

Mathematical modelling and investigation of macrophages heterogeneity and their impact on the evolution of cancer

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27 February, 2020

The Tumor Microenvironment at a Glance

Frances R. Balkwill, Melania Capasso and Thorsten Hagemann

Lymphatic endothelial cells



- Tumor cells can invade existing lymphatics or stimulate lymphatic vessel sprouting with the production of factors, such as VEGFR or VEGF-D.
- Lymphatic vessels are involved in the dissemination of malignant cells, but they might also promote tumor development by mechanostimulation of the TME and altering the host immune response to the tumor.

T lymphocytes



- Abundant in the majority of human and experimental cancers (up to 10% of all cells in the tumor).
- Found within and surrounding the tumor mass.
- Phenotypes of pro- and anti-tumor T cells can vary with disease type and stage. CD8⁺ cytotoxic T cells, CD4⁺ TH1 helper T cells and γδ T cells are usually associated with a good prognosis.
- FOXP3⁺ T regulatory cells, CD4⁺ TH2 helper T cells and TH17 cells are usually associated with a poor prognosis.

B lymphocytes



- Sometimes found at the invasive margin of some tumors, but more often in secondary and tertiary structures adjacent to the TME.
- B cell infiltration is associated with good prognosis in some human cancers. However, deposition of B cells and immunoglobulin tumor promoting in some mouse cancer models.
- Immunosuppressive IL-10 producing subtypes of B cells, B10 or Breg cells also have tumor promoting activity in mouse models.

Myeloid cells



- Consist of several subtypes, probably the most abundant cell lineage in the TME.
- Tumor-associated macrophages (TAMs)**
 - Typically tumor promoting.
 - IL-10⁺, IL-12⁺ phenotype and mannose receptor positive.
 - TAMs also produce angiogenic factors and accumulate in hypoxic or necrotic areas of the TME.
- Myeloid derived suppressor cells (MDSCs)**
 - Inhibitory immune cells producing large amounts of IL-10.
 - Inhibit cytotoxic T cells and polarize TAMs to a tumor promoting phenotype.
- Tumor-associated neutrophils (TANs)**
 - Can have both pro- and anti-tumor activity.
- Terminally differentiated myeloid dendritic cells**
 - Might be defective in the TME and cannot adequately stimulate an immune response to tumor-associated antigens.

NK and NKT cells



- Innate cytotoxic lymphocytes. NK cells and NKT cells are usually found outside the tumor area.
- For some cancers they can predict a good prognosis.

Cancer-associated fibroblasts



- Found in many human and experimental cancers, especially at the invasive margins.
- Produce tumor-promoting growth factors, chemokines, cytokines, ECM components and ECM remodeling enzymes.
- Can also have important immunosuppressive activity.

Vascular endothelial cells



- Angiogenic factors produced by malignant cells, myeloid cells or CAFs in the TME stimulate sprouting of endothelial cells.
- The new blood vessels have chaotic branching and uneven vessel lumen.
- The vessels are also leaky, raising interstitial pressures, with uneven blood flow, oxygenation, nutrient and drug delivery in the TME.

Pericytes



- Perivascular stromal cells, pericytes, provide structural support for blood vessels in the TME.
- Low pericyte coverage of TME vessels correlates with poor prognosis and increased metastasis.

Mesenchymal stem cells



- Mesenchymal stem cells can be recruited from the bone marrow and give rise to CAFs, pericytes, adipocytes and smooth muscle cells in the TME.

Adipocytes



- In some cancers, adipocytes actively aid recruitment of malignant cells through the secretion of adipokines.
- They also promote malignant cell growth by providing fatty acids as fuel for cancer cells.

Key



Malignant cells



Lymphatic endothelial cell



Pericyte



Malignant cells in necrotic or hypoxic areas



Endothelial cell



CAF



NK and NKT cells



Macrophage



Dendritic cell



Mesenchymal stem cell



Red blood cell



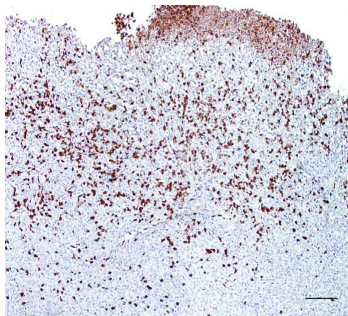
Adipocyte



Extracellular matrix

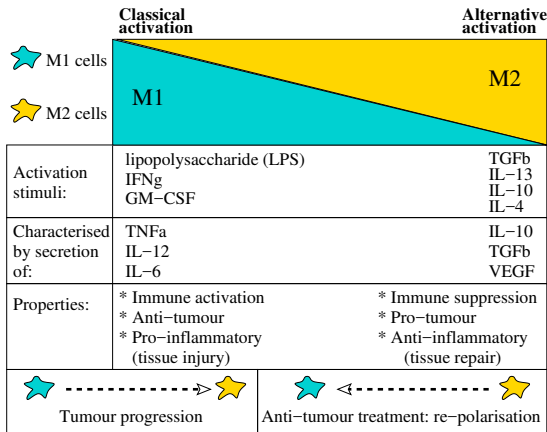
An important component of the tumour microenvironment: macrophages

- **Macrophages** play a central role in regulating both innate & adaptive immune responses (Th1&Th2 responses, modulate NK cells,...)
- **Macrophages** are one of the most common cell types in solid tumours, sometimes forming up to 40% of total tumour mass
- Activated macrophages can kill cancer cells by themselves (directly: TNF, NO, phagocytosis), or in an indirect manner through recruitment of other immune cells (e.g., CTLs)
- Increased macrophage infiltration of tumours is generally associated with poor patient prognosis
- **Macrophages** are a heterogeneous population of cells ...



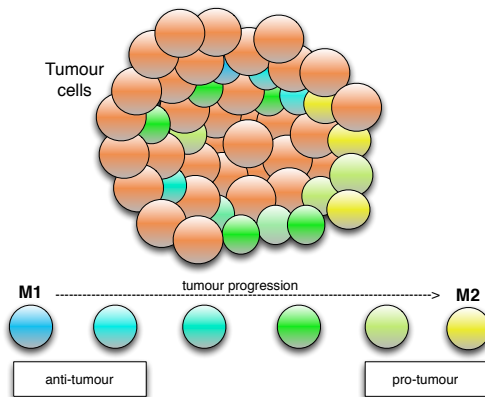
Pires et al, (2011). Ch. 10 in
"Melanoma in the clinic: Diagnosis, management
and complications of malignancy"

Macrophages plasticity: mediated by microenvironment signals



"These are extremes in a continuum of polarization states in an universe of diversity." (Mantovani, Locati, 2013)

Most **tumour-associated macrophages (TAMs)** are “**M2-like**” in established tumours, but “**M1-like**” cells have also been observed in **early** as well as **advanced** tumours ...



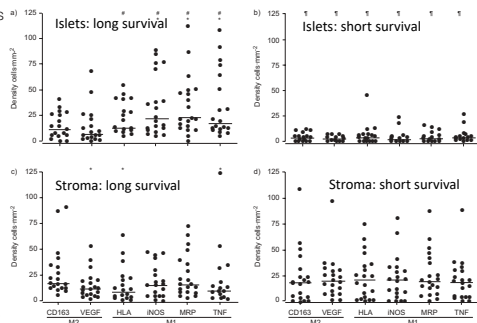
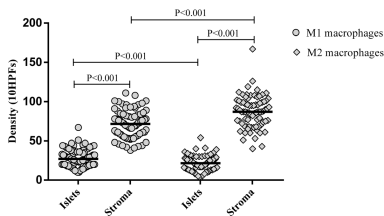
Questions surrounding the density of M1&M2 inside tumour islets/stroma...

Macrophages within NSCLC tumour islets are predominantly of a cytotoxic M1 phenotype associated with extended survival

C.M. Ohri^{1,2}, A. Shikotra^{3,4}, R.H. Green⁵, D.A. Waller² and P. Bradding^{6,7}

Distribution of M1 and M2 macrophages in tumor islets and stroma in relation to prognosis of non-small cell lung cancer

Jurgita Jackute¹, Marius Zemaits¹, Darius Pransys², Brigita Sitkauskienė³, Skaidrius Milauskas¹, Simona Vaitkiene⁴ and Raimundas Sakalauskas¹



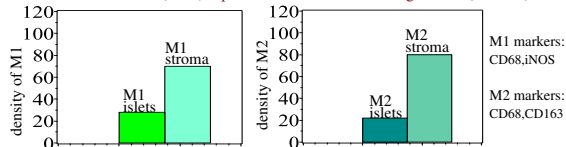
The M1 form of tumor-associated macrophages in non-small cell lung cancer is positively associated with survival time

Junliang Ma¹, Lunxue Liu², Guowei Che¹, Nanbin Yu^{1,2}, Fuzhang Dai^{1,3}, Zongting You⁴

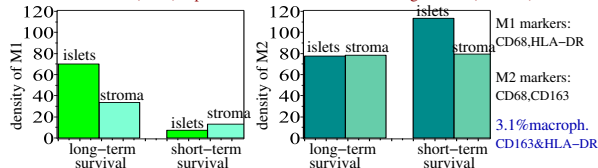
Table 2 Density and microlocalization of macrophages in non-small cell lung cancer

MΦ Form	Long survival			Short survival		
	Islets	Stroma	I + S	Islets	Stroma	I + S
M1	70.1 (0 - 255.3)	33.6 (0 - 257.1)	70.4 (0 - 255.7)	7.3 (0 - 74.9)	13.1 (0 - 129.9)	17.2 (0 - 132.2)
M2	77.6 (0 - 356.9)	78.4 (0 - 327.9)	97.9 (0 - 299.2)	113.4 (0 - 311.5)	79.5 (0 - 234.3)	109.5 (0 - 257.5)

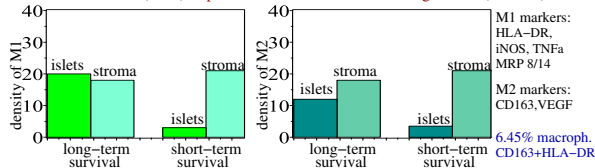
Data from Jackute et al (2018) – patients with Non Small Lung Cancer (NSCLC)



Data from Ma et al (2010) – patients with Non Small Cell Lung Cancer (NSCLC)



Data from Ohri et al (2009) – patients with Non Small Cell Lung Cancer (NSCLC)



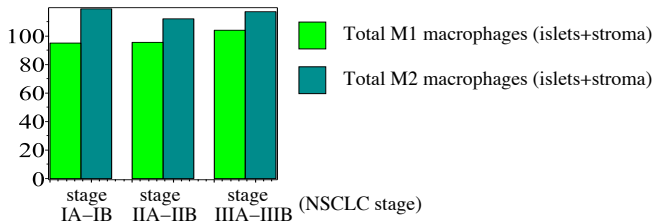
RESEARCH ARTICLE

Open Access



Distribution of M1 and M2 macrophages in tumor islets and stroma in relation to prognosis of non-small cell lung cancer

Jurgita Jackute^{1*}, Marius Zemaitis¹, Darius Pranys², Brigita Sitkauskienė³, Skaidrius Miliuskas¹, Simona Vaitkiene¹ and Raimundas Sakalauskas¹



No data on the association between NSCLC stages & macrophage infiltration in the papers by Ma et al (2010) or Ohri et al (2009) ...

- Patients with stage I or II NSCLC
 - Ex-vivo phenotype of TAMs vs.
- M1 & M2 macrophages differentiated in vitro

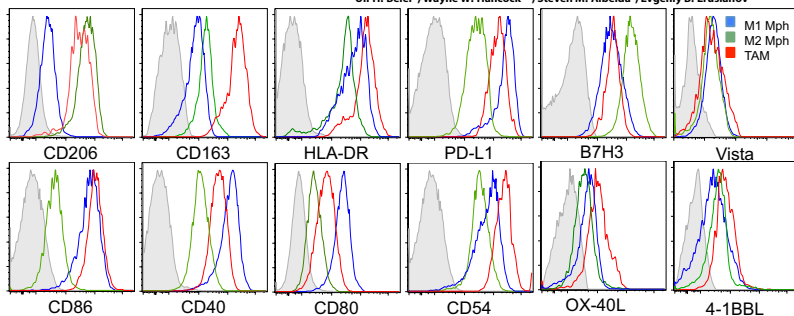
CANCER

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Human tumor-associated monocytes/macrophages and their regulation of T cell responses in early-stage lung cancer

Sunil Singhal¹, Jason Stadanlick¹, Michael J. Annunziata¹, Abhishek S. Rao¹, Pratik S. Bhojnagarwala¹, Shaun O'Brien², Edmund K. Moon², Edward Cantu³, Gwenn Danet-Desnoyers⁴, Hyun-Jeong Ra⁴, Leslie Litzky⁵, Tatiana Akimova^{5,6}, Ulf H. Beier⁷, Wayne W. Hancock^{5,6}, Steven M. Albelda², Evgeniy B. Eruslanov^{1*}

Fig. 2 Mixed phenotype of NSCLS-associated macrophages

E

(E) Flow cytometric analysis of the expression of macrophage markers on TAMs and M1/M2 macrophages differentiated in vitro.

(Singhal et. al, Science Translational Medicine, 2019)

*“Although monocyte-derived M1 and M2 macrophages showed clear differences in expression of respective markers, TAMs simultaneously expressed both M2 and M1 markers, and sometimes to an even higher degree than in vitro-differentiated M2 and M1 macrophages (Fig.2E). **Hence, the phenotype of macrophages in early-stage tumours is “mixed”** and not predominantly biased toward either M1 or M2 classical macrophage phenotypes”.*

(Singhal et. al, Science Translational Medicine, 2019)

*“Although monocyte-derived M1 and M2 macrophages showed clear differences in expression of respective markers, TAMs simultaneously expressed both M2 and M1 markers, and sometimes to an even higher degree than in vitro-differentiated M2 and M1 macrophages (Fig.2E). **Hence, the phenotype of macrophages in early-stage tumours is “mixed”** and not predominantly biased toward either M1 or M2 classical macrophage phenotypes”.*

... still many unknowns about the classification TAMs (based on markers) in NSCLC... and in many other cancers...

... and many unknowns about the role of mixed-phenotype macrophages on tumour progression...

Goal...

Use modelling/computational approaches to investigate the effect of
macrophages heterogeneity on tumour dynamics:
distinct M1 & M2 phenotypes vs. mixed M1-M2 phenotypes

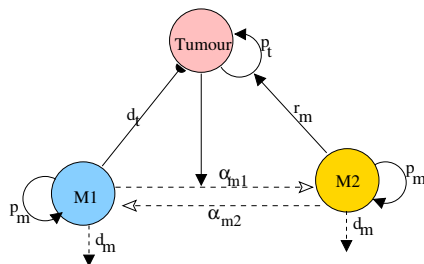
Goal...

Use modelling/computational approaches to investigate the effect of macrophages heterogeneity on tumour dynamics:
distinct M1 & M2 phenotypes vs. mixed M1-M2 phenotypes

[Eftimie, Math. Biosci. 2020]

- Model for the anti-tumour/pro-tumour roles of the 2 extreme macrophage phenotypes: M1, M2
- Model for the anti-tumour/pro-tumour roles of a phenotype-structured population of macrophages

Modelling tumour–macrophages interactions: a discrete-phenotype ODE model



$$\text{Tumour: } \frac{du_T}{dt} = p_t u_T \left(1 - \frac{u_T}{K_T}\right) (1 + r_m u_{M2}) - d_t u_T u_{M1},$$

$$\text{M1 cells: } \frac{du_{M1}}{dt} = p_m u_{M1} \left(1 - \frac{u_{M1} + u_{M2}}{K_M}\right) - d_m u_{M1} - \alpha_{m1} u_{M1} \frac{u_T}{K_T^* + u_T} + \alpha_{m2} u_{M2}$$

$$\text{M2 cells: } \frac{du_{M2}}{dt} = p_m u_{M2} \left(1 - \frac{u_{M1} + u_{M2}}{K_M}\right) - d_m u_{M2} + \alpha_{m1} u_{M1} \frac{u_T}{K_T^* + u_T} - \alpha_{m2} u_{M2}$$

TAM-targeted therapeutic strategies for cancer

[Frontiers in Bioscience, Elite, 7, 334-351, January 1, 2015]

Tumour-associated macrophage polarisation and re-education with immunotherapy

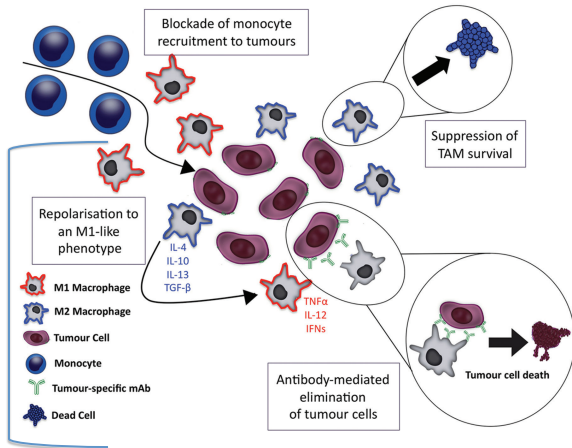
Debra H. Josephs^{1,2}, Heather J. Bax^{1,2}, Sophia N. Karagiannis¹

Figure 1. Tumour-associated macrophage (TAM)-targeted therapeutic strategies for cancer. The pro-tumorigenic functions of TAMs depend on their accumulation and survival within tumours and their M2-like polarisation status. Current TAM-targeted treatment strategies include: (i) blockade of monocyte/macrophage recruitment; (ii) suppression of TAM survival; (iii) repolarisation of TAMs towards an M1-like phenotype; and (iv) antibody-mediated elimination of tumour cells by monocytes/macrophages. Cytokines listed are the key cytokines required for M1- or M2- skewing of macrophages.

Test computationally some of these therapeutic strategies:

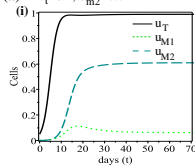
$$\text{Tumour: } \frac{du_T}{dt} = p_t u_T \left(1 - \frac{u_T}{K_T}\right) (1 + r_m u_{M2}) - d_t u_T u_{M1},$$

$$\text{M1 cells: } \frac{du_{M1}}{dt} = p_m u_{M1} \left(1 - \frac{u_{M1} + u_{M2}}{K_M}\right) - d_m u_{M1} - \alpha_{m1} u_{M1} \frac{u_T}{K_T^* + u_T} + \alpha_{m2} u_{M2}$$

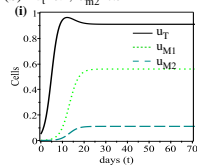
$$\text{M2 cells: } \frac{du_{M2}}{dt} = p_m u_{M2} \left(1 - \frac{u_{M1} + u_{M2}}{K_M}\right) - d_m u_{M2} + \alpha_{m1} u_{M1} \frac{u_T}{K_T^* + u_T} - \alpha_{m2} u_{M2}$$

- Antibody-mediated phagocytosis of tumour cells: increase d_t
- Re-polarisation to an M1-like phenotype: increase α_{m2}
- Blockade of monocyte recruitment to tumours: decrease p_m
- Suppression of TAM survival: increase d_m

(a) $d_t=0.1, \alpha_{m2}=0.01$



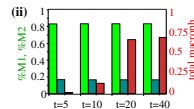
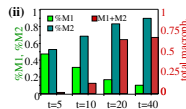
(b) $d_t=0.1, \alpha_{m2}=0.5$



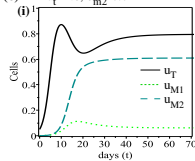
Short-term dynamics:

- (a),(c): increase d_t
(phagocytosis of tumour cells)

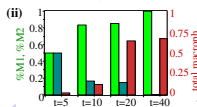
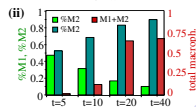
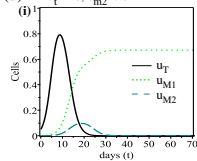
- (b),(d): increase α_{m2}
(re-polarisation towards M1)



(c) $d_t=2.0, \alpha_{m2}=0.01$



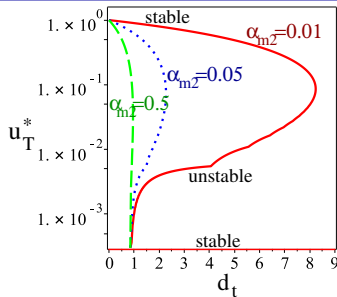
(d) $d_t=2.0, \alpha_{m2}=0.5$



Long-term dynamics:

■ hysteresis phenomenon:

- tumour-free steady state
- coexistence steady state

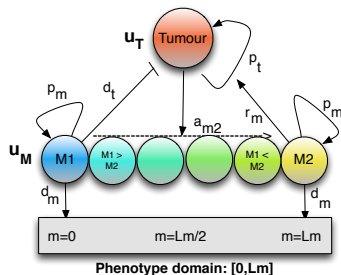


Increasing α_{m2} (while keeping d_t fixed & large) pushes the system towards the stable tumour-free state

What is the effect of a continuous phenotype structure for the macrophages population, in the context of persistence/elimination of tumour cells?



A phenotype-structured continuous model

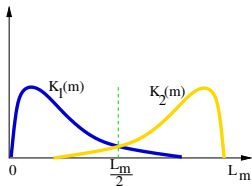
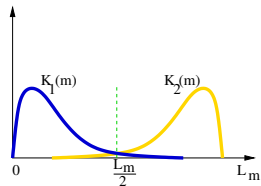
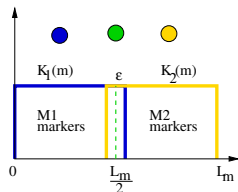
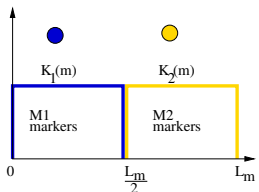


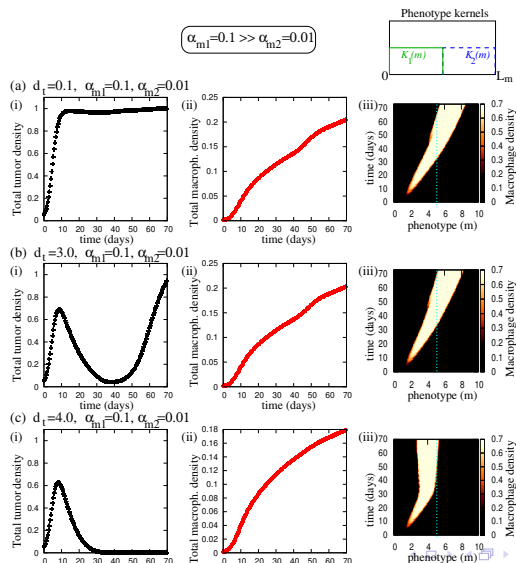
$$\frac{du_T}{dt} = p_t u_T \left(1 - \frac{u_T}{K_T}\right) \left(1 + r_m \int_0^{Lm} K_2(m) u_M(m, t) dm\right) - d_t u_T \int_0^{Lm} K_1(m) u_M(m, t) dm,$$

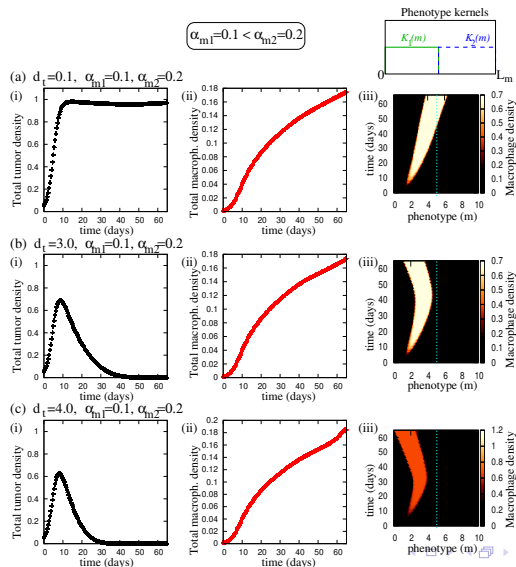
$$\frac{\partial u_M(m, t)}{\partial t} = - \frac{\partial (\gamma(t) u_M F(u_M, u_T))}{\partial m} + p_m u_M \left(1 - \frac{u_M}{K_M}\right) - d_m u_M,$$

$$\text{with } F(u_T, u_M) = \alpha_{m1} \frac{u_T}{K_T^* + u_T} - \alpha_{m2} \int_0^{Lm} K_1(m) u_M(m, t) dm, \quad \gamma(t) = e^{-g_0 \int_0^{Lm} K_2(m) u_M(m, t) dm}$$

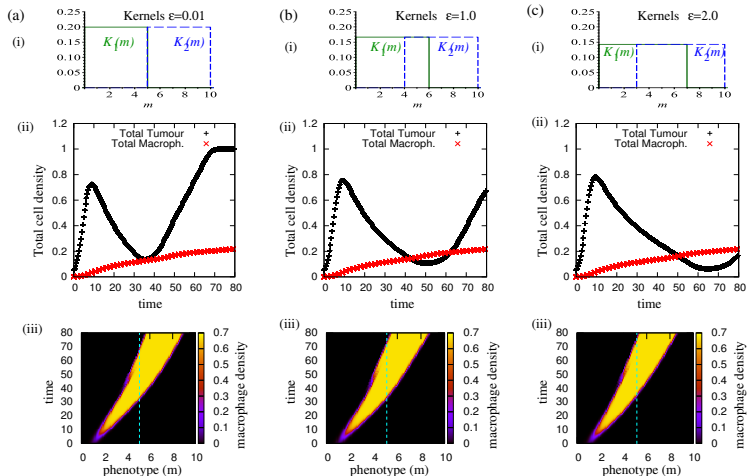
Examples of macrophages phenotype kernels



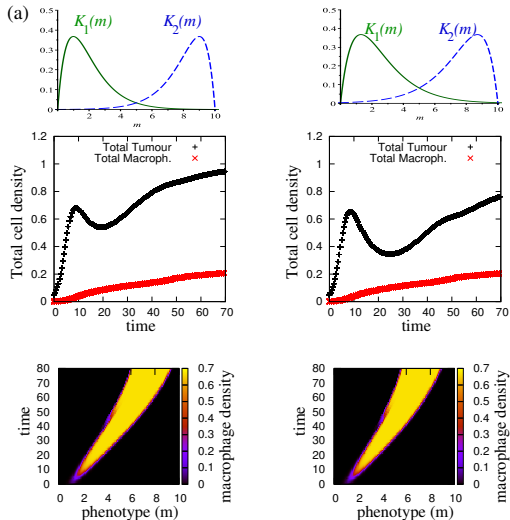
Numerical results: increase the tumour elimination rate d_t 

Numerical results: increase the M2→M1 re-polarisation rate a_{m1} 

Increasing the overlap between the M1 and M2 phenotypes

Increasing the overlap of M1 & M2 $\Rightarrow$ delay tumour relapse

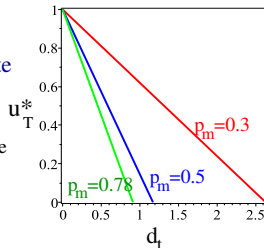
Increasing the overlap between the M1 and M2 phenotypes...



Long-term dynamics: **phenotype-homogeneous** steady states

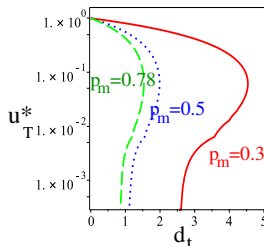
Co-existence
homogeneous steady state
(PDE):

p_m = Macroph. prolif. rate
 d_t = M1 tumour-killing rate



VS.

Co-existence
homogeneous steady state
(ODE)



Long-term dynamics: **phenotype-heterogeneous** steady states

$$u_T^* = \frac{K_T}{p_t} \left[\frac{p_t (1 + r_m \int_0^{L_m} K_2(m) u_M^*(m) dm) - d_t \int_0^{L_m} K_1(m) u_M^*(m) dm}{1 + r_m \int_0^{L_m} K_2(m) u_M^*(m) dm} \right],$$

$$\frac{du_M^*(m)}{dm} = \frac{u_M^*(m)}{\gamma^* F(u_T^*, u_M^*)} \left[(p_m - d_m) - \frac{p_m}{K_M} u_M^*(m) \right],$$

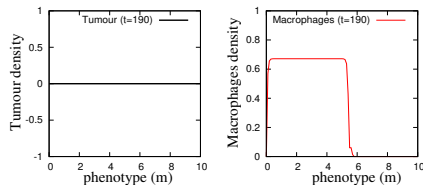
where

$$\gamma^* = e^{-g_0 \int_0^{L_m} H_2(m) u_M^*(m) dm},$$

and

$$F(u_T^*, u_M^*) = \alpha_{m1} \frac{u_T^*}{u_T^* + K_T^*} - \alpha_{m2} \int_0^{L_m} K_2(m) u_M^*(m) dm.$$

For $u_T^* = 0$:



Summary...

- Tumour is eliminated/controlled in the presence of a large M1/M2 ratio & large d_t
- Tumour can persist in the presence of
 - large M1/M2 ratio and small d_t
 - large M2/M1 ratio

Summary...

- Tumour is eliminated/controlled in the presence of a large M1/M2 ratio & large d_t
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- For these models: the long term behaviour of ODE system more complex than for the PDE system

Summary...

- Tumour is eliminated/controlled in the presence of a large M1/M2 ratio & large d_t
- Tumour can persist in the presence of
 - large M1/M2 ratio and small d_t
 - large M2/M1 ratio
- For these models: the long term behaviour of ODE system more complex than for the PDE system
- The type of phenotype kernel chosen for the PDE system can lead to different predictions regarding tumour elimination (i.e., faster/slower)
- The effect of M1-M2 overlap (i.e. mixed macrophages):
 - No M1-M2 overlap: relatively similar tumour dynamics for discrete & continuous models
 - Increasing the overlap between M1 & M2 phenotype (i.e., more macrophages with mixed M1-M2 markers) leads to a delay in tumour reduction & subsequent relapse

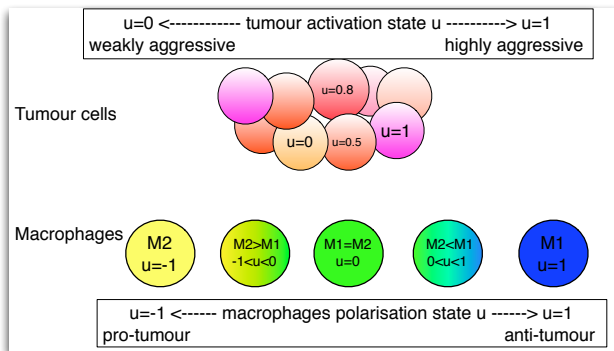
Macrophage phenotypic heterogeneity & tumour clonal heterogeneity...



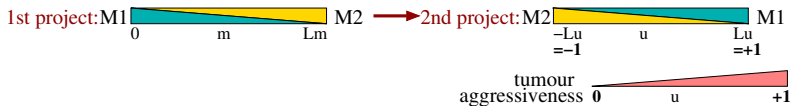
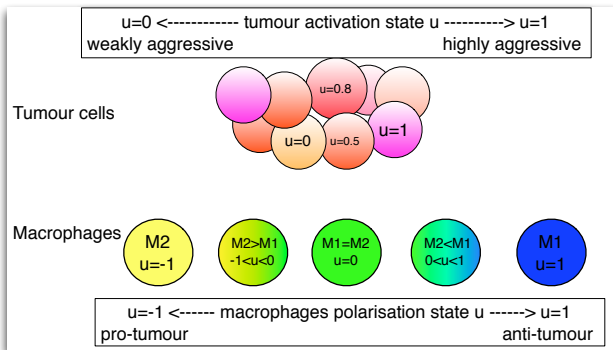
Dr. L. Gibelli (Univ. Edinburgh)

R. E., L. Gibelli, 2020. *A kinetic theory approach for modelling macrophages heterogeneity and plasticity during cancer progression.*
Mathematical Models and Methods in Applied Sciences (M3AS). In press

Macroph. phenotypic heterogeneity + tumour clonal heterogeneity (E., Gibelli; M3AS, 2020)



Macroph. phenotypic heterogeneity + tumour clonal heterogeneity (E., Gibelli; M3AS, 2020)



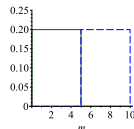
Macrophage phenotypic heterogeneity + tumour clonal heterogeneity

(Eftimie, Gibelli; M3AS, 2020)

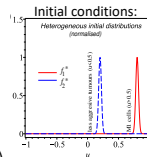
macrophages: $f_1 = f_1(t, u) : [0, T] \times [-1, 1] \rightarrow \mathbb{R}_+$,

tumour cells: $f_2 = f_2(t, u) : [0, T] \times [0, 1] \rightarrow \mathbb{R}_+$.

$$\begin{aligned} \partial_t f_1(t, u) = & \lambda_1 \int_{-1}^1 \int_0^1 \mathcal{B}_{12}(u_* \rightarrow u | u_*, u^*) f_1(t, u_*) f_2(t, u^*) du^* du_* \\ & - \lambda_1 f_1(t, u) \int_0^1 f_2(t, u^*) du^* - \mu^d f_1(t, u) \\ & + \alpha f_1(t, u) \left(1 - \frac{\int_{-1}^1 f_1(t, u^*) du^*}{K_1} \right) \int_0^1 f_2(t, u^*) du^*, \\ \partial_t f_2(t, u) = & \lambda_2 \int_{-1}^1 \int_0^1 \mathcal{B}_{21}(u_* \rightarrow u | u_*, u^*) f_1(t, u^*) f_2(t, u_*) du_* du^* \\ & - \lambda_2 f_2(t, u) \int_{-1}^1 f_1(t, u^*) du^* - \gamma f_2(t, u) \int_0^1 f_1(t, u^*) du^* \\ & + f_2(t, u) \left(\beta^n + \beta^f \int_{-1}^1 f_1(t, u^*) du^* \right) \left(1 - \frac{\int_0^1 f_2(t, u^*) du^*}{K_2} \right). \end{aligned}$$



$\mathcal{B}_{1,2}, \mathcal{B}_{2,1} =$
normalised
step functions

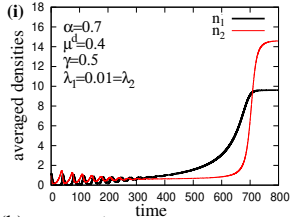


Macrophage phenotypic heterogeneity + tumour clonal heterogeneity (E., Gibelli; M3AS, 2020):

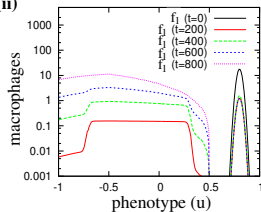
 n_1 =total macrophages, n_2 =total tumour

=> dormancy ...

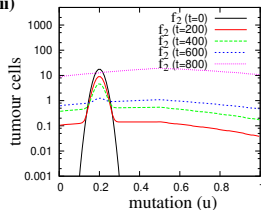
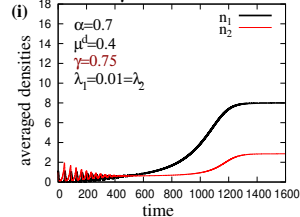
(a) Baseline



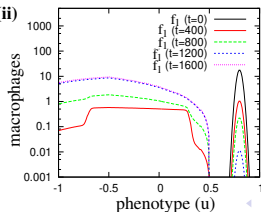
(ii)



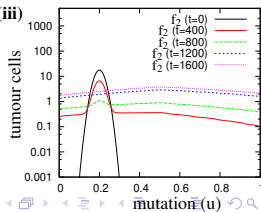
(iii)

(b) Increased γ 

(ii)



(iii)



Summary...

- dormant tumour dynamics is characterised by an increase in **clonal heterogeneity of tumours** & **phenotypic heterogeneity of macrophages**
- dormant tumour behaviour was mediated by M1-like macrophages
- tumour relapse was associated with a significant increase (from $f_1 \leq 1$ to $f_1 \approx 10$) in the density of macrophages with the extreme M2 phenotype ($u \approx -1$)

Work in progress: Multi-scale modelling of tumour-macrophage interactions & spatial spread of tumour cells and macrophages...



S. Suveges, PhD student
(Univ. Dundee)

S. Suveges, R. E., D. Trucu, 2020. *Multi-scale modelling of cancer invasion in the presence of M2 TAMs*. Submitted.

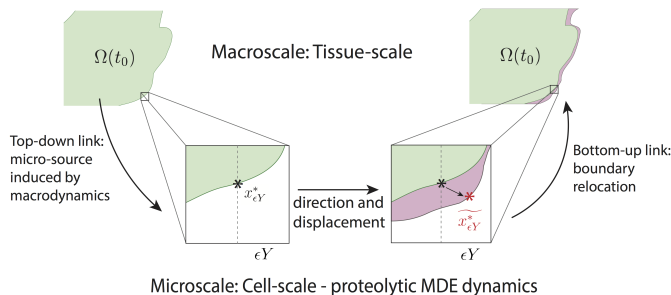


Dr. D. Trucu
(Univ. Dundee)

Multi-scale modelling of tumour-macrophage interactions (Süveges, E., Trucu; submitted, 2020)

Investigate the tumour-macrophages dynamics at 2 spatial scales:

- **Macro-scale:** movement of macrophages & tumour cells (& their interactions with ECM)
mid/late-stage cancer => focus on M2-like macrophages (migrate & degrade ECM)
- **Micro-scale:** degradation and re-arrangement of ECM fibres, and tumour-boundary movement during invasion



From:

R. Shuttleworth, D. Trucu, (2019), *Multiscale modelling of fibres dynamics and cell adhesion with moving boundary cancer invasion*, BMB, 81, 2176–2219.

Current work: Multi-scale modelling of tumour-macrophage interactions (Süveges,

E., Trucu; submitted, 2020)

Macroscale:

- Cancer cells: $\frac{\partial c}{\partial t} = \nabla \cdot [D(M)\nabla c - cA(\mathbf{u}, \Theta)] + \mu c[1 - \rho(\mathbf{u})][1 + f_1(M)]$
 $\mathbf{u}=(c(x,y,t),F(x,t),l(x,t),M(x,t))$
 $\left(\begin{array}{l} \Theta = \text{related to macroscopic} \\ \text{fibre orientation, which further} \\ \text{connects to the micro - dynamics} \\ \text{of fibres} \end{array} \right)$
- ECM fibres: $\frac{\partial F}{\partial t} = -Ff_2(c, M)$
- ECM non-fibres: $\frac{\partial l}{\partial t} = -lf_3(c, M) + \alpha M(1 - \rho(\mathbf{u}))$
- M2 cells: $\frac{\partial M}{\partial t} = D_M \nabla^2 M + f_4(c, M)$

Microscale:

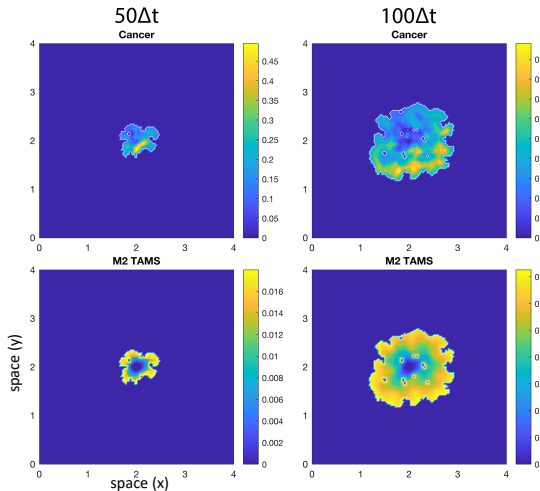
- MDEs density over each micro domain on tumour interface: $\frac{\partial m}{\partial t} = D_m \nabla^2 m + h[c, M]$

Multi-scale modelling of tumour-macrophage interactions (Süveges, E., Trucu, 2020, submitted)

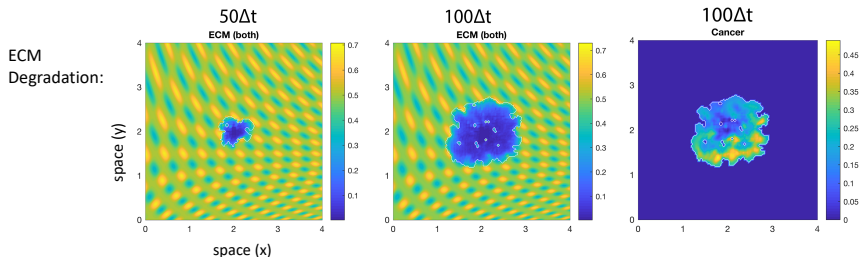
Example of Tumour - M2
macrophages spatial
co-migration
(via ECM degradation)

*"TAMs are mainly localized in the peripheral
tumour stroma and decrease in number
towards the center."*

(Makela et al., Scientific Reports, 2016)



Multi-scale modelling of tumour-macrophage interactions (Süveges, E., Trucu, 2020, submitted)

**Work in progress:**

- The role of M1 macrophages on slowing-down tumour spread
- The spatial distribution of M1 & M2 cells inside the tumour...?
- Role of mixed-phenotype macrophages on the spatial spread of tumours...?

To conclude...

- Mathematical/computational approaches can be used to generate (& test) hypotheses regarding the role of mixed M1/M2 phenotype of tumour dynamics
 - models need validation using murine/human data...still to do...
- Mathematical models with discrete and continuous macrophage phenotype (with no overlap!) show similar dynamics
- The overlap in phenotype markers (i.e., macroph. with both M1&M2 markers) can delay the elimination/growth of tumours
- Tumour dormancy is characterised by: (i) increase in tumour clonal heterogeneity, and (ii) increase in macrophage phenotypic heterogeneity
- TAMs contribute to the spatial invasion of cancer cells: the effect of mixed M1-M2 phenotype still unknown...

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Thematic issue on

“Mathematical Modelling of Cancer Therapies: Analytical and Computational Approaches”

Editors for this Thematic Issue:

Dr. Raluca Eftimie (Dundee), Dr. Dumitru Trucu (Dundee)