

P3.377: Cell Specialization and Cooperation Define Spatial and Single-Cell Heterogeneity in Pleural Mesothelioma

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INTRODUCTION

- **Pleural mesothelioma (PM)** is a deadly rare cancer¹
- **Histology alone is insufficient** to explain inter-patient heterogeneity^{2,3,4}
- Our proposed morpho-molecular classification places tumors along a continuum defined by **3 biological tasks**^{2,5}
- Most PM are “generalists” engaging all three but at various degrees²
- **However these findings rely on bulk data**

- I. Is a generalist PM tumor composed of a homogeneous population of generalist cells or a heterogeneous population of cells with different task specializations?
- II. How does a task-heterogeneous tumor maintain this heterogeneity?

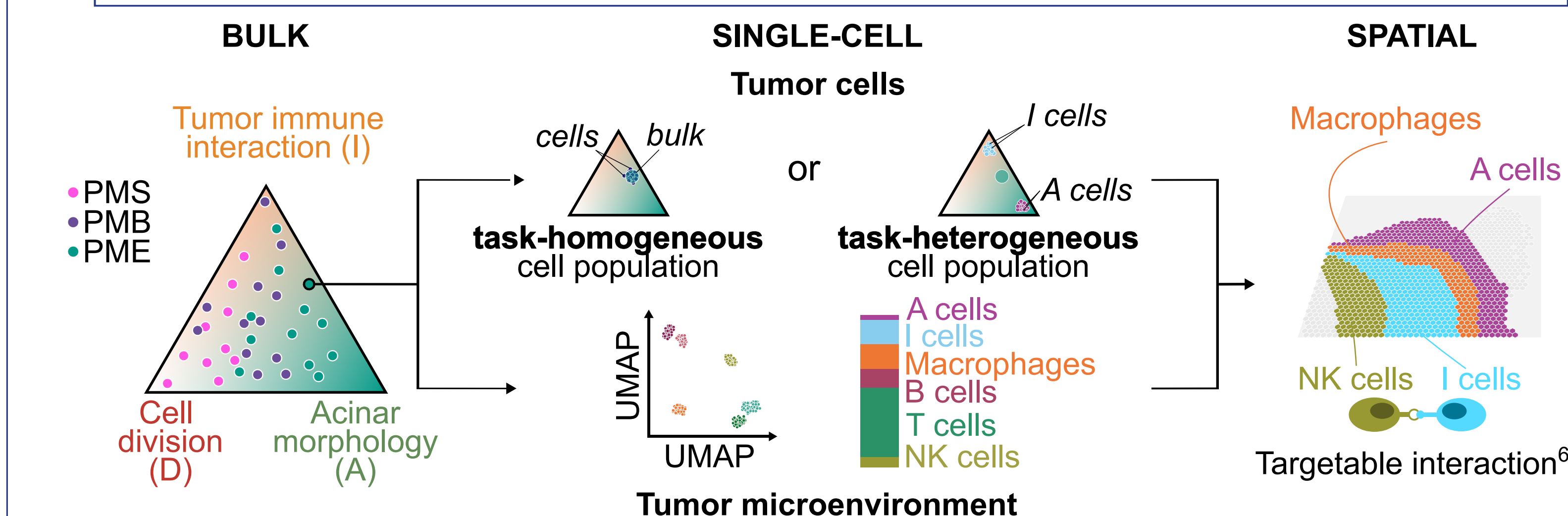
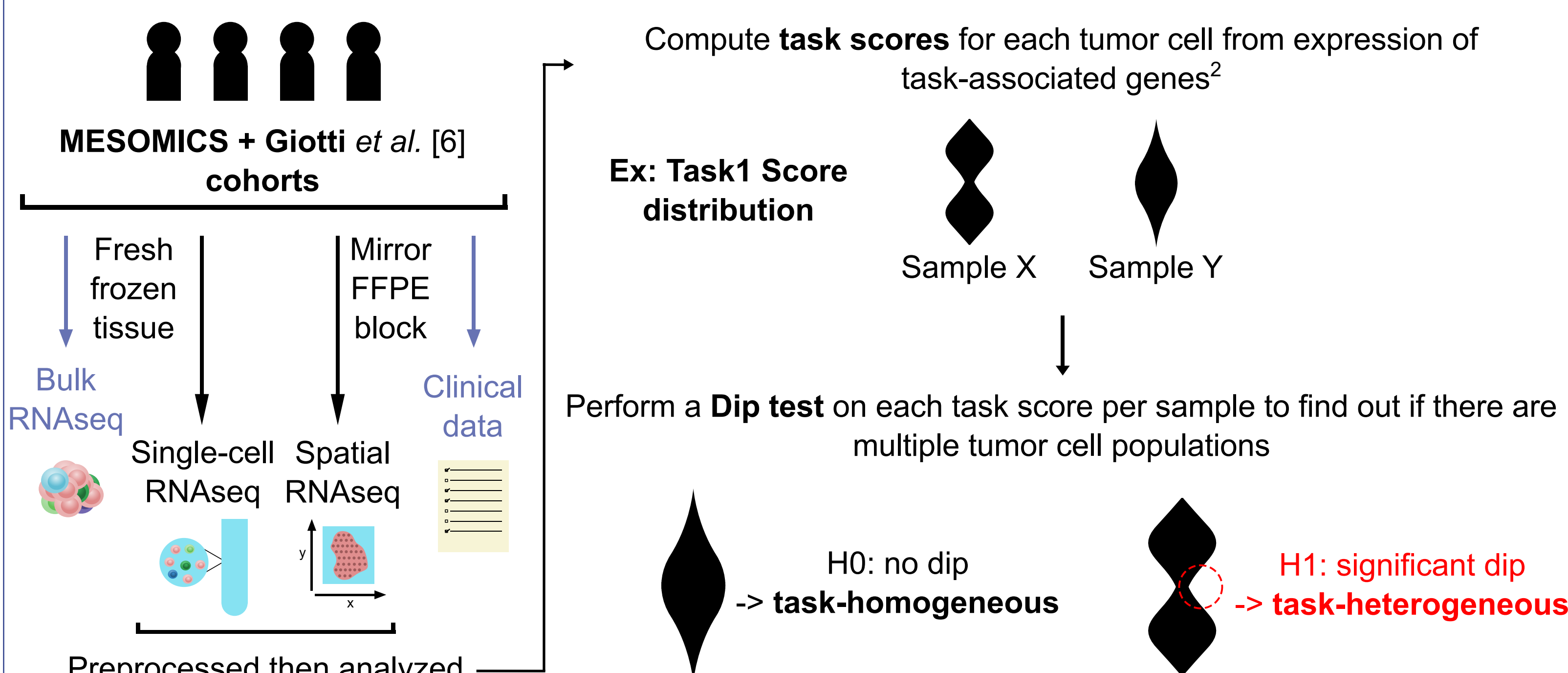


Figure 1 | Single-cell and spatial transcriptomics can shed light on malignant cell specialization and suggest future therapeutic targets. Adapted from [3].

METHODS

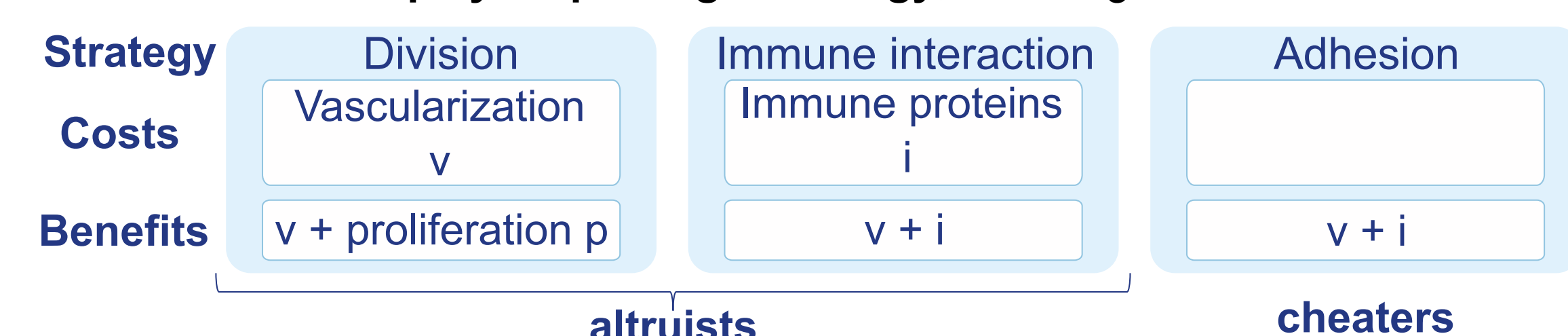
I. Identify task-homogeneous vs task-heterogeneous tumor cell populations



II. Model tumor cell interactions

Create a **Game Theory model** that emulates PM phenotype based on task payoff

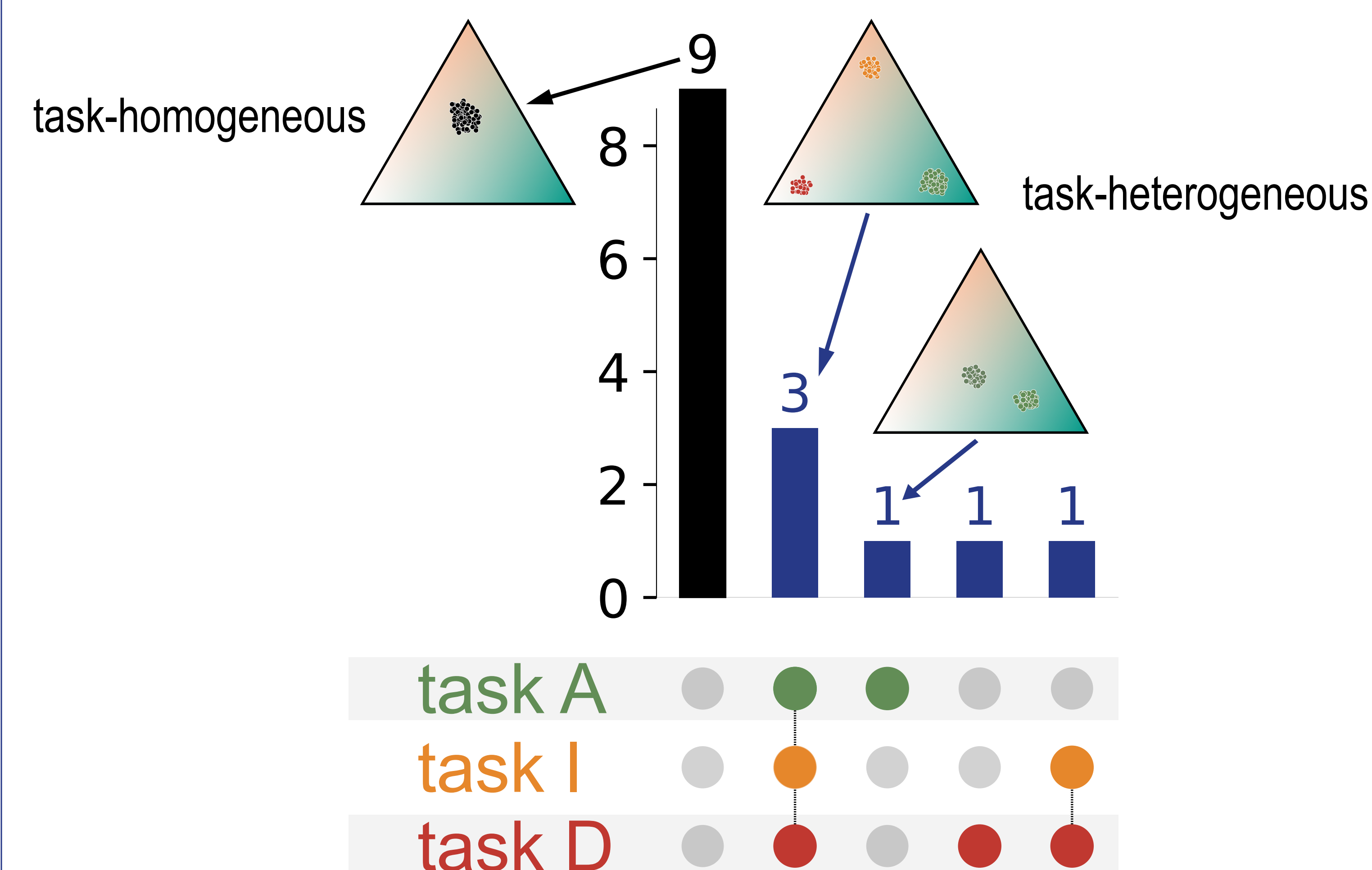
Cells are **players picking a strategy**, investing in the 3 tasks



Perform **cell-cell interaction analysis** to find out if cells behave as altruists vs cheaters

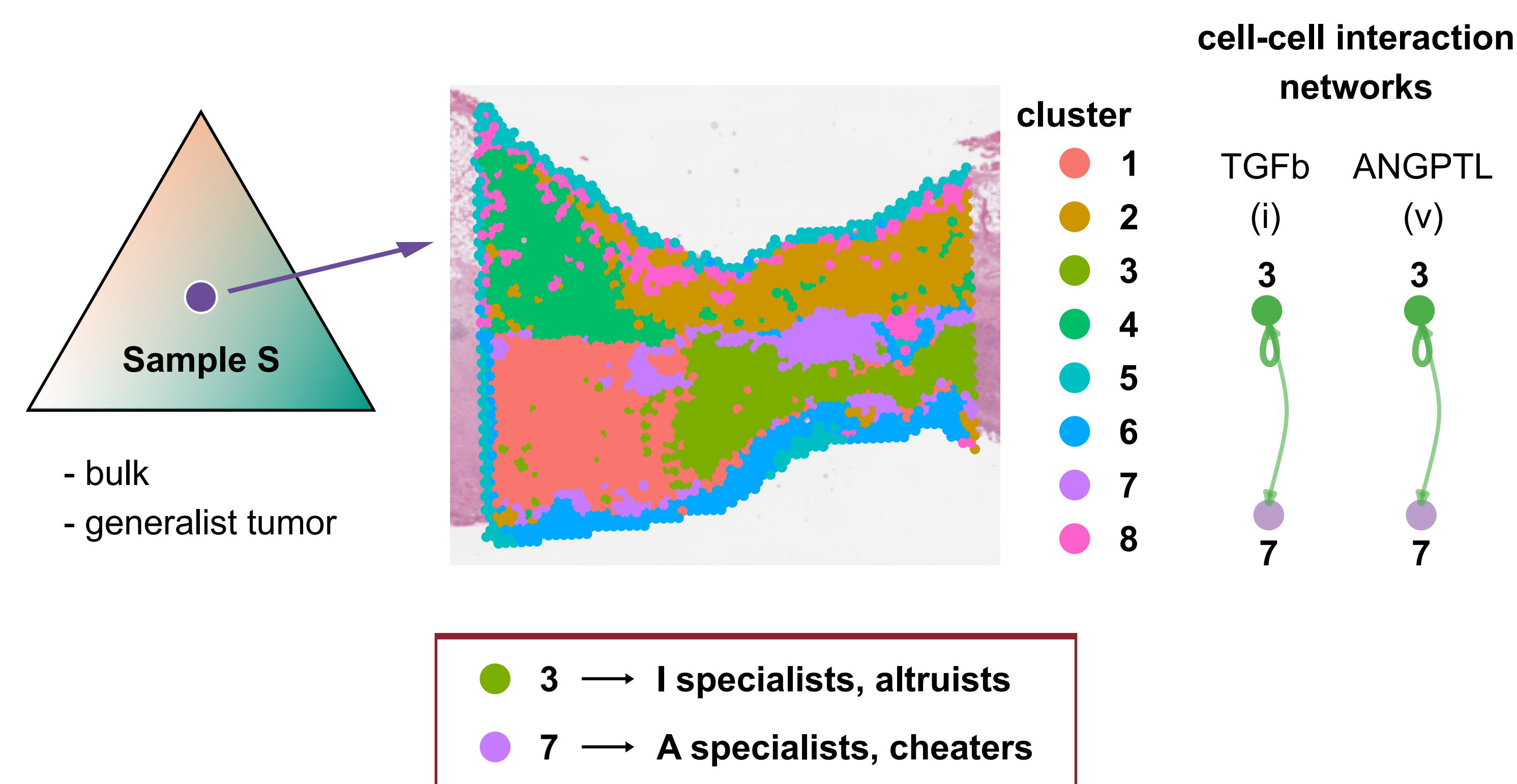
RESULTS

I. Most PM tumors are composed of a task-homogeneous population, but 1/3 of PMs have a task-heterogeneous one



- Noticable **tumor cell diversity**
- Not what we would expect in such an aggressive cancer
- How can it be maintained?

II. Tumors composed of a task-heterogeneous population maintain tumor cell heterogeneity through cooperation and cheating



DISCUSSION AND CONCLUSION

Take Away Message

- Both task-homogeneous and task-heterogeneous tumor cell populations exist in PM
- Tumors composed of a task-heterogeneous population are able to maintain their heterogeneity through **cooperation and "cheating"**
- Our model allows to **identify targetable interactions** and **test treatment strategies** to counteract tumor strategies
- Strong implications for **future therapy and clinical trials**

Future Direction for Research

- Combining **cancer biology** with **evolution, ecology & math** allows us to study under-appreciated mechanisms
- By understanding the "game" of PM, we can try to "change the rules" at any stage to influence outcome

Future Directions for the Project

- Offer **markers** for each task
- Identify **clinical characteristics** associated with each task

REFERENCES & ACKNOWLEDGEMENTS

¹ World Health Organization *Thoracic tumours: WHO classification of tumours (5th ed.)* 2021

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⁵ Di Genova *et al. GigaScience* 2023

⁶ Giotto *et al. Cancer Discovery* 2024

Thank you to the patients for their participation

