LUNG-MECH: The lung mechanomics initiative

First physics-informed lung atlas to predict, prevent, and reverse lung function decline.

1. What are you trying to do?

The world faces a **growing crisis of chronic lung diseases**, such as COPD, fibrosis, asthma, and lung cancer, because we diagnose them too late and rely on drug discovery methods that only look at genes. But the real problem starts long before symptoms appear. Our lungs reach their peak performance in our mid-20s, and from then on, they slowly lose function as we age. This decline happens because the lung tissue itself changes, it becomes stiffer, less flexible, and less able to respond to everyday stresses. The physical properties of our lungs, their "mechanics", play a key role in how well we breathe, from early development through aging and disease. Yet today, we don't have a clear way to measure these changes or even define what mechanical factors matter most. Are they stiffness, flexibility, or something else? And most importantly, can we act on these changes to keep our lungs healthy, slow down decline, or even reverse it? **LUNG-MECH** is our initiative to create the world's **first detailed map of how the physical properties of the lung change over time**. We will combine knowledge from physics, biology, and advanced computing to understand how aging affects lung tissue and identify the key changes that matter most. Our goal is to make it possible to predict, prevent, or reverse lung decline by targeting these changes. By the end of the program, we will have identified three **specific therapeutic targets that, when adjusted, can restore or improve lung flexibility and function in human lung tissue models**. This will give us the blueprint for therapies that could one day help people keep their lungs healthy as they age.

2. How is it done today, and what are the limitations of current practice?

Today, lung health is assessed using tools like **spirometry** (invented in 1846) and **imaging** scans. These methods only detect disease after major damage, typically when 30–50% of lung function is already lost. For pulmonary fibrosis, gold standard high-resolution computed tomography (HRCT) scan only shows scarring after it becomes irreversible[1]. Blood biomarkers provide limited little insight into early lung tissue changes[2]. Modern research uses advanced molecular profiling such as single-cell sequencing and spatial transcriptomics to map cell types and gene activity[3,4,5,6]. These approaches have transformed our understanding of lung biology but ignore the physical properties of tissues, such as stiffness and elasticity, which are critical for lung function.

Mechanical changes are not just consequences of disease, they drive it. Stiffness and tension are factors that are critical regulators of cell behaviour, differentiation, and immune function[7,8]. Extracellular matrix (**ECM) stiffness** directly influences cell behaviour and disease progression, with fibrotic lung tissue often being 10–50 times stiffer than healthy lung[9]. These mechanical changes are not merely consequences but active **drivers of pathology**, affecting fibroblast activation, inflammation, and drug responsiveness[10,11,12]. Yet current tools cannot measure these changes early or link them to molecular drivers. **Magnetic resonance elastography** (MRE) can estimate lung stiffness[13], but data are rare, non-standardised, and lack molecular correlation. As a result, the "stiffness precursor" phase, where intervention could reverse decline, remains invisible. Recent high-resolution spatial transcriptomics work[14] detected molecular niche dysregulation that precedes overt tissue remodelling in pulmonary fibrosis. Yet we lack an integrated approach to map both molecular and mechanical changes in lung tissue. Without this we cannot predict, prevent, or reverse lung decline.

3. What is new in your approach, and why do you think it will be successful?

We will create the first population-scale atlas that links lung mechanics to molecular signatures, enabling prediction and reversal of lung decline. Unlike current approaches that only measure genes, we integrate physics, biology and AI to uncover earliest drivers of tissue stiffening and design interventions to restore function.

Five years ago, spatial omics lacked resolution and scale, and computational tools couldn't integrate mechanical and molecular data. Today, breakthroughs in multimodal mapping, Brillouin microscopy,

[1] https://publications.ersnet.org/content/breathe/20/1/240006
[2] https://www.sciencedirect.com/science/article/abs/pii/S0009898125003523
[3] https://genomebiology.biomedcentral.com/articles/10.1186/s13059-022-02824-6
[4] https://www.science.org/doi/10.1126/science.abq4964
[5] https://www.nature.com/articles/s41591-023-02327-2
[6] https://portal.hubmapconsortium.org
[7] https://academic.oup.com/gpb/advance-article/doi/10.1093/gpbjnl/qzaf053/8160015?login=false
[8] https://www.nature.com/articles/s41588-022-01243-4
[9] https://pmc.ncbi.nlm.nih.gov/articles/PMC6013326/
[10] https://www.sciencedirect.com/science/article/pii/S0006295224002387?via%3Dihub
[11] https://pmc.ncbi.nlm.nih.gov/articles/PMC10552248/
[12] https://pmc.ncbi.nlm.nih.gov/articles/PMC10088466/
[13] https://pmc.ncbi.nlm.nih.gov/articles/PMC4019718/
[14] https://www.nature.com/articles/s41588-025-02080-x

and casual inference modelling make this possible. Without this initiative, these advanced will remain siloed and fail to deliver a transformative solution.

TA1: Mechanistic linkage: defining the mechano-molecular signature of lung age

The primary goal is to rigorously establish the casual link between age-related mechanical changes (stiffness, viscoelasticity) and the molecular signatures (gene/protein expression) that drive functional decline. **Strategy:**

- Utilize the N=50 Deep Reference Atlas (fresh/frozen tissue) as the **Ground Truth** to acquire direct mechanical maps (AFM/Brillouin) and full spatial omics **across a diverse age range** and early-stage disease (pre-fibrotic). [15,16,17,18,19,20,21].
- Train the **Mechano-Molecular Inference Engine (MMIE)** to predict both the mechanical state and, critically, the **Molecular Signatures of Mechanical Failure** from low-cost histology, specifically focusing on pathways relevant to ECM degradation/remodelling and epithelial/immune cell mechanics.

Actionable Outcome: A validated set of **Mechanical Biomarkers** that define a quantitative "Biological Age" for lung tissue and the associated **Mechano-Molecular Targets** that underpin it.

TA2: The Restoration Pipeline: Identifying and Validating Novel Mechano-Targets

Leveraging the MMIE-driven cost reduction to rapidly identify and **validate** novel targets that can **restore mechanics/function**. **Strategy:**

- Deploy the Hybrid Spatial Strategy across the full N=500 Atlas to map the **mechanical signatures** and **inferred molecular maps** across ages and disease stages (focusing on COPD, fibrosis, and asthma)[1].
- Use causal inference modelling on the completed Atlas to **prioritize 5-10 top mechanosensitive targets** (e.g., Piezo1, specific ECM regulators).
- **Validation Wet Lab Pipeline:** Selected targets will be tested *in vitro* and in complex *ex vivo* human lung models (e.g., Ex Vivo Lung Perfusion systems, or bioengineered tissue constructs) to test if their modulation **enhances epithelial barrier mechanics, prevents ECM accumulation, or reprograms innate immune cells** to resolve fibrosis.

Actionable Outcome: A portfolio of **3-5 validated mechanotherapeutic targets** that demonstrate the ability to restore a quantifiable metric of lung function.

TA3: Democratizing Actionable Data for Clinical Intervention

Delivering a Zero-HPC **"Decision Support" Tool** that provides immediately actionable data for clinicians and biotech partners. **Strategy:**

- Finalize the **Zero-Download Virtual Hub** to allow external researchers and collaborators to analyse the **complete dataset** without HPC.
- Support future development of enabling technologies arising from the atlas: e.g. a Clinical Pathology Enhancement Module that uses the MMIE to generate an inferred mechanical risk map from standard histology/biopsies, providing a novel, quantifiable physical metric to the pathologist **at the point of diagnosis**.

Feasibility is reinforced by recent large-scale human lung spatial maps[4], the rapid maturation of multimodal omics platforms[1,3] and access to human tissues through biobanks. Moreover, studies show that **mechanical stimuli regulate key pathways** in lung fibroblasts, immune cells and epithelial cells[22,23,24], and impact of lung mechanics with aging[25], supporting the hypothesis that combining these dimensions can reveal early mechanosensitive biomarkers.

4. Who cares? If you are successful, what difference will it make?

Chronic lung disease kills millions and costs the NHS and UK economy over £11bn annually[26] (in US national medical costs attributed to COPD are estimated to reach $60.5bn by 2029[27]). Today's tools detect damage only after 30–50% lung function is lost. If successful, LUNG-MECH will enable early detection and intervention, before irreversible scarring, shifting care from rescue to prevention. This could reduce mortality by 20–30%, cut treatment costs by billions, and extend healthy lung function by decades. **Who benefits:**

Stakeholder	What difference will it make?

[15] https://www.nature.com/articles/s41592-025-02618-1
[16] https://www.nature.com/articles/s41590-025-02161-3#Sec11
[17] https://www.jhltonline.org/article/S1053-2498(24)01531-6/pdf
[18] https://www.nature.com/articles/s41598-020-79434-4
[19] https://journals.physiology.org/doi/full/10.1152/ajplung.00415.2017
[20] https://www.nature.com/articles/s41592-023-01822-1
[21] https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0204765
[22] https://www.science.org/doi/10.1126/sciadv.adp4726
[23] https://rupress.org/jem/article/221/5/e20231835/276655/Piezo1-channels-restrain-ILC2s-and-regulate-the
[24] https://doi.org/10.1016/j.bioadv.2023.213516
[25] https://www.frontiersin.org/journals/cell-and-developmental-biology/articles/10.3389/fcell.2024.1381470/full
[26] https://www.asthmaandlung.org.uk/economic-burden-report
[27] https://journal.chestnet.org/article/S0012-3692(23)05832-4/fulltext

Biotech & Pharma	Access to 3-5 novel, validated mechano-associated targets for age-related lung decline. A completely new therapeutic class.
Clinicians & Pathologists	A decision support tool that flags high-risk patients from routine biopsies, enabling a proactive care.
Global Researchers	A population-scale, physics-informed atlas fuelling frontier research on aging and chronic disease.
Tech/AI companies	Multimodal datasets to build predictive models for personalised lung health.

Current solutions are reactive and based on molecular paradigm. Our approach integrates mechanics, the missing dimension, creating a new paradigm for lung health. Without LUNG-MECH, this integration will not happen at scale. Even if partial success: the atlas will remain a foundational resource, accelerating mechanobiology-driven therapies and diagnostics for decades.

5. What are the risks?

The LUNG-MECH program faces several critical risks. **Technical risks** include the challenge of precisely aligning mechanical measurements with molecular data and ensuring these reflect true in vivo physiology. There is also the risk that AI models may underperform if data are sparse or noisy, or that ex vivo validation may not predict in vivo outcomes. To mitigate these, we will use multi-modal validation, expand sample diversity, and iteratively refine models. **Ethics and regulatory risks** include data governance for the open-source atlas, which we will address through secure, cloud-native architecture, pseudonymization, and role-based access controls to protect patient data. **Adoption and commercialization risks** involve the possibility that therapeutic targets fail in late-stage trials or that clinicians resist new mechanical metrics. We will reduce these risks by prioritizing validation in clinically relevant ex vivo models and engaging pathology societies early to integrate workflows. **Programme risks** include coordination challenges across physics, biology, and AI teams, which we will mitigate through standardized data protocols and regular cross-disciplinary workshops. Finally, **equity risks** arise if biobank samples lack demographic diversity; we will ensure broad representation in sample collection. Even if full objectives are not met, the atlas will remain a foundational resource for mechanobiology research, fuelling future therapies and diagnostics.

6. How much will it cost?

The LUNG-MECH program is designed as a large-scale, research-intensive initiative with an estimated total budget of **£35 million**. The core 4-year program will require **£25 million**, distributed across phases: **Year 1** for infrastructure setup and technology deployment (~£6M), **Year 2** for scaling data acquisition and initiating target prioritization (~£7M), **Year 3** for completing the atlas and validating targets in ex vivo models (~£7M), and **Year 4** for translation, clinical integration, and virtual hub deployment (~£5M). Additional funds (~£10M) are allocated for independent verification, data governance, and contingency planning to ensure robustness and scalability. This budget reflects the complexity of integrating multimodal omics, high-resolution mechanobiology, and AI-driven inference at population scale, capabilities that cannot be achieved through incremental funding or isolated efforts.

7. How long will it take?

The LUNG-MECH program will run for **48 months**, structured into four intensive but achievable phases. **Year 1** focuses on building the infrastructure and deploying technologies for high-resolution mapping of lung tissue mechanics. **Year 2** scales these technologies to a larger cohort and initiates target prioritization using the integrated atlas. **Year 3** completes the population-scale atlas and validates top mechanosensitive targets in clinically relevant ex vivo lung models. **Year 4** transitions the program outputs into practice by launching the virtual hub as a long-term academic data common and supporting translation of validated targets toward therapeutic development. This phased approach includes clear Go/No-Go gates at the end of each year to ensure technical feasibility and de-risk the program.

8. What are the midterm and final "exams" to check for success?

The program will include rigorous mid-term and final evaluations with quantitative success metrics. **Mid-term exams (Month 24)** will validate the discovery pipeline. First, the Mechano-Molecular Inference Engine (MMIE) must achieve **$R^2 > 0.80$** when predicting the expression of the top 500 variable genes using only low-cost, inferred inputs, confirming a **~90% reduction in data generation costs** and validating the economic model for scaling of Lung Atlas. Second, we will identify **at least five robust mechano-molecular modules** that link local stiffness thresholds to early molecular signatures of tissue remodelling in pre-disease states. **Final exams (Months 36–48)** will focus on translation. By Month 36, we will complete Atlas generation, deliver a **portfolio of 3–5 novel mechanobiology targets validated in vitro**, ready for out-licensing or spin-out. By Month 48, the predictive diagnostic model will achieve **AUROC > 0.8** in independent external validation, demonstrating readiness for clinical integration, Atlas will be released as Virtual Hub, and at least 3 targets show druggability. These milestones provide clear Go/No-Go gates and ensure that progress is objectively measurable and impactful.