Modelling the Interface between Lung Cancer and the Immune System for Early Detection Biomarkers

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The Clinical Problem

- Currently in the UK, 75% of lung cancer cases are diagnosed at late stage, when only 3% of patients will survive beyond five years from diagnosis [1].
- Clinical trials have proven that early detection by chest low-dose CT scan is effective, but current population-based screening criteria excludes many people at significant risk of lung cancer [2, 3].
- There is a clear requirement for an early-stage biomarker for lung cancer to select patients for LDCT, prior to macroscopic visibility.

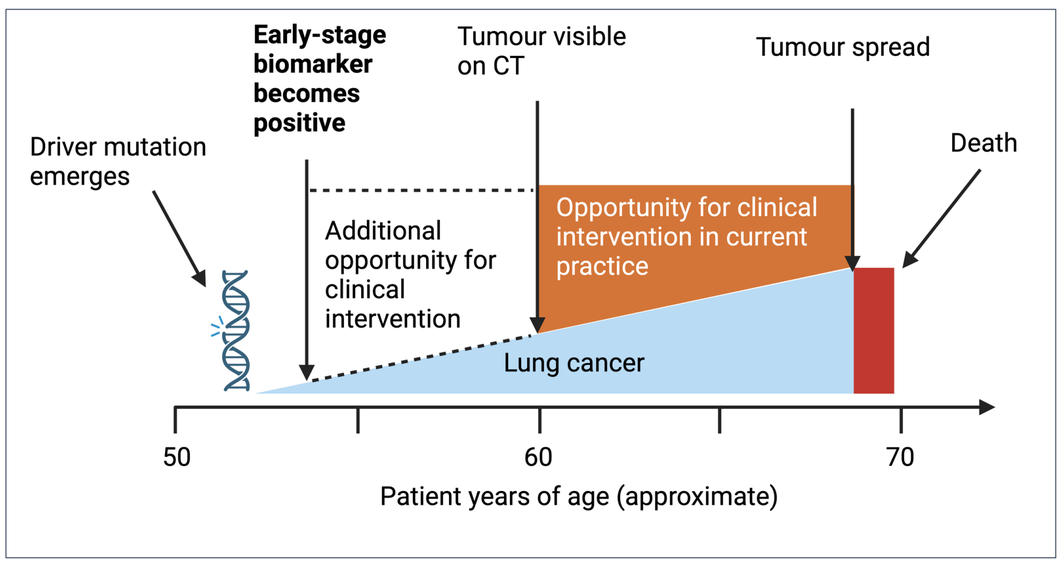

Fig.1: Blood based biomarker screening concept: *Biomarker to select patients with early-stage lung cancer, to receive monitoring by CT scan at the most appropriate time for effective treatment.*

Hypothesis, Aims and Methods Summary

Hypothesis

An immune response will become detectable upon interaction with cancer at the earliest stages of malignancy deemed undetectable by current methods.

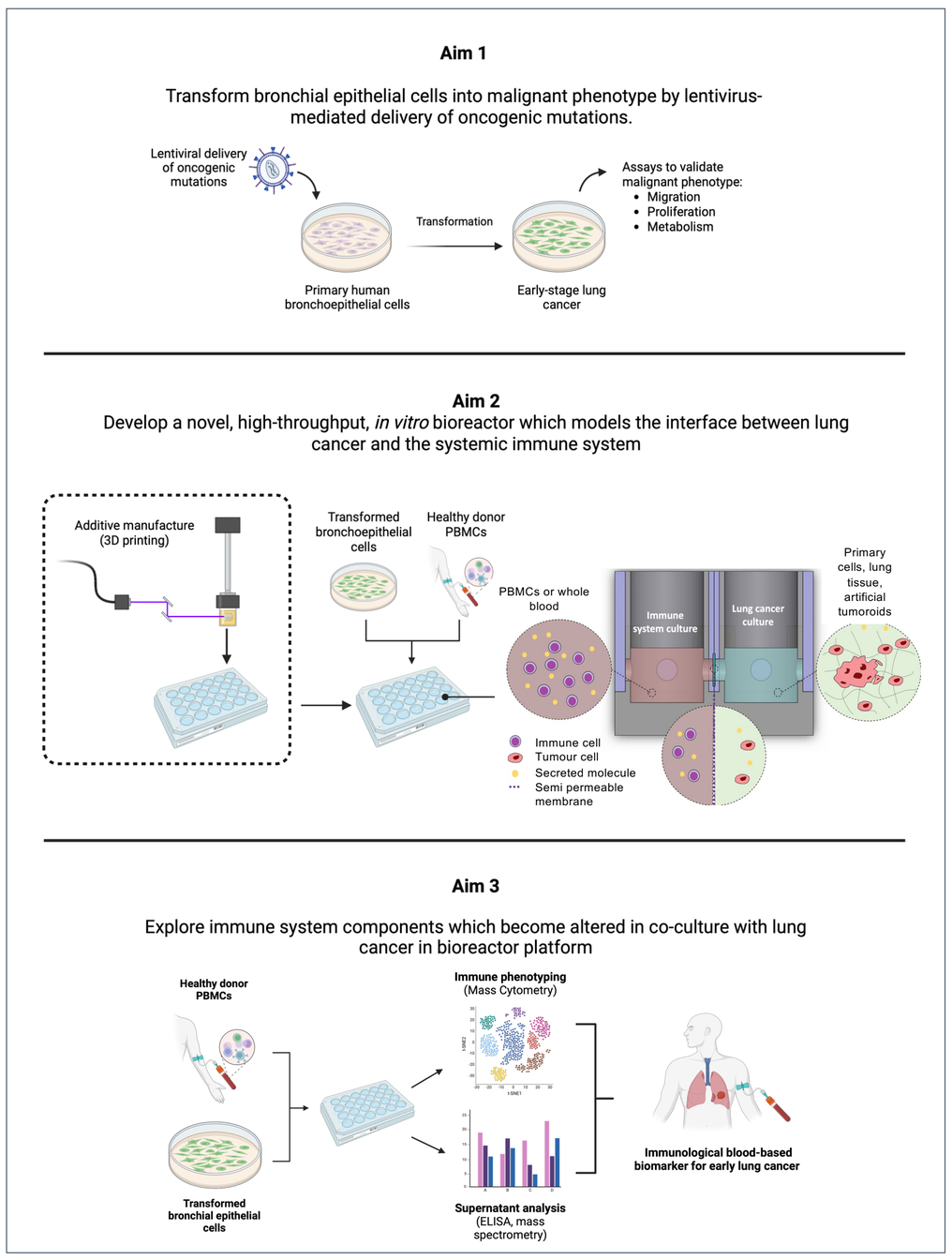

Fig.2: Project workflow: Project summarised into three aims with explanations *(Figure created in BioRender). (PBMCs) peripheral blood mononuclear cells, (ELISA) enzyme linked immunosorbent assay.*

RESULTS 1: Prototype Culture Platform Modelling the Lung Cancer and Immune System Interface

Horizontal co-culture design will prevent cell seeding on exchange surface and enables plate imaging and dynamic culture in single autoclavable device.

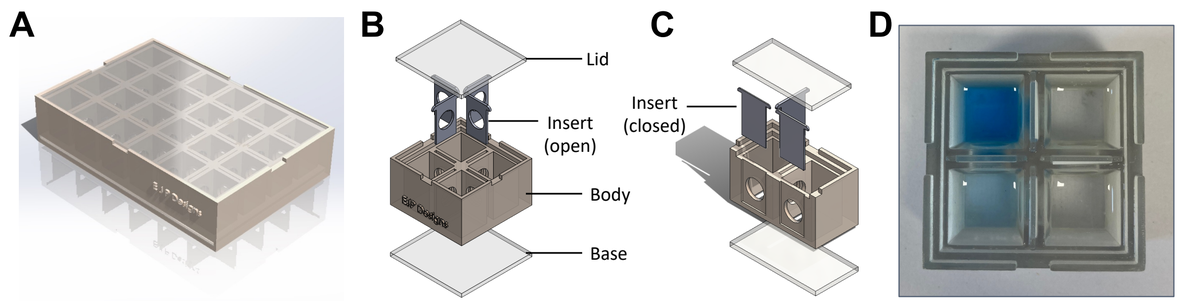

Fig.3: Bioreactor prototype design: 3D computer aided design full-size render (A) and explosion labelled (B-C) generated using SolidWorks. Prototype bioreactor printed from VeroClear polymethyl methacrylate resin with food dye + PBS to demonstrate watertight design which permits diffusion (D).

RESULTS 2: Dendritic Cell Expansion in Localised Lung Tumour Resects and Lung Adenocarcinoma Model

We are interested in early immune signals of lung cancer. Immune profiling by mass cytometry (CyTOF) enables unbiased high-dimensionality single-cell analysis in heterogenous peripheral blood mononuclear cell (PBMC) samples.

Fig.4: CyTOF analysis of immune phenotypes in PBMCs in human squamous cell lung tumour resects (A-C) and in early cancer co-culture model (D-F): Schematic of lung resects origin (A) and co-culture setup (D). PBMC frequency in each of 20 clusters (B, E). Magnitude of marker expression measured in 20 clusters (C,F). Red boxes indicate clusters and markers of interest. Clustering and plots generated in Rstudio. Debris and CD45- cells removed using FlowJo.

Conclusions and Future Work

- We have developed a prototype *in vitro* platform for high-throughput co-culture experiments which will model the interface and first between lung cancer and the systemic immune system. We will further prototype to ensure design and material is optimal for co-culture experiments.
- We reveal an expansion of DCs in localised lung tumour resects from squamous cell carcinoma patients. A similar population expand in co-culture with lung adenocarcinoma cells. Further characterisation of responding immune cells will be carried out in high-throughput bioreactor.
- Framework in place to generate lentiviral vector suite for delivery of oncogenic mutations into bronchial epithelial cells to mimic earliest stages of malignancy in human cancer.

References

1. World Health Organisation, 2023. Cancer Today; Lung.
2. UK National Screening Committee, 2022. UK NSC Recommendation; Lung Cancer.
3. National Lung Screening Trial Research Team, 2011. Reduced lung-cancer mortality with low-dose computed tomographic screening. *New England Journal of Medicine*, *365*(5), pp.395-409.

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