevance (aged PCLS)



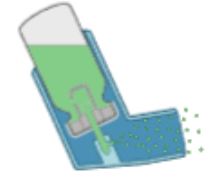
The session ahead

Per Gerde et al.

Effect on lung permeation of various formulation efforts invested in the inhaled antibiotic apramycin as measured in the ex vivo isolated, perfused, and ventilated rat lung

Refined whole-organ systems and targeted aerosol engineering provides:

- Higher physiological relevance and predictivity
- Mechanistic and functional insight
- Precise, localized dosing
- Faster formulation/device optimization
- Improved safety profiling and regulatory confidence



In silico models
(mechanistic/disease
simulators, PK/PD,
aerosol deposition).

Human-relevant in vitro
(nasal/airway epithelial
cultures; macrophage
functional assays).

Ex vivo organotypic
(precision-cut lung
slices, including aged
tissue).

Refined whole-organ
systems and targeted
aerosol engineering

Integration



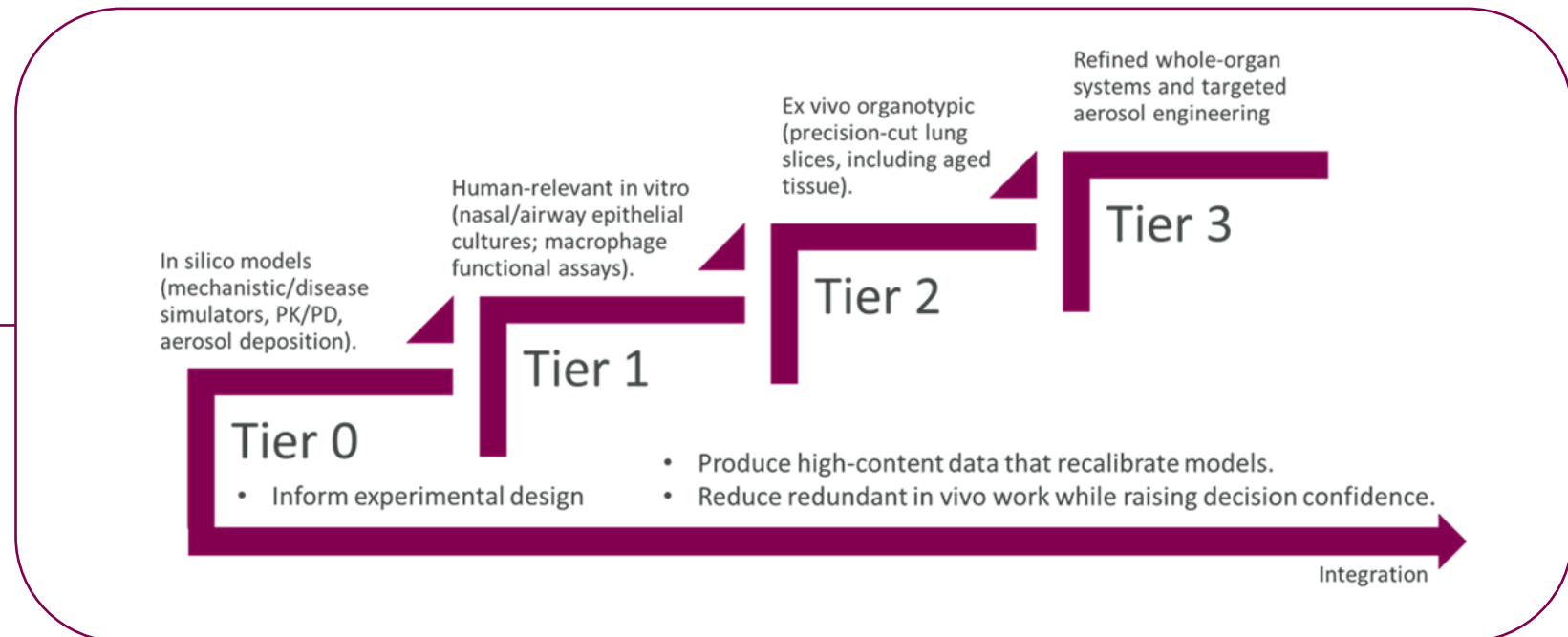
The session ahead

Paul FitzPatrick

A multi-tiered approach to inhalation risk assessment – Development of advanced in vitro models for pre-clinical safety

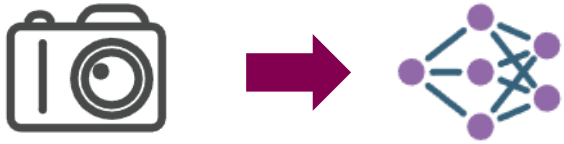
Key driver:

Enable earlier, higher-throughput safety screening, improves candidate selection, and helps elucidate toxicity mechanisms, informing more predictive models and compound design.



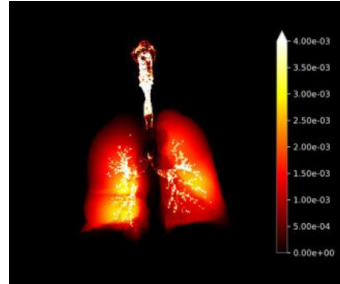
AI, Simulation, and Data Integration

AI: Images + Omics



AI imaging and omics gives us a view of identifying morphology, motility, cilia, phagocytosis and multimodal integration (transcriptomics/proteomics) Identify mode-of-action signatures, early safety/efficacy phenotypes.

PBPK: Tissue/Plasma



Usmani et al 2020

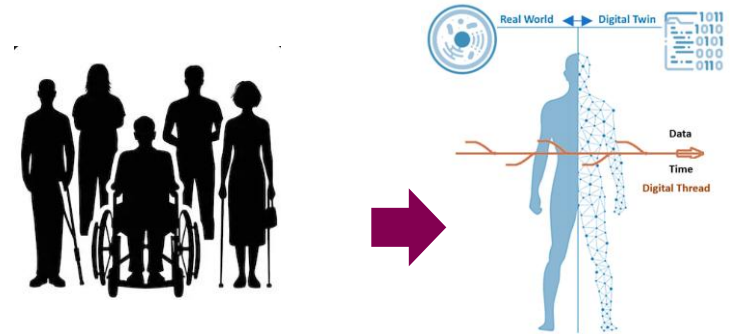
➡ PBPK/CFD

Computational Fluid Dynamics (CFD) predicts airflow and particle deposition across airways

Physiologically Based Pharmacokinetics (PB-PK) models drug absorption/clearance across tissue compartments

Bridges in vitro potency/toxicity to expected in vivo exposure ranges—supporting dose selection and reducing exploratory animal studies

QSP + Digital Twins



Quantitative Systems Pharmacology links exposure to biological pathways and clinical endpoints; mechanism, variability, and responder prediction

Digital twins combine all of the above to simulate “what if” scenarios for a given patient or cohort.

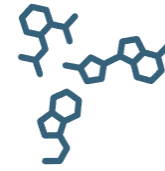


AI, Simulation, and Data Integration

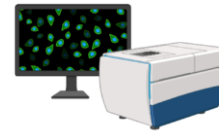
Integration and governance

- A shared data fabric standardises metadata, units, and ontologies across assays;
- Make model-ready data reusable.
- Versioning and model cards document assumptions, validation metrics (e.g., AUROC for classification, RMSE for PK predictions), and context-of-use.
- Supporting regulatory dialogue and internal reproducibility.

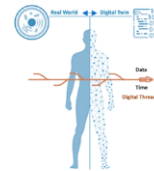
Example “day-in-the-life”



Candidate X produces a macrophage activation signature



CFD predicts 25% small-airways deposition; PBPK estimates 5–15 μM tissue exposure for a 50 μg inhaled dose.

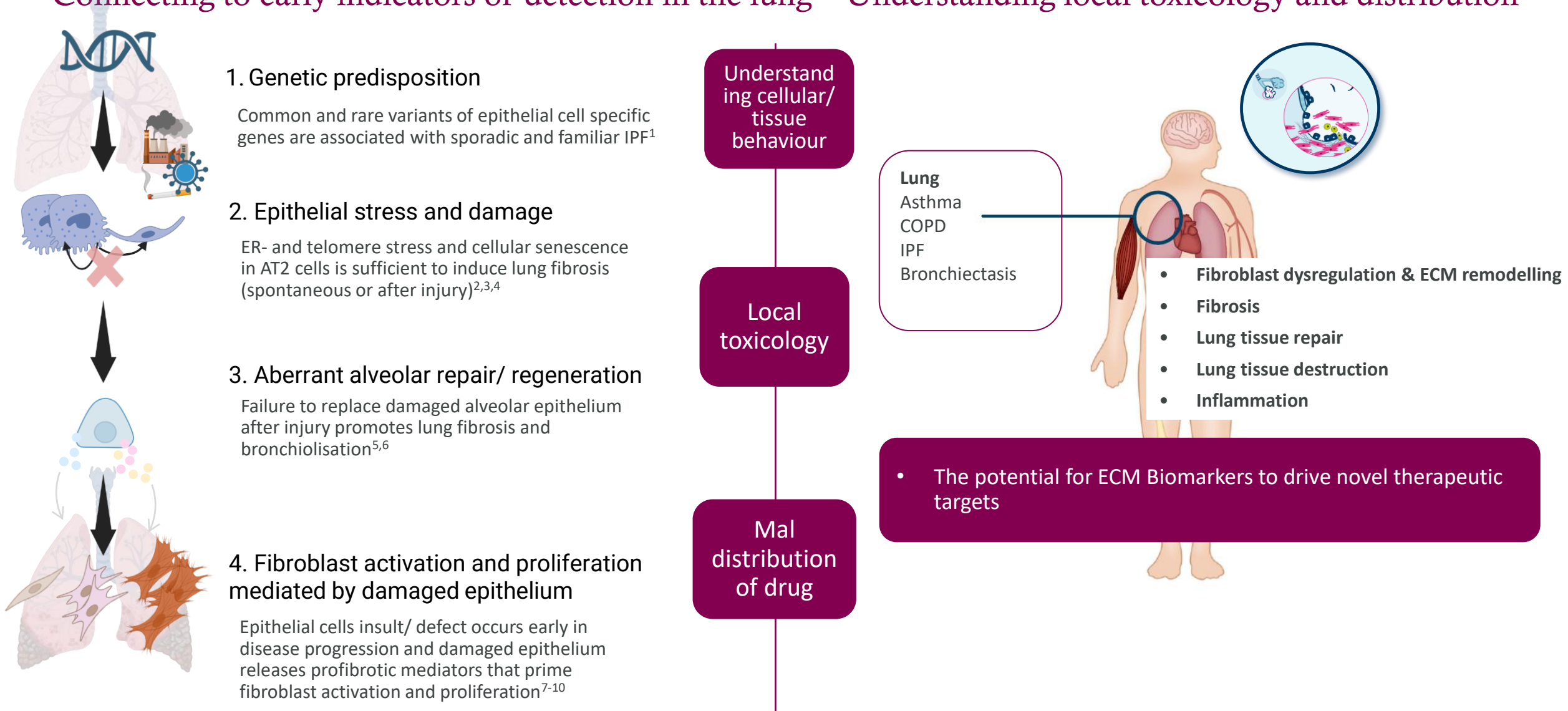


QSP simulates modest cytokine reduction in T2-low asthma but limited effect in COPD with high mucus burden

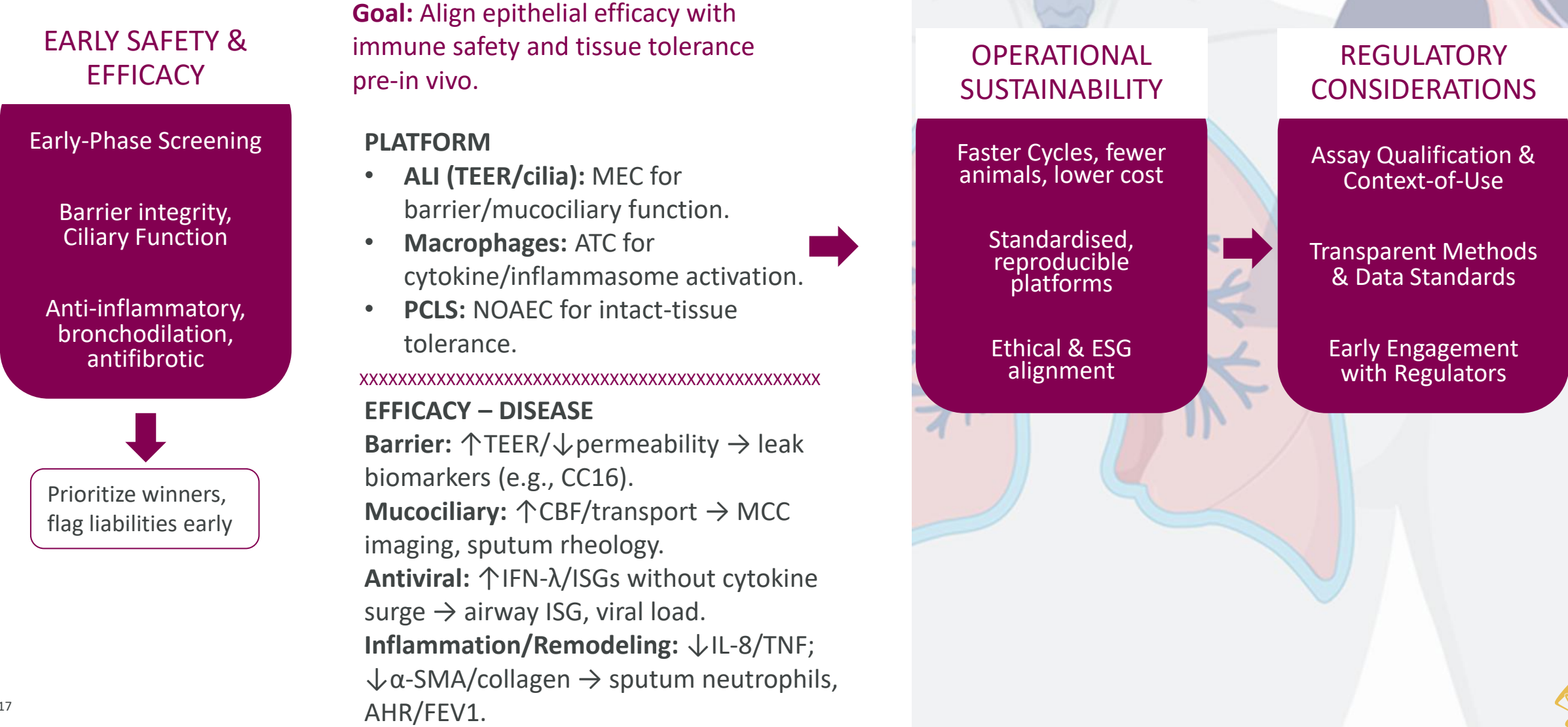
Decision: adjust formulation to reduce small-airways peak exposure and prioritize T2-low asthma cohort; defer COPD.

Alveolar epithelium can initiate and drive lung fibrosis –

Connecting to early indicators of detection in the lung – Understanding local toxicology and distribution



Enabling the Change – Build translational confidence by aligning epithelial efficacy with immune safety and intact-tissue tolerance before in vivo.



Road to Success

Resources:

- Tissue access, imaging, analytics, modelling expertise, data governance.
- Consider partnerships for donor diversity and cloud analytics.
- Establish governance for model and assay updates.

Now:
ALI/macrophage +
PBPK/CFD

Mid: scale PCLS,
expand QSP, image
AI

Long: Digital
twins; broader
replacement

Implementation Roadmap



Road to Success

Risks & Mitigations

- Garbage-in → garbage-out:.
- Translation gap in model transfer ...(.invitro to insilico)
- Overfitting, donor variability, assay drift
- Regulatory uncertainty -
- Mitigate with QC, multi-donor panels, preregistration, hybrid validation

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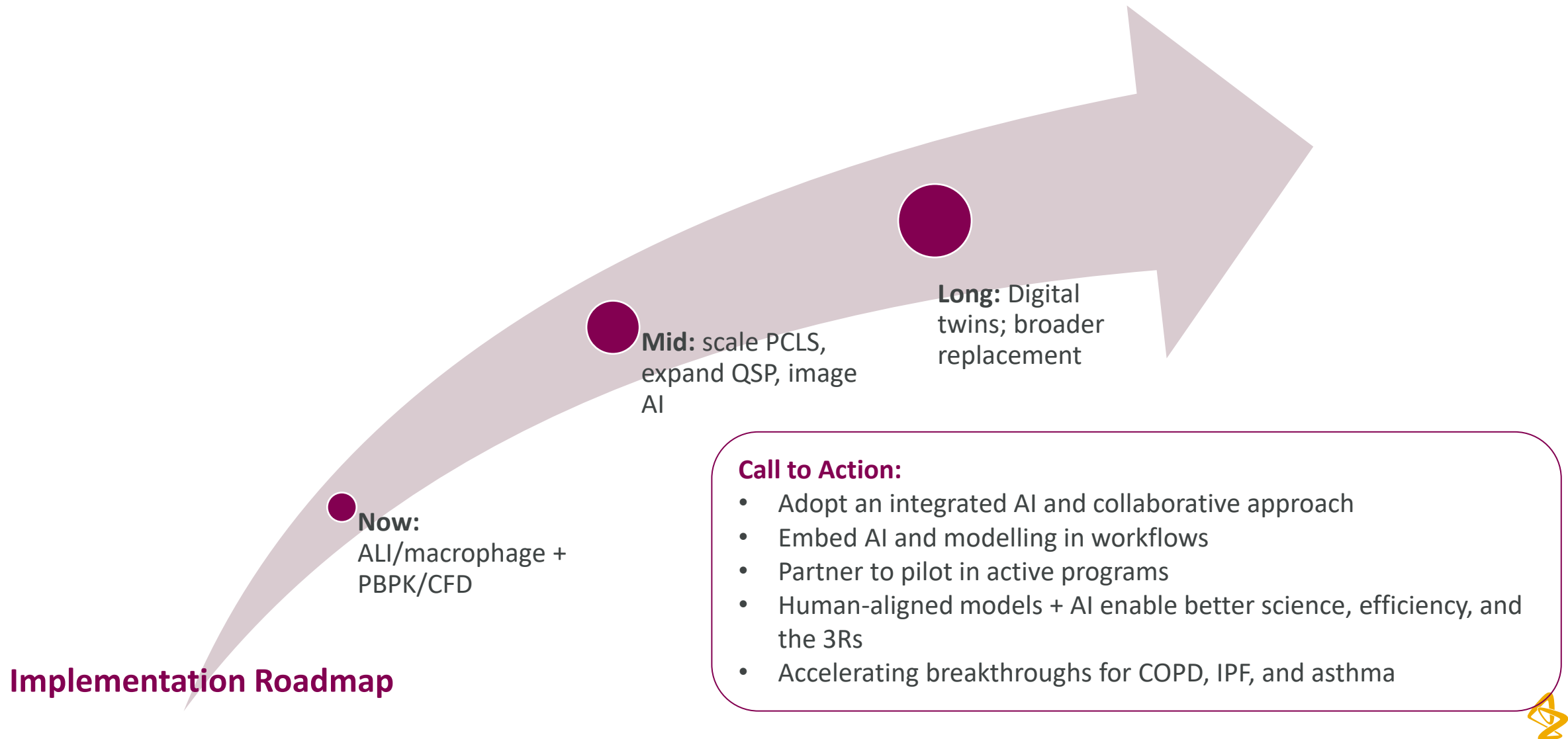
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Measuring Success

- Fewer animal studies; faster time-to-decision
- Predictive accuracy vs. clinical outcomes
- Adoption across programs; regulatory acceptances



Road to Success



THANK YOU

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