

Direct T cell mediated killing in solid tumours is insufficient to explain tumour regression

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Immunotherapy in Cancer

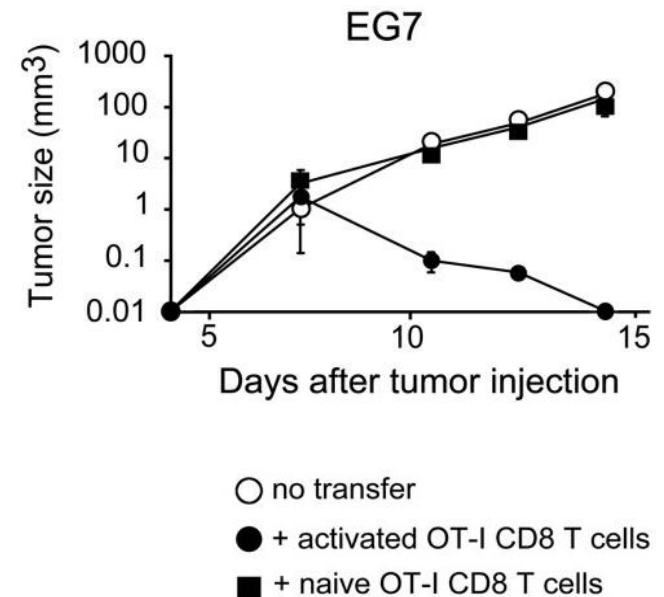
- Activating and enhancing anti – tumour response
- Adoptive cell transfer
- Modelling to gain mechanistic insight and quantitative understanding

Rosenberg, S. A., & Dudley, M. E. (2009). Adoptive cell therapy for the treatment of patients with metastatic melanoma. *Current opinion in immunology*, 21(2), 233-240.



Investigating T cell killing rate in an in-vivo model of a solid tumour

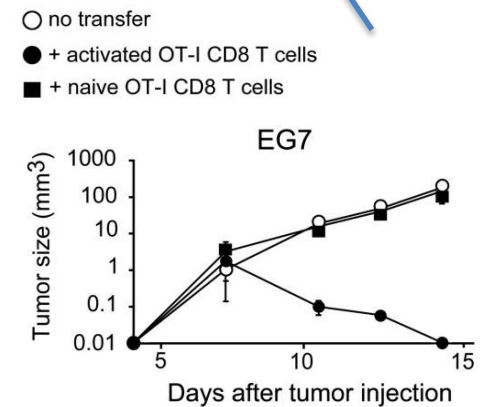
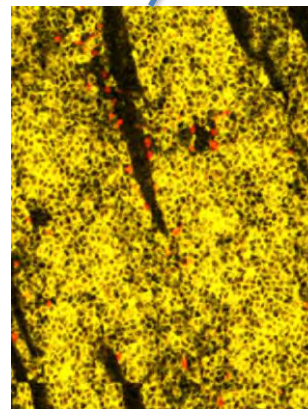
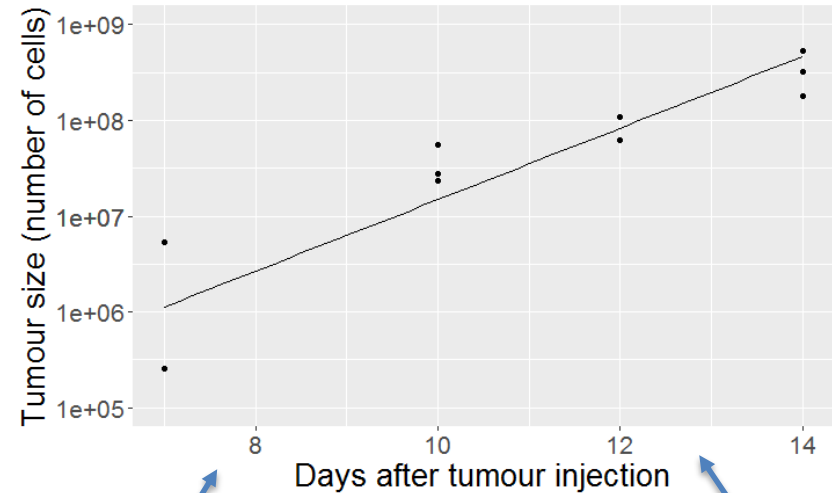
- Killing rate: 3/day
- All deaths T cell mediated
- Low infiltration (E:T \approx 1: 100)
- Is this sufficient for tumour regression?



Breart, Béatrice, et al. "Two-photon imaging of intratumoral CD8+ T cell cytotoxic activity during adoptive T cell therapy in mice." *The Journal of clinical investigation* 118.4 (2008): 1390-1397.

Data overview (growth rate)

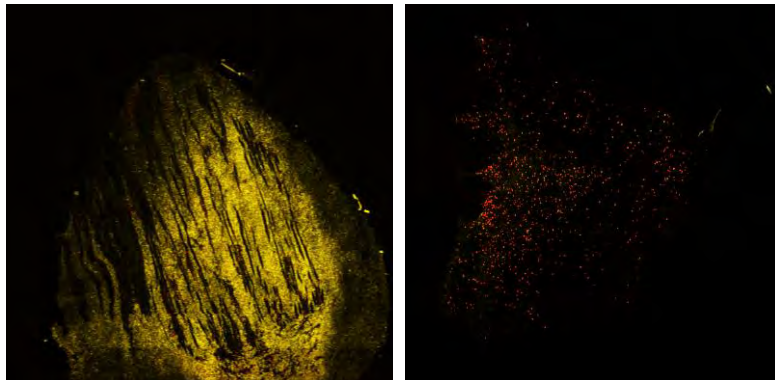
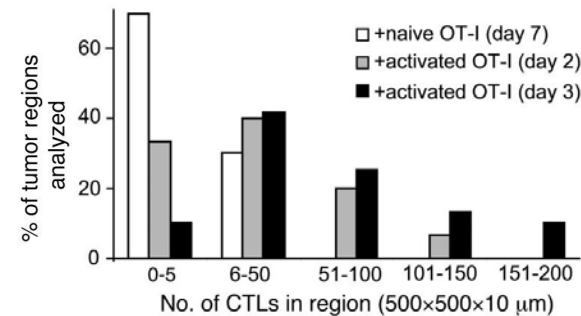
- Tumour cell replication rate estimated from growth rate of untreated tumours
- Tumour cell density used to estimate number of cells



Breart, Béatrice, et al. "Two-photon imaging of intratumoral CD8+ T cell cytotoxic activity during adoptive T cell therapy in mice." *The Journal of clinical investigation* 118.4 (2008): 1390-1397.

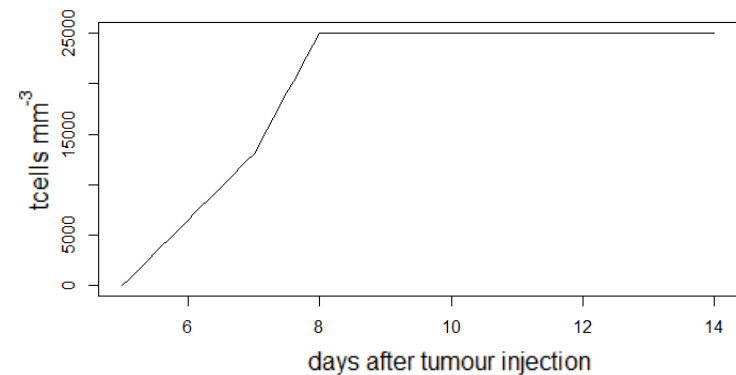
Data overview (Tcells)

- CTL density is known
- T Cells remain even in areas where tumour has disappeared



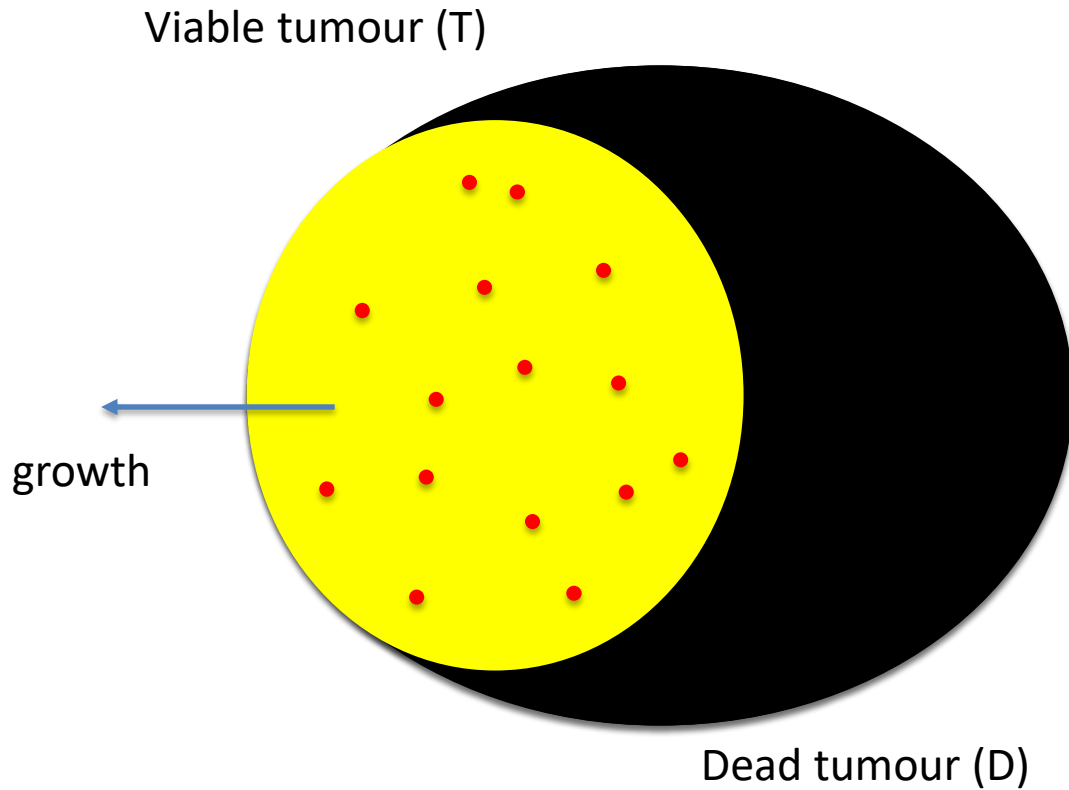
Day 7

Day 12



Breart, Béatrice, et al. "Two-photon imaging of intratumoral CD8+ T cell cytotoxic activity during adoptive T cell therapy in mice." *The Journal of clinical investigation* 118.4 (2008): 1390-1397.

Ordinary Differential Equation model



$$\frac{dT}{dt} = gT - kE$$

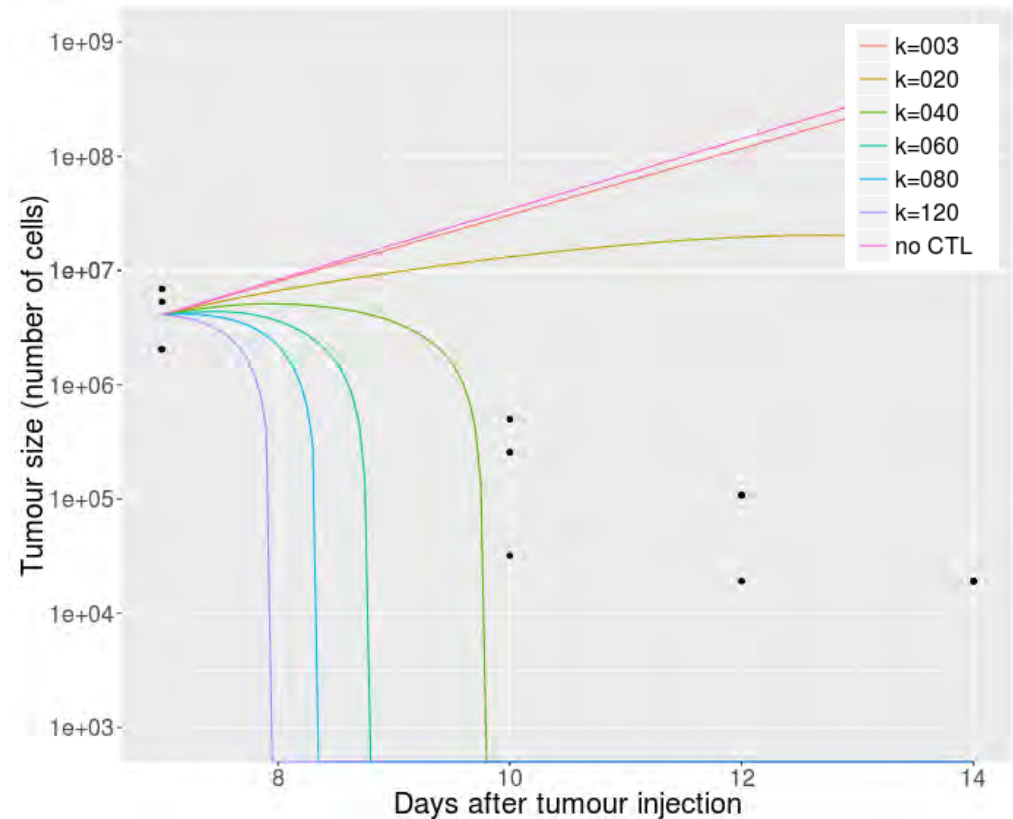
$$\frac{dD}{dt} = kE$$

$$E = \rho_E V_c (D + T)$$

$$\{T, D > 0\}$$

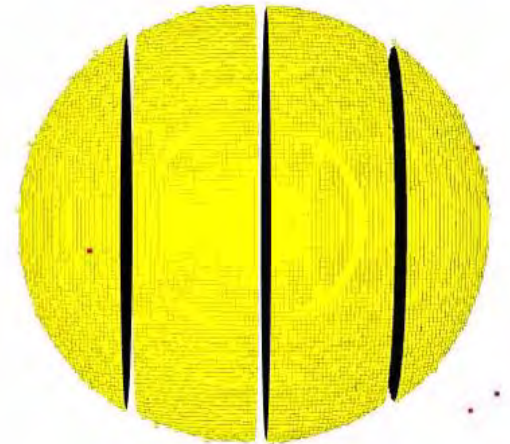
Ordinary Differential Equation model results

- Regression not achieved with killing rate 3/day
- Killing rate 10-fold higher required



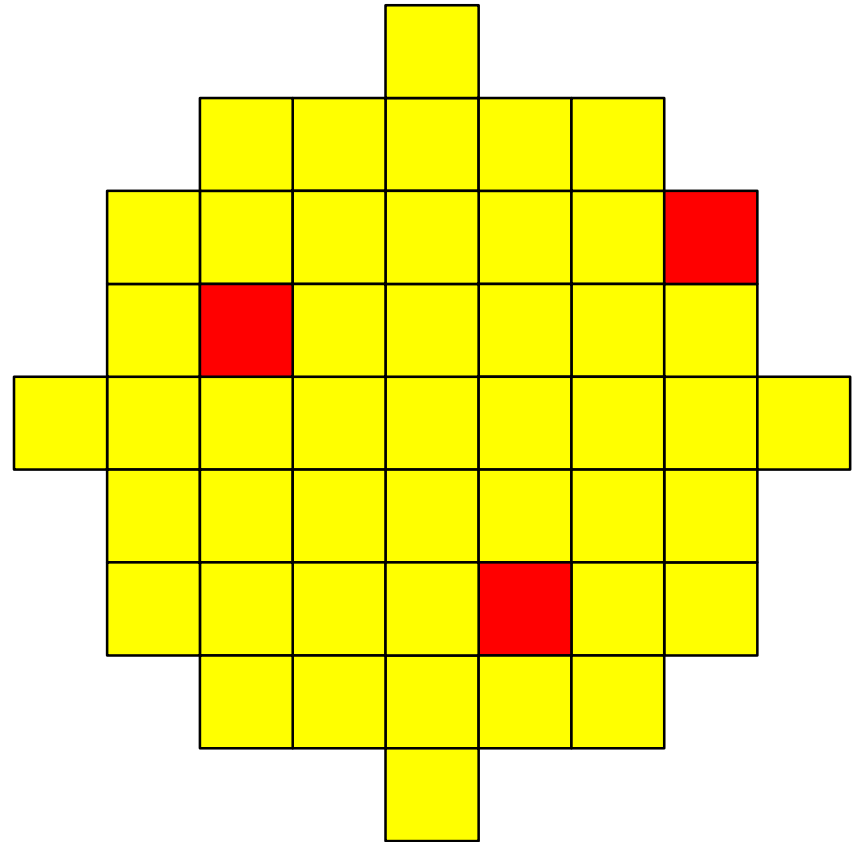
Agent based model

- More accurately quantify contribution of direct killing
- Suggest additional mechanisms

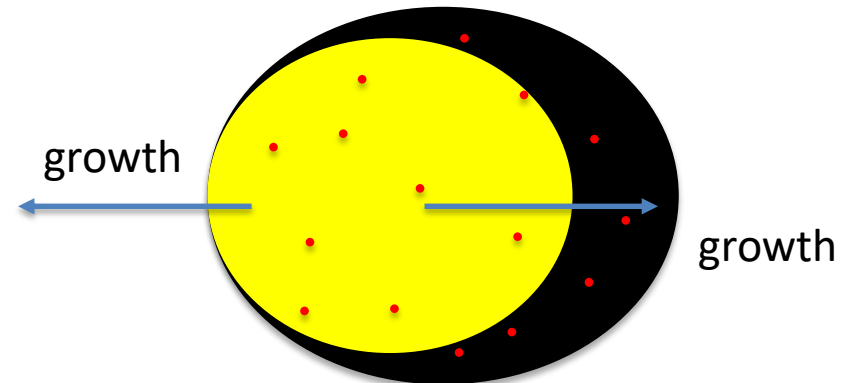
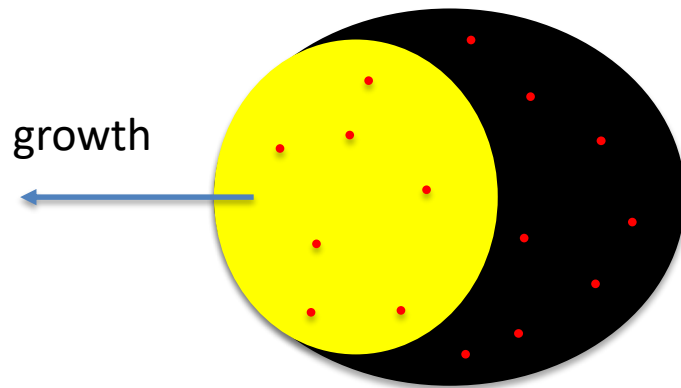
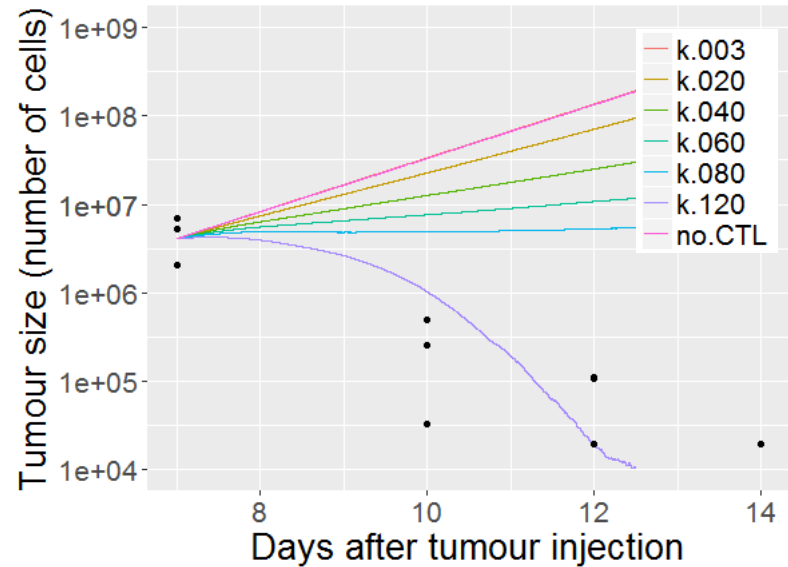
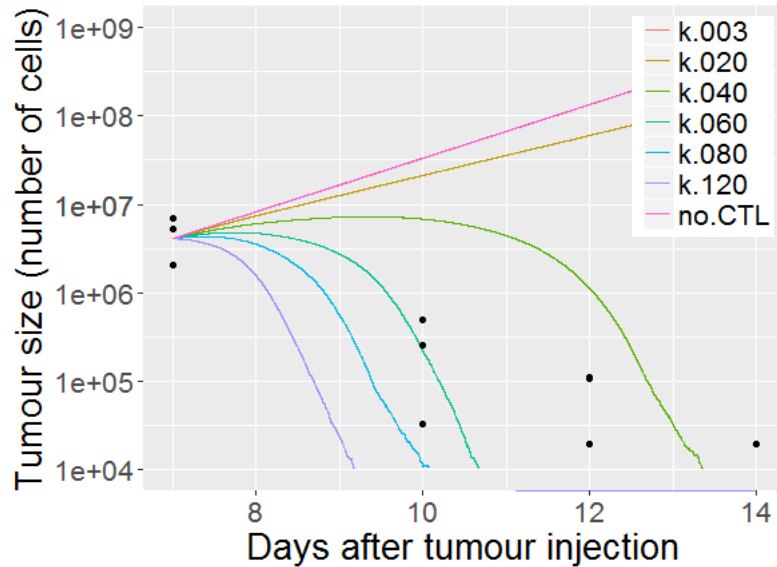


Agent based model

- Cells represented as grid points
- Tumour cells reproduce into neighbouring squares
- T Cells appear at random throughout tumour
- T cells kill single target over 8 hrs

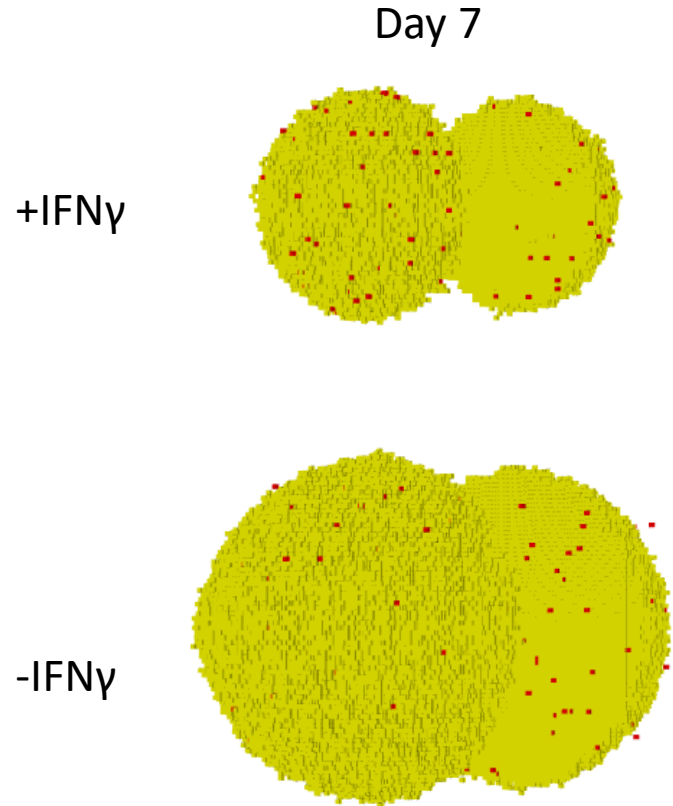


Agent based model - results



CTL induced cell cycle arrest

- T Cells produce IFN γ
- IFN γ causes cell cycle arrest
- Shown to be important in ACT tumour control



Matsushita, Hirokazu, et al. "Cytotoxic T lymphocytes block tumor growth both by lytic activity and IFN γ -dependent cell-cycle arrest." *Cancer immunology research* 3.1 (2015): 26-36.

Acknowledgements

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