Modelling the CD8$^+$ T cell immune response to heterogeneous tumours

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Plan

Biological context

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Numerical simulations and biological implications

Conclusion

Biological context

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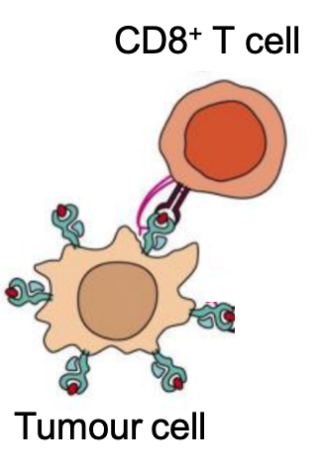
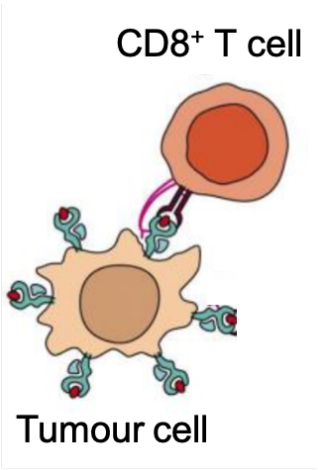
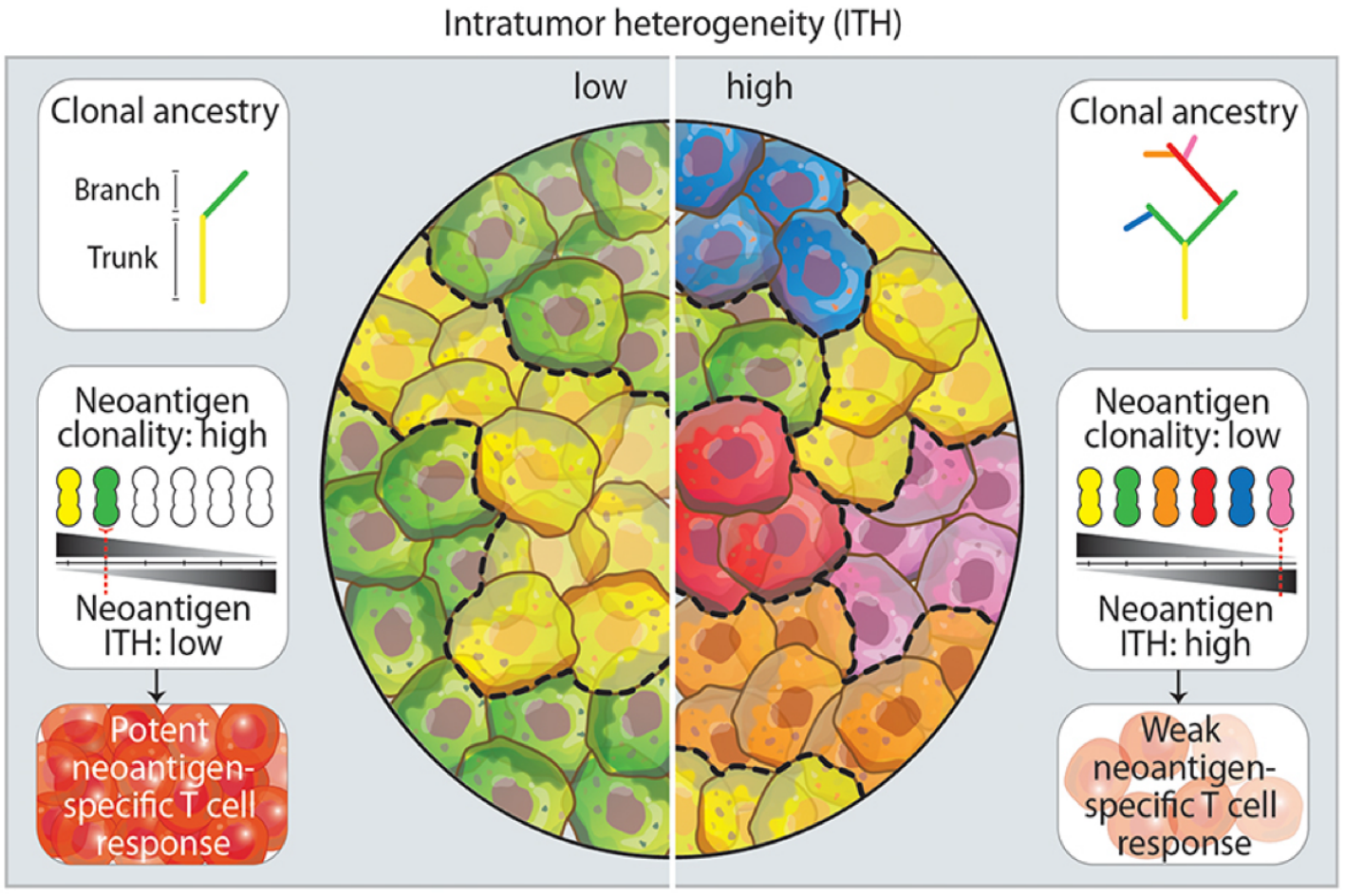


Biological context





Adapted from: Fennemann et al. [2019]

Mathematical model

Individual-based model

THE MODEL:

- Individual-based model: 1 cell $\rightarrow$ 1 agent
- Cell behaviours and interactions: rules with probabilities
- 2D model
- Two cell types: tumour cells and $CD8^+$ T cells

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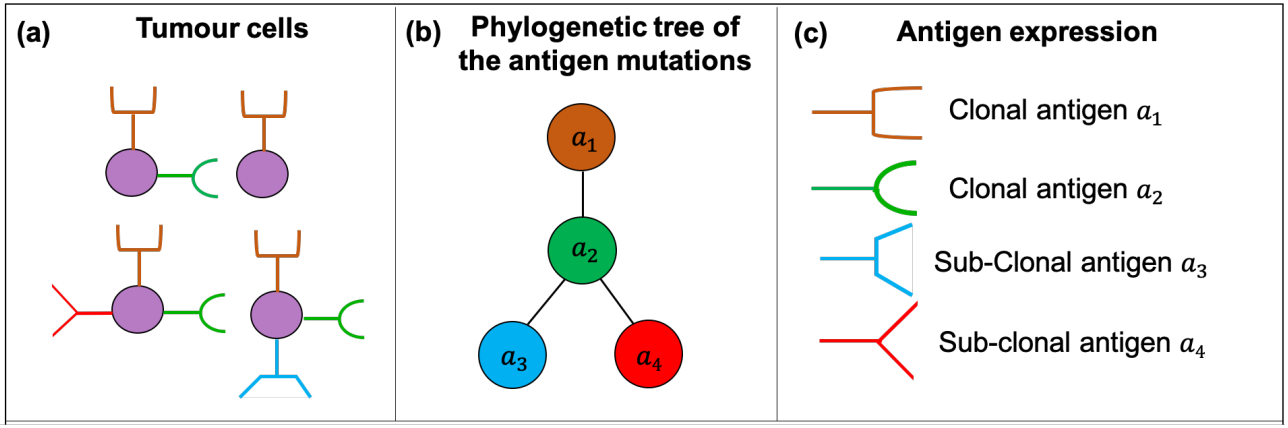
TUMOUR CELLS:

- 1/+ antigens
- Antigens: clonal or sub-clonal

Individual-based model



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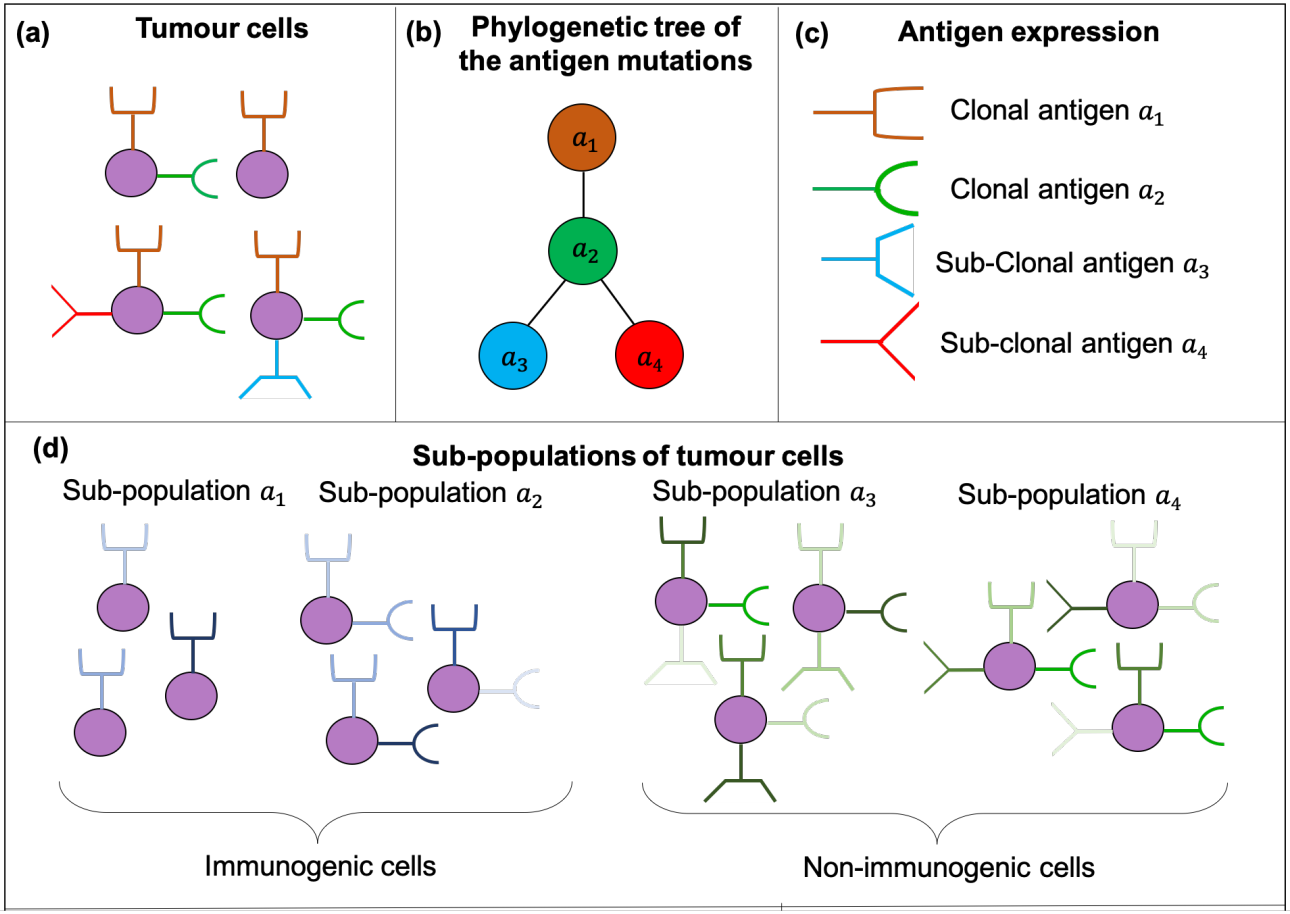
TUMOUR CELLS:

- 1/+ antigens
- Antigens: clonal or sub-clonal
- **Sub-populations of tumour cells**
- **Antigens: presented at different levels**

Individual-based model



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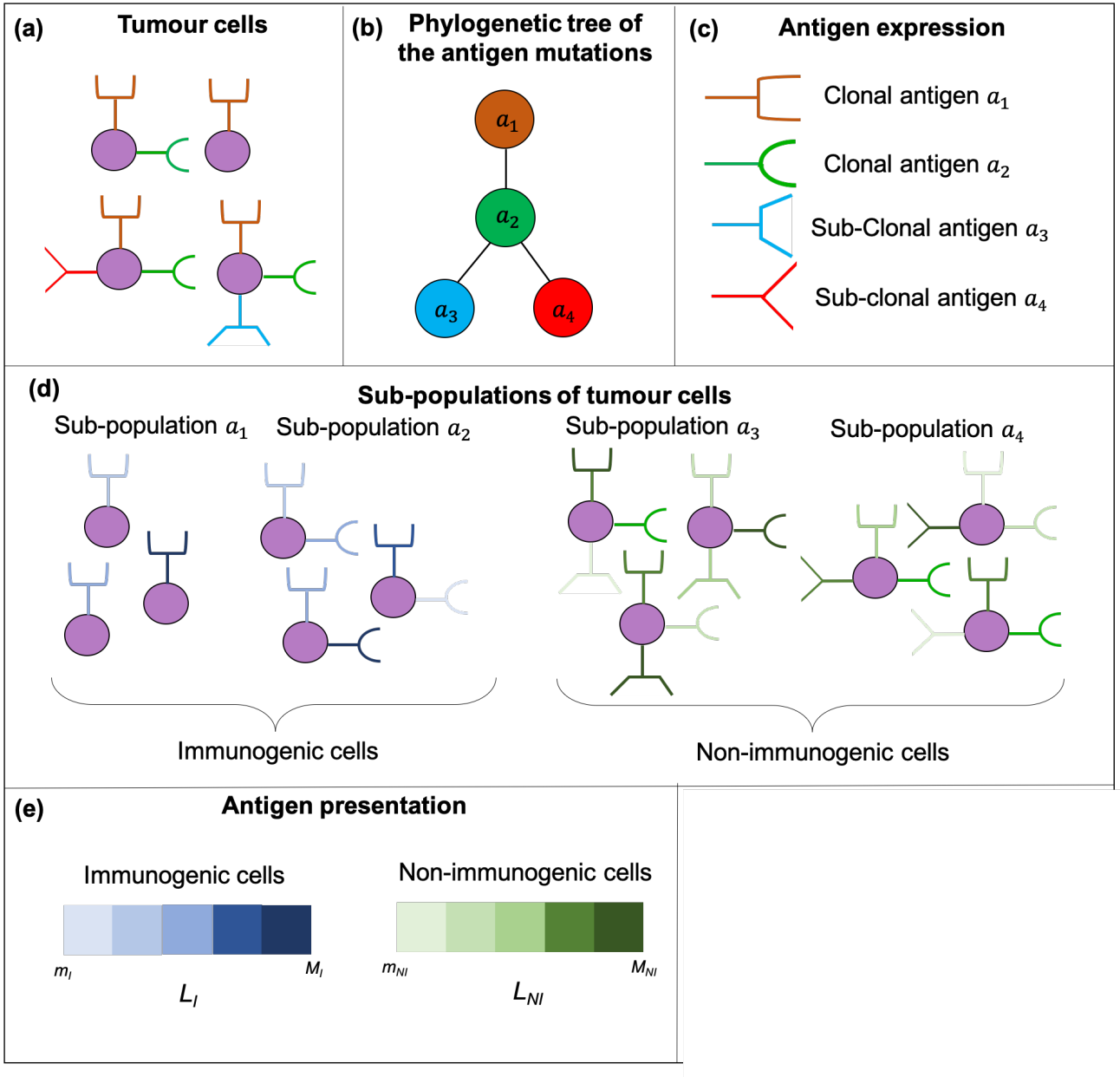

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- Individual-based model: 1 cell $\longrightarrow$ 1 agent
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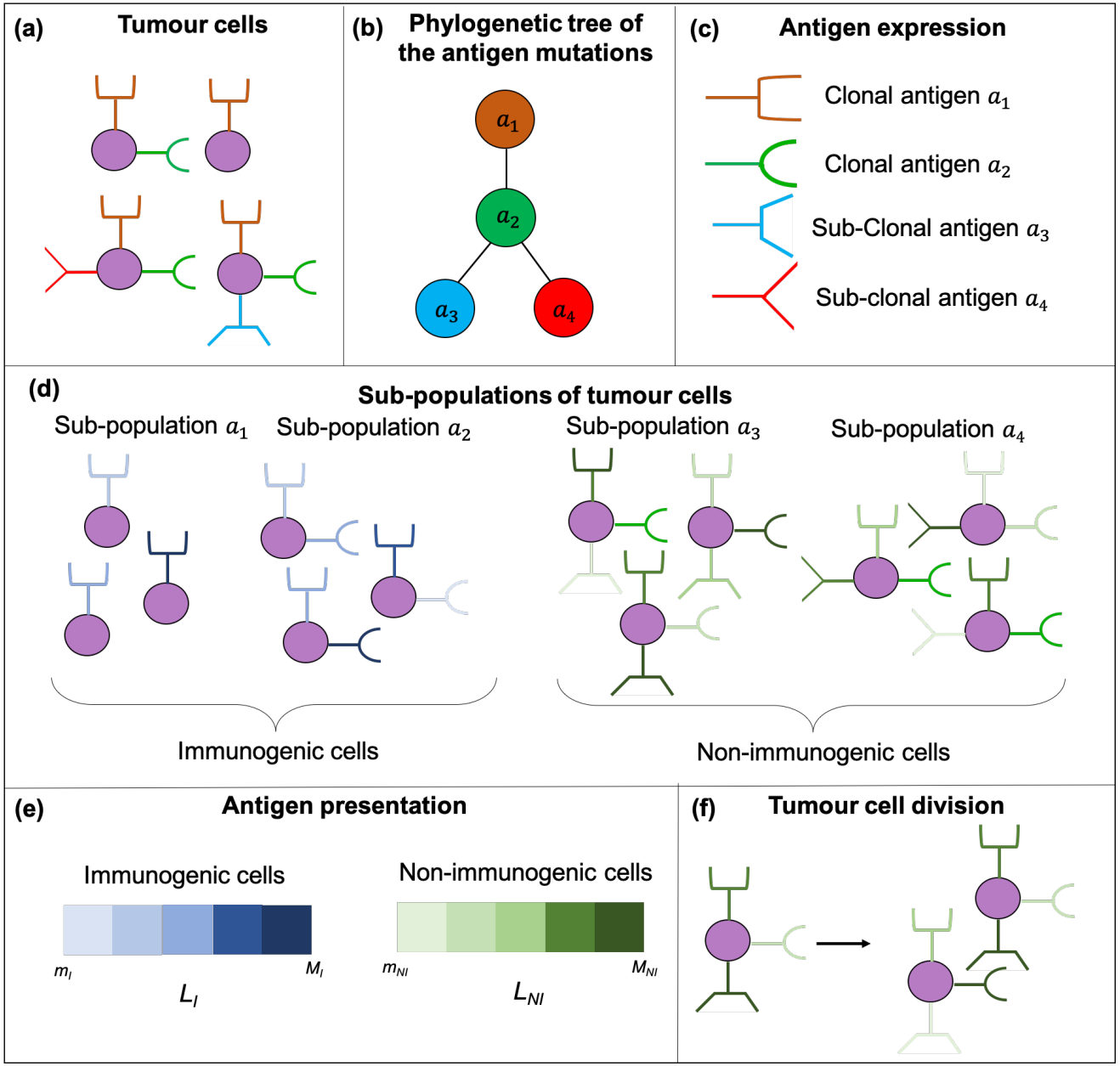
TUMOUR CELLS:

- Express 1/+ antigens
- Antigens: clonal or sub-clonal
- Sub-populations of tumour cells
- Antigens: presented at different levels
- **Mitosis**

Individual-based model

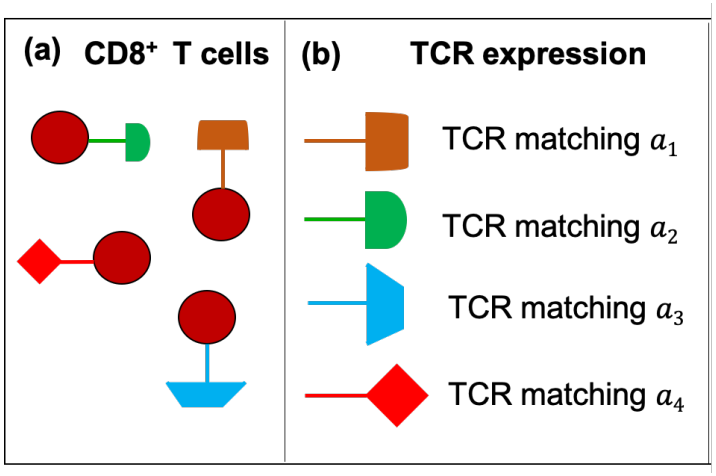


Individual-based model

$CD8^+$ T CELLS:

- 1 TCR specific to 1 antigen

Individual-based model

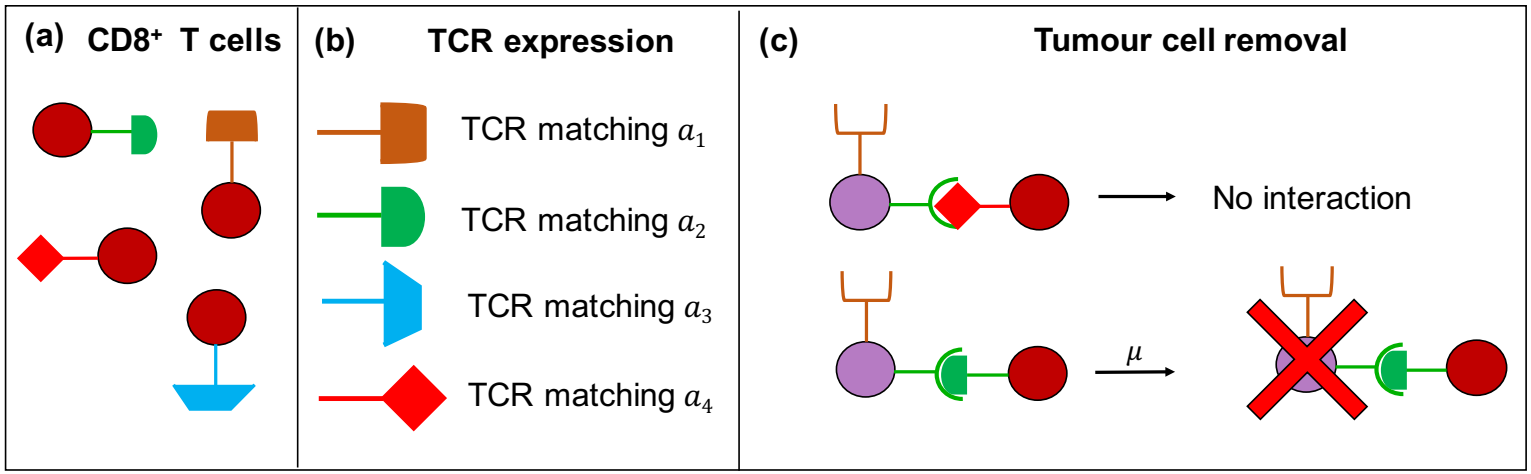


Individual-based model

$CD8^+$ T CELLS:

- 1 TCR specific to 1 antigen
- Chemotactic movement toward tumour cells expressing the matching antigens
- Interaction with tumour cells

Individual-based model



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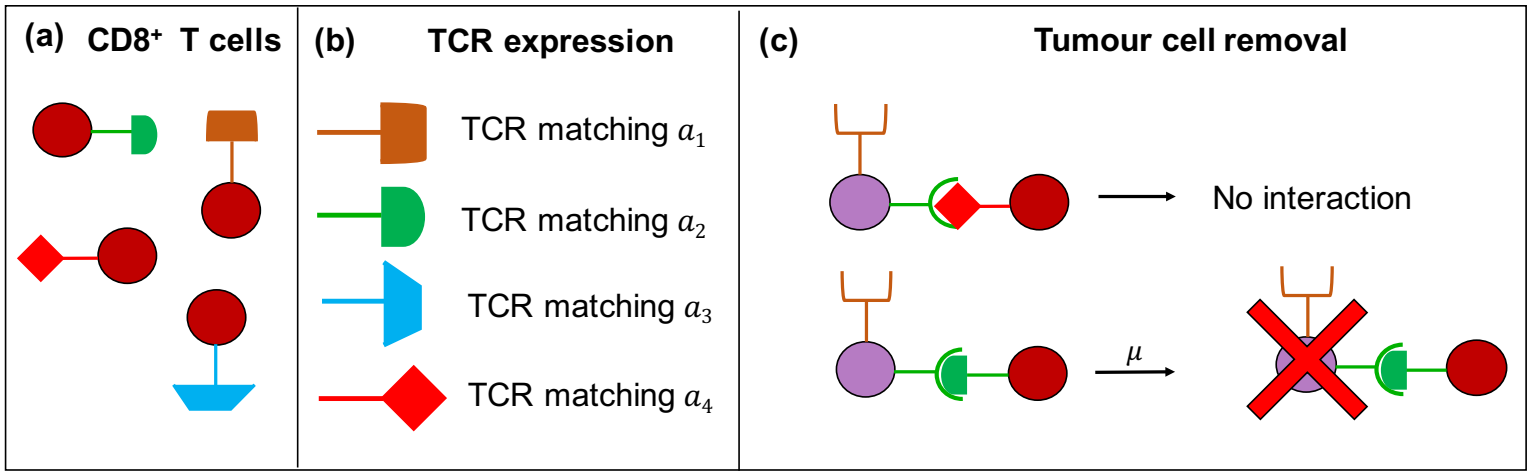
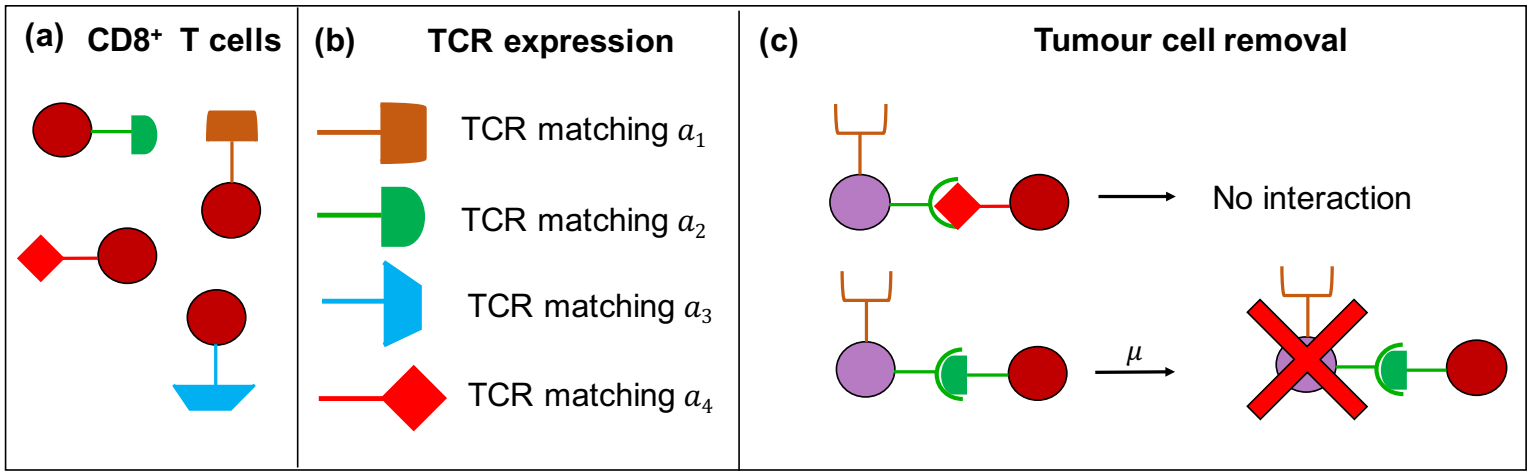


μ : $\propto$ level of antigen presentation

Individual-based model



μ : $\propto$ level of antigen presentation

$\Rightarrow$ immunogenic cells: killed more easily than non-immunogenic cells

Individual-based model

$CD8^+$ T CELLS:

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CHEMOATTRACTANT(S):

- Cytokines and signalling proteins able to induce directed chemotaxis of $CD8^+$ T cells toward their targets

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- **As many chemoattractants as antigens expressed by the tumour**

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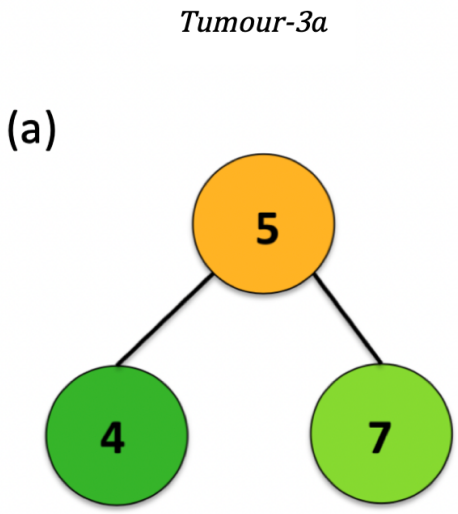
CHEMOATTRACTANT(S):

- Cytokines and signalling proteins able to induce directed chemotaxis of CD8$^+$ T cells toward their targets
- Secreted by tumour cells
- As many chemoattractants as antigens expressed by the tumour
- Secretion: $\propto$ level of antigen presentation
- **Influx of T cells: $\propto$ total amount of chemoattractants**

Initial conditions

Inspired by: Wolf et Al. Uvb-induced tumor heterogeneity diminishes immune response in melanoma. *Cell*, 2019.

- *Tumour-3a*: 3 antigens $\longrightarrow$ 1 clonal (5) and 2 sub-clonal (4 and 7)



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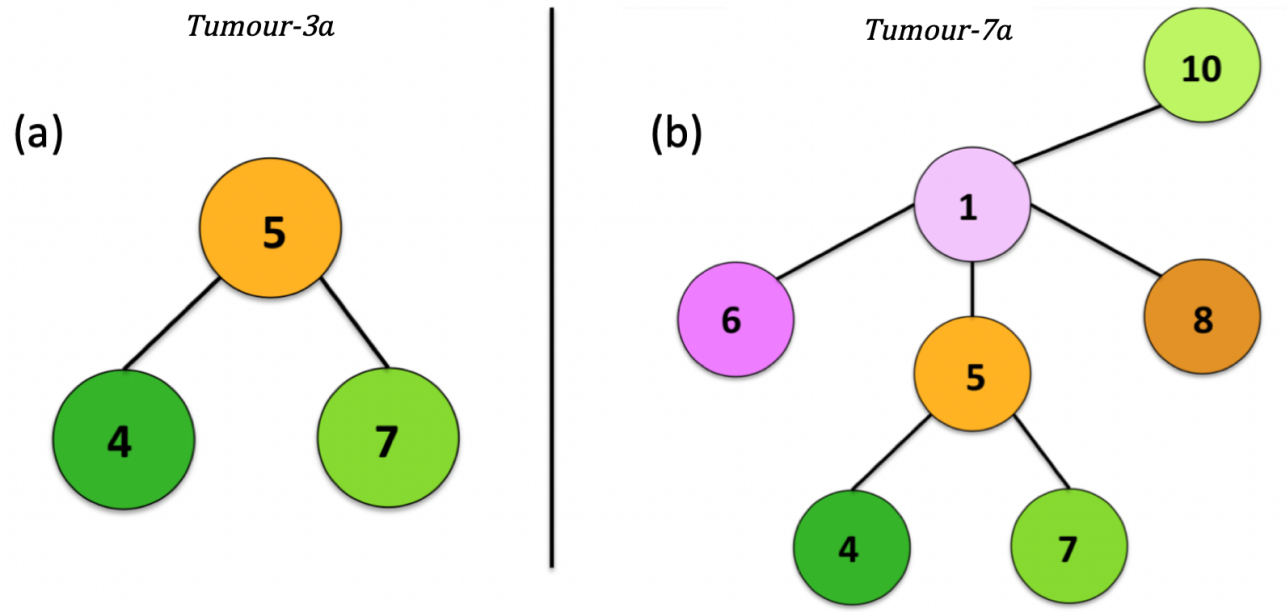
Inspired by: Wolf et Al. Uvb-induced tumor heterogeneity diminishes immune response in melanoma. *Cell*, 2019.

- *Tumour-3a*: 3 antigens $\longrightarrow$ 1 clonal (5) and 2 sub-clonal (4 and 7)
- *Tumour-7a*: 7 antigens $\longrightarrow$ 2 clonal (1 and 5) and 5 sub-clonal (4, 6, 7, 8, 10)



Numerical simulations and biological implications

Results

2 possible outcomes:

- $\rightarrow$ immune clearance
- $\rightarrow$ immune escape

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Goal: investigate the effects of ITH by varying:

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1. **the number of antigens (*i.e.* the number of sub-populations) constituting the tumour**

Results

2 possible outcomes:

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Goal: investigate the effects of ITH by varying:

1. the number of antigens (*i.e.* the number of sub-populations) constituting the tumour
2. **the immunogenicity of the tumour (*i.e.* the ratio between immunogenic and non-immunogenic cells)**

Results

2 possible outcomes:

→ immune clearance

→ immune escape

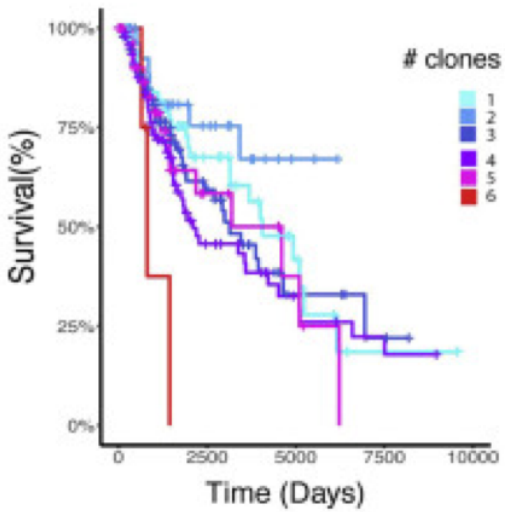
Goal: investigate the effects of ITH by varying:

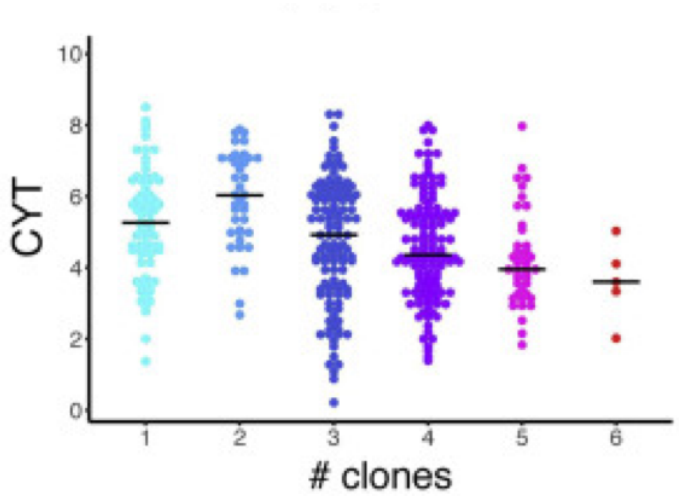
1. the number of antigens (*i.e.* the number of sub-populations) constituting the tumour
2. the immunogenicity of the tumour (*i.e.* the ratio between immunogenic and non-immunogenic cells)
3. **both the number of antigens AND the immunogenicity of the tumour**

Results(1)

Goal(1): investigate of the effects of ITH by varying the number of sub-populations constituting the tumour

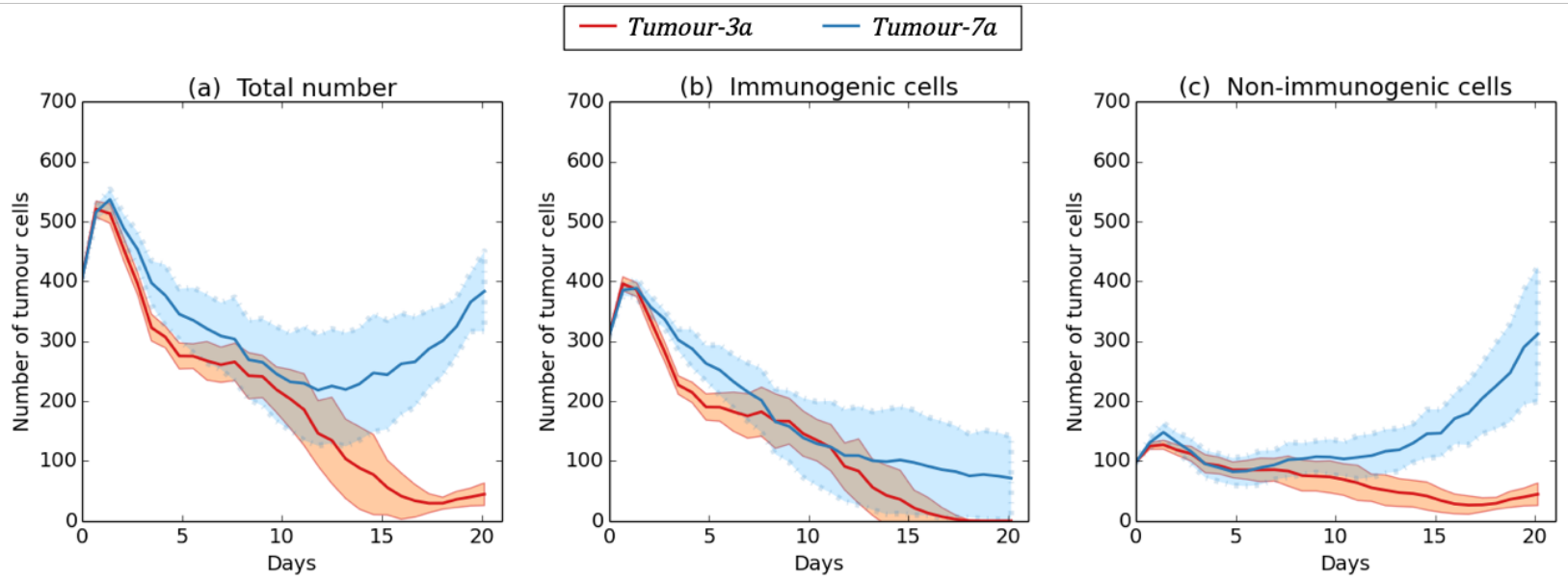
Wolf et al. [2019]: increasing the number of sub-populations of tumour cells results in less effective immune response and significantly larger tumours





Results(1)

Our results:



Tumour-3a: 1 sub-population of immunogenic cells and 2 sub-populations of non-immunogenic cells

Tumour-7a: 2 sub-populations of immunogenic cells and 5 sub-populations of non-immunogenic cells

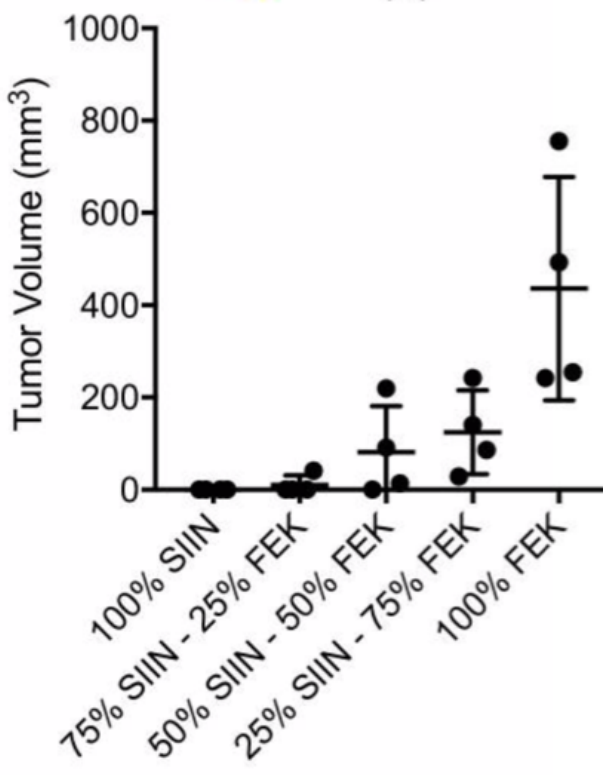
Both tumours: 75% I - 25% NI

Results(2)

Goal(2): investigate of the effects of ITH by varying the immunogenicity of tumour cells (*i.e.* the ratio between immunogenic and non-immunogenic cells)

Inspired by: Gejman et Al. Rejection of immunogenic tumor clones is limited by clonal fraction. *Elife*, 2018

A different ratio between immunogenic (SIIN) and non-immunogenic (FEK) cells influence immune surveillance



Results(2)

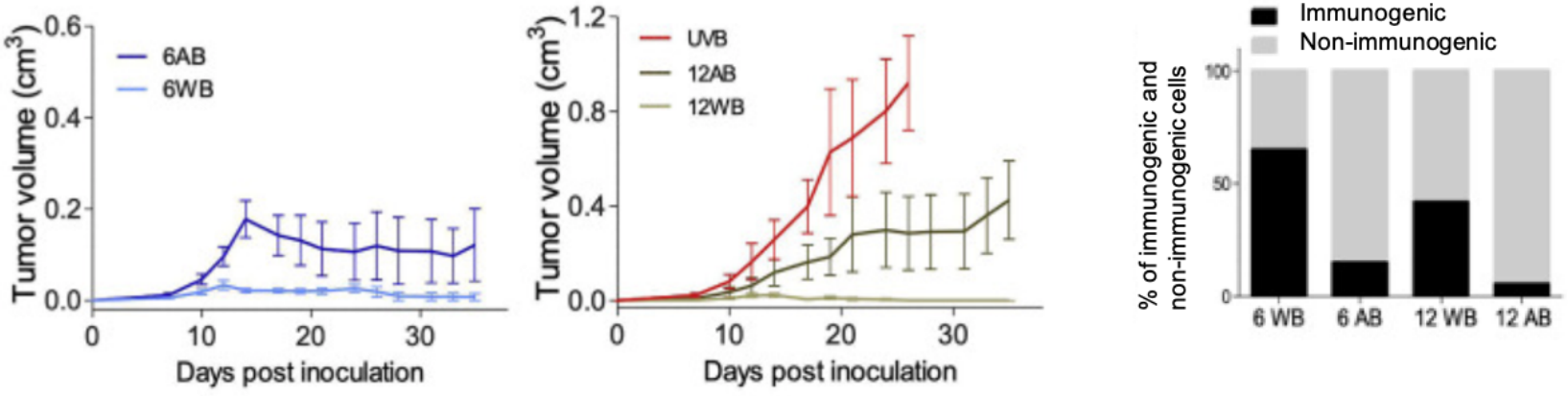
Our results:

— *Tumour-3a*: 1 sub-population of immunogenic cells and 2 sub-populations of non-immunogenic cells

Results(3)

Goal(3): investigate of the effects of ITH by varying both the number of antigens AND the immunogenicity of the tumour

Wolf et al. [2019]: both the number of sub-populations and the ratio of immunogenic and non-immunogenic cells are responsible of immune escape



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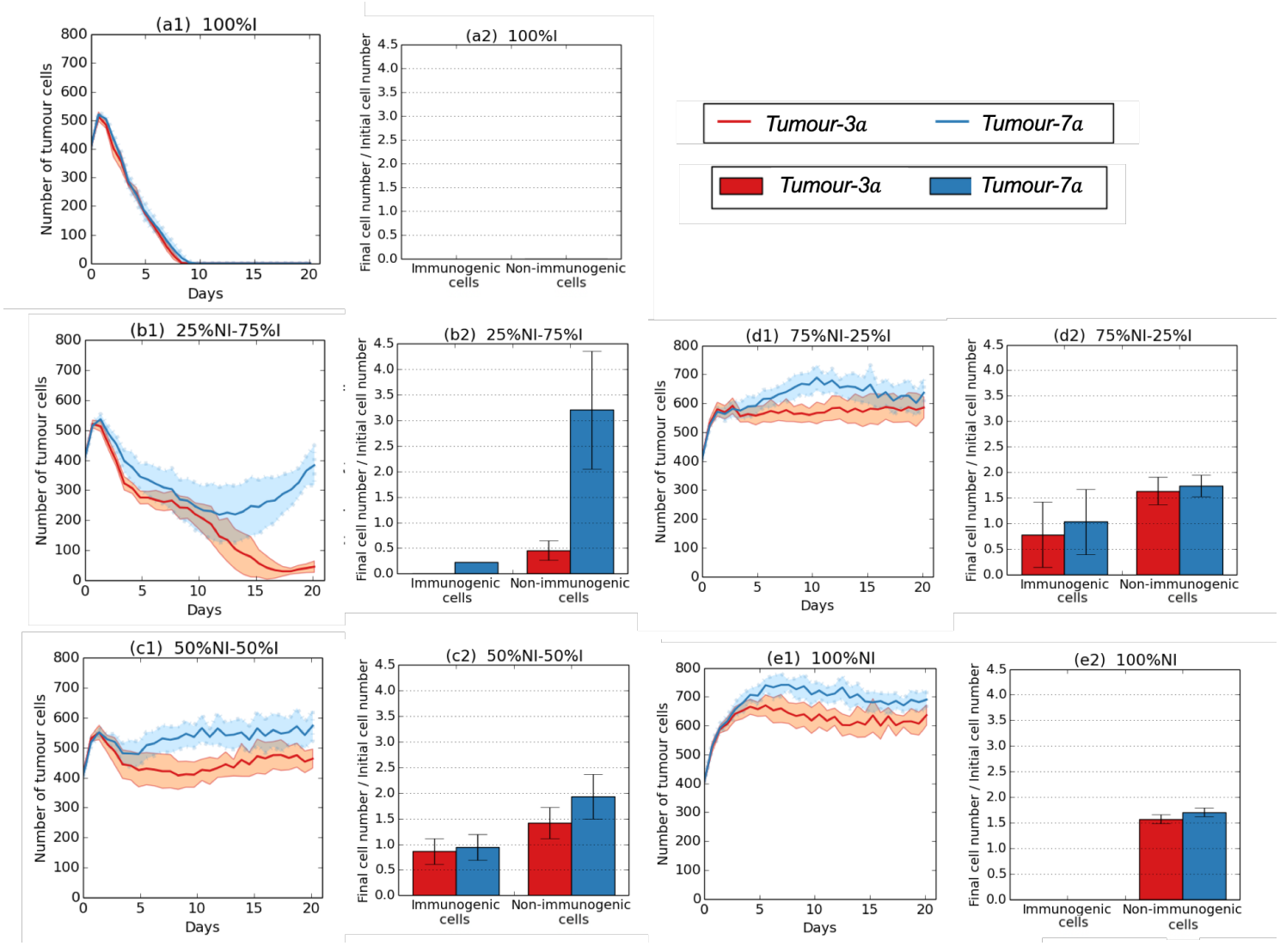
Results(3)

Our results:



Conclusion

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- Investigation of the effects of ITH for tumours characterized by:
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  - different level of immunogenicity

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- Investigation of the effects of ITH for tumours characterized by:
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- **Both the number of sub-populations AND the ratio of immunogenic cells are responsible of immune escape**

Conclusion

- Individual-based model for tumour-immune cell interactions

- Investigation of the effects of ITH for tumours characterized by:
  - different antigen profiles
  - different level of immunogenicity

- Both the number of sub-populations AND the ratio of immunogenic cells are responsible of immune escape

- **Next steps:**
  - **role of T cell infiltration on immune response**
  - **derivation of a continuum model**

Thank you for your attention !

Emma Leschiera

References

F. L. Fennemann, I. J. M. de Vries, C. G. Figdor, and M. Verdoes. Attacking tumors from all sides: personalized multiplex vaccines to tackle intratumor heterogeneity. *Frontiers in immunology*, 10:824, 2019.

Y. Wolf, O. Bartok, S. Patkar, G. B. Eli, S. Cohen, K. Litchfield, R. Levy, A. Jiménez-Sánchez, S. Trabish, J. S. Lee, et al. Uvb-induced tumor heterogeneity diminishes immune response in melanoma. *Cell*, 179 (1):219–235, 2019.