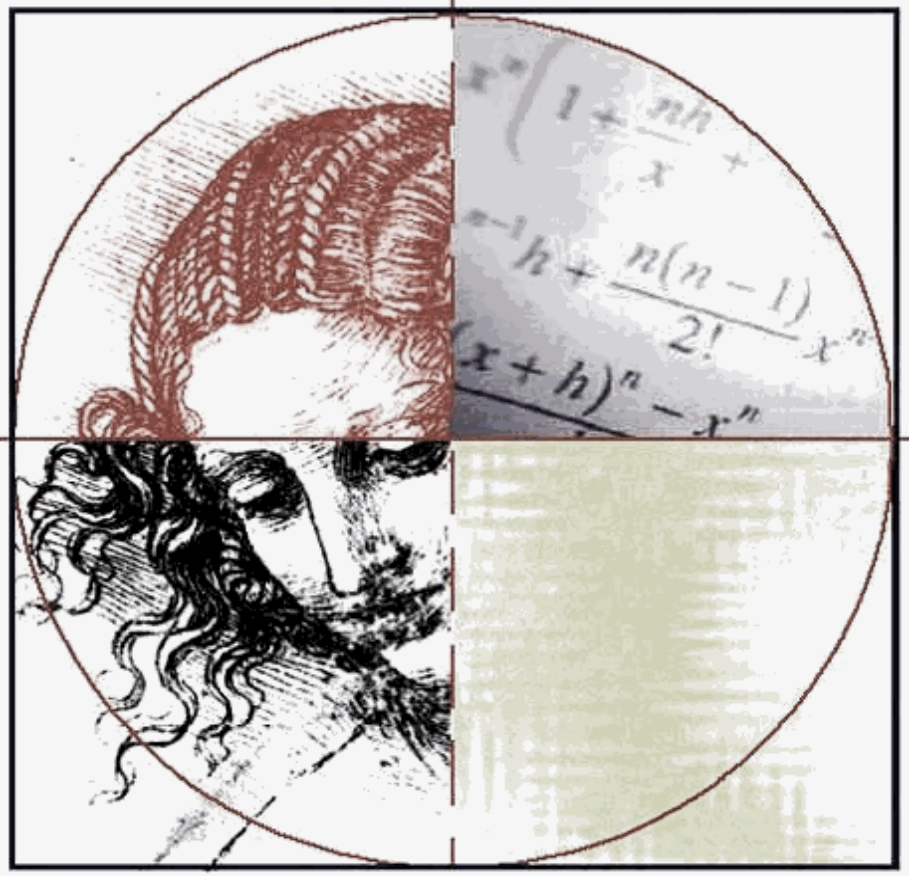
Employing ODEs to Personalize Immunotherapy in Metastatic melanoma – History and Current State



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Agenda

- History:
  - The **Resonance Phenomenon** and its experimental verification
  - Development of the **Virtual Patient** concept
  - Validation in a patient with metastatic chondrosarcoma
  - **Treatment personalization** – concept development
  - Limitation due to lack of data and computing resources
  - **Big data** revolution
- Application to Melanoma immunotherapy
  - First mathematical model
  - Model is too complex for immunotherapy personalization
  - Model simplification
  - Model predictions
  - Current efforts

Population Dynamics under a periodic loss process effective only during part of the life cycle

- I described the population dynamics of organisms with a complex life cycle in regimes of periodic disturbances.
- Customarily, a complex life cycle is described by a system of ODEs.
- Instead, I condensed the complex life cycle into one delay-differential equation

$$x'(t+\Delta t) = \{x'(t) + \lambda'^{x'}(t-\tau)[1-x'(t)] - \mu x'(t)\}[1-D(t)]\Delta t.$$

$x(t)$ – number of adults at time, t; (x′=(t))/K; K is the environmental carrying capacity).
λ' - reproduction rate, containing an element of juvenile mortality,
μ - mortality rate of adults
D - environmental process, assuming the values 0 and 1 with their duration either exponentially distributed or fixed.

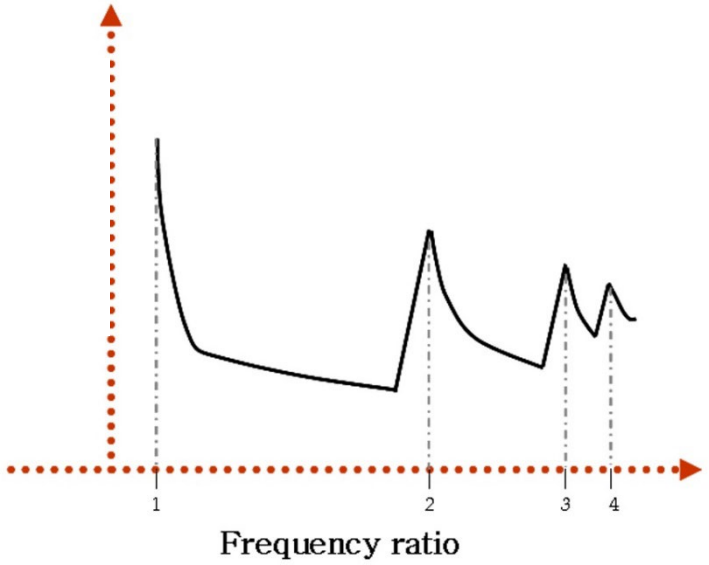
(Agur, Jour Theor Biol 1985, Agur Deneubourg, Theor Pop Biol, 1985)

Universal Results of Model Analysis

Resonance in population survival exists for **any** population under a periodic loss process, effective only during part of the life cycle.

Population growth is enhanced when the average period of the imposed loss process is an integer or fractional multiple of the population's inherent generation time.

Population size can be controlled by choosing the period of the disturbance



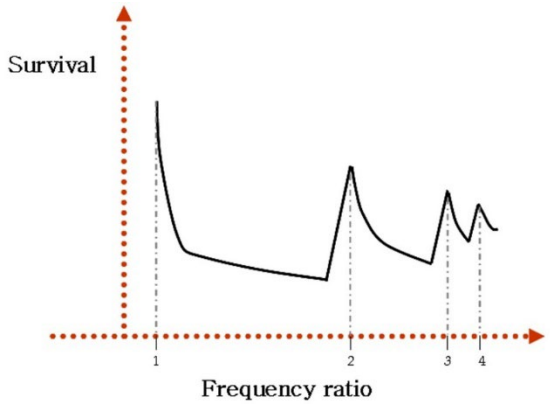
(Agur, Jour Theor Biol 1985, Agur Deneubourg, Theor Pop Biol, 1985)

$$x'(t+\Delta t) = \{x'(t) + \lambda' x'(t-\tau)[1-x'(t)] - \mu x'(t)\}[1-D(t)]\Delta t.$$

The universality of the solution motivated its application to somatic processes

Application to Cancer

This result may be especially interesting for increasing the success of chemotherapy as it may be feasible to select drug regimens that are toxic to the cancer (minima) and little toxic to the target host tissues (maxima).



Need for validation experiments

Prospective Validation in Lymphoma Bearing Mice Treated by Cytarabine (ara-c)

Ara-C q14h maximizes murine BM cell growth (t~14h)
(L+E – lymphocytes and Erythroids; M+B – myeloids and blasts)

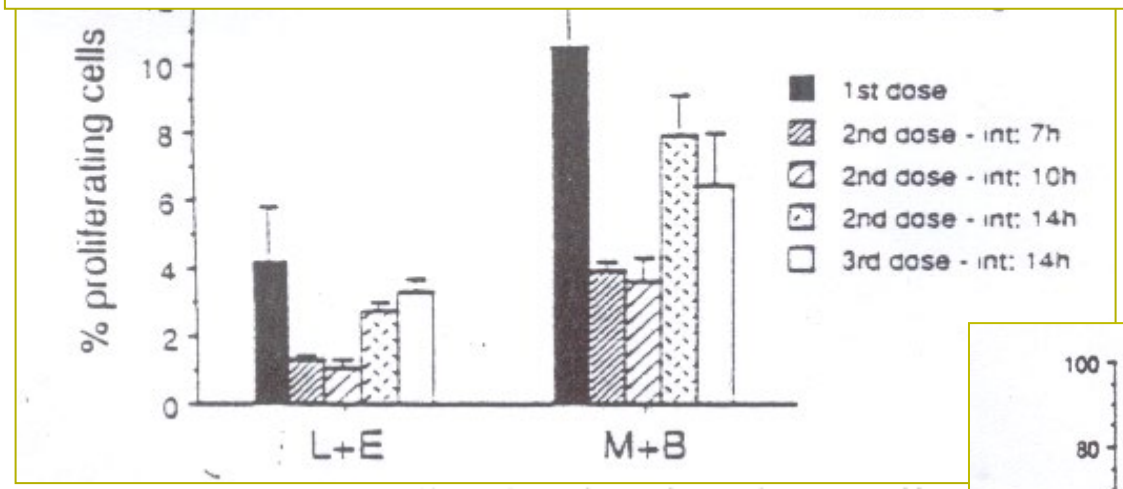
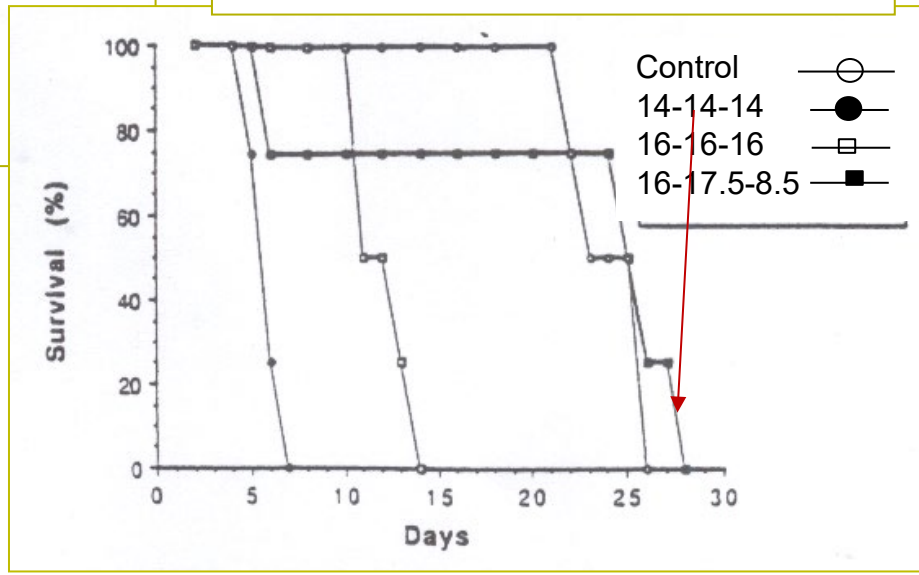


Fig. 7. BM cytotoxicity induced by different time regimens of repeated treatments with 5 mg ara-C (at 7 h, 10 h and 14 h spacing). A BrdUrd injection was given 8 h–10 h after the last treatment and percent BrdUrd+ cells was determined.

Ara-C q14h minimizes ara-C toxicity to lymphoma bearing mice



Ubezio, Schechter, Tagliabue, Agur,
Cancer Research, 1994

Conclusions

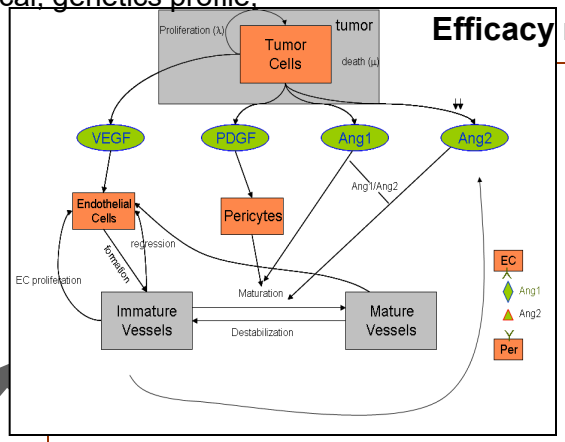
- ✓ One can capture the essential dynamics in the complex mammal body through simple mathematical models
- ✓ Simple mathematical models can shed light on cancer therapy
- ✓ The Resonance Phenomenon is validated in cancer
- ✓ Success of chemotherapy depends on the inter-dosing interval

- ➢ Clinical application of the general theory requires increased realism, hence, detail:
  - ➢ Develop models of vascular tumor growth, including **angiogenesis**
  - ➢ Develop models of hematopoiesis and other **toxicities**
  - ➢ Develop realistic **treatment optimization** methods...

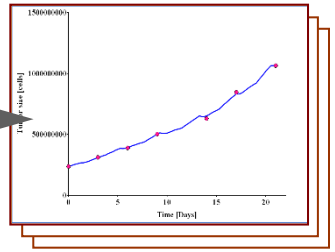
Motivated the Virtual Patient concept.

Virtual Patient Concept

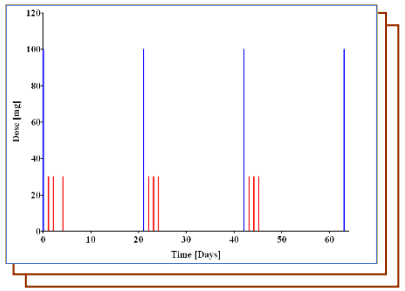
Preclinical (in vitro, xenograft, biomarkers)
Clinical data of patient examinations
(biochemical, immunological, genetics profile,
tumor dynamics).



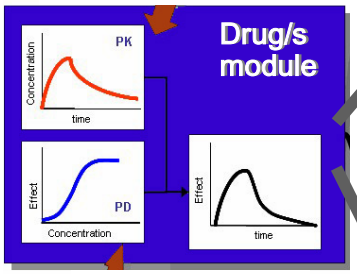
Predict efficacy



Optimize schedule

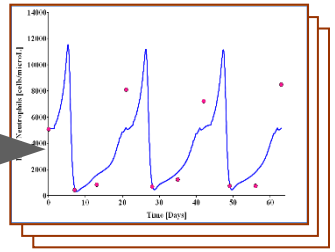


Drug modules



Preclinical (in vitro,
xenograft, biomarkers)
and clinical PD data

Predict toxicity & adverse effects



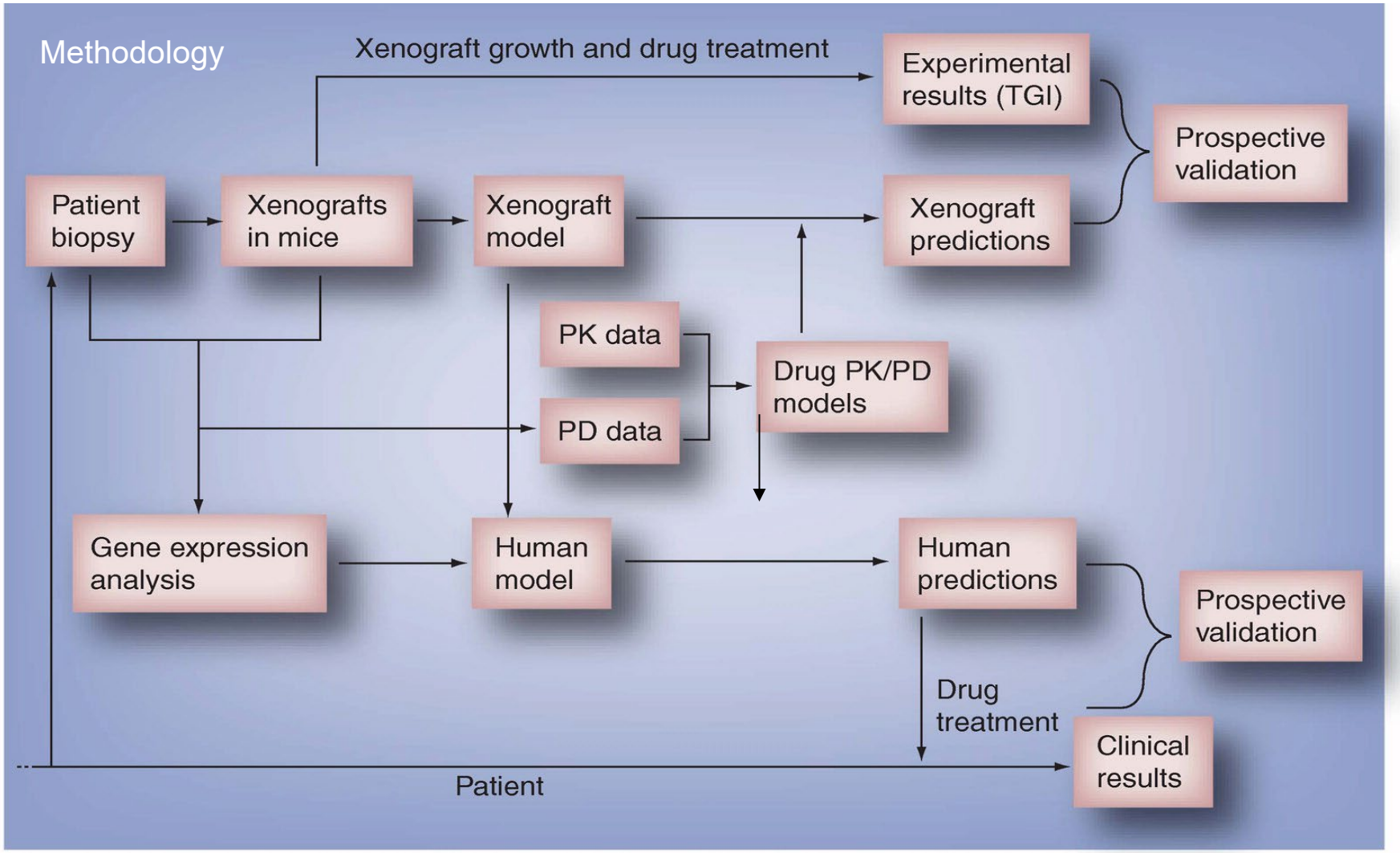
- Estimate model parameters

Preclinical biomarkers Clinical trials
patients individual biomarkers
(biochemistry, hematology, immunology,
genetics profile).

Case Study: a Mesenchymal Chondrosarcoma (MCS) Patient

- VN – a 45-year-old white male in excellent health
- Cancer diagnosed in 2004
- Primary tumor was resected
- Multiple new lung metastases discovered
- Aggressive chemotherapy
- Additional liver and bone metastases
- Severe myelosuppression with pancytopenia
- Prognosis: 6 weeks.

Case Study: Personalized Treatment for Mesenchymal Chondrosarcoma (MCS) Patient



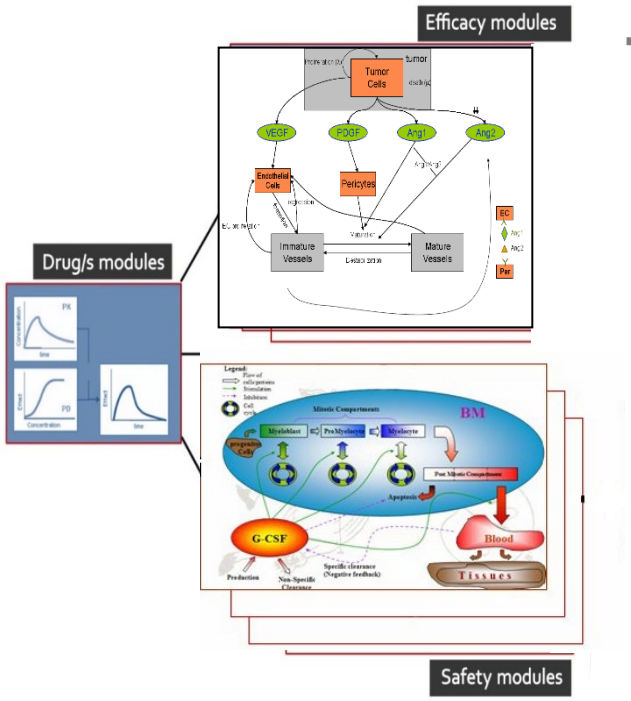
Case Study: a Mesenchymal Chondrosarcoma (MCS) Patient

- Applying weekly Docetaxel chemotherapy to the patient resulted in stable metastatic disease and relief of pancytopenia
- Patient lived longer with improved quality of life
- The period of drug administration proved crucial, supporting the Resonance Phenomenon in man

But this was a very special “clinical trial of one person.”
We searched for a method for feasible clinical application

Gorelik et al, Cancer Research, 2008

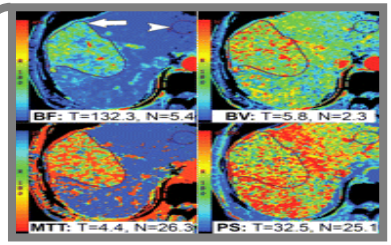
New Idea: Model Personalization



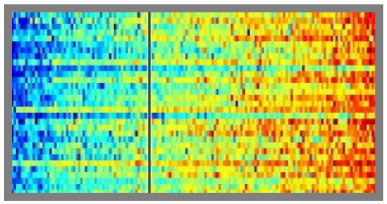
Personalization

Using modern technologies to formulate the relations between biomarkers and patient's model

Modern diagnostics



Imaging



NGS: Genomics, mRNA, proteomics

Patient	Mitotic Index	Apoptotic Index
AJ	0.9	0.1
BC	0.2	0.6
KR	0.6	0.3

Biomarkers Histopathol

Much preceded its time

- No clinical databases
- No computing power
- No advanced data analysis

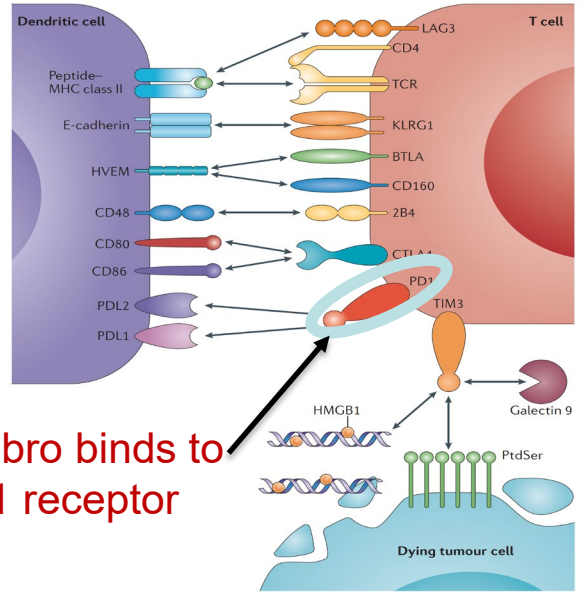
Currently

- Big Data
- Machine Learning
- Cloud computing

Apply in immunotherapy

Melanoma Immunotherapy

- Cancer highjacks the host immune control mechanism
- Immunotherapy by pembrolizumab (pembro) was approved for melanoma ca. 10 yrs ago.
- Pembro prevents downregulation of the immune system by binding to the Programmed Cell Death 1 (PD-1) receptor on T cells.



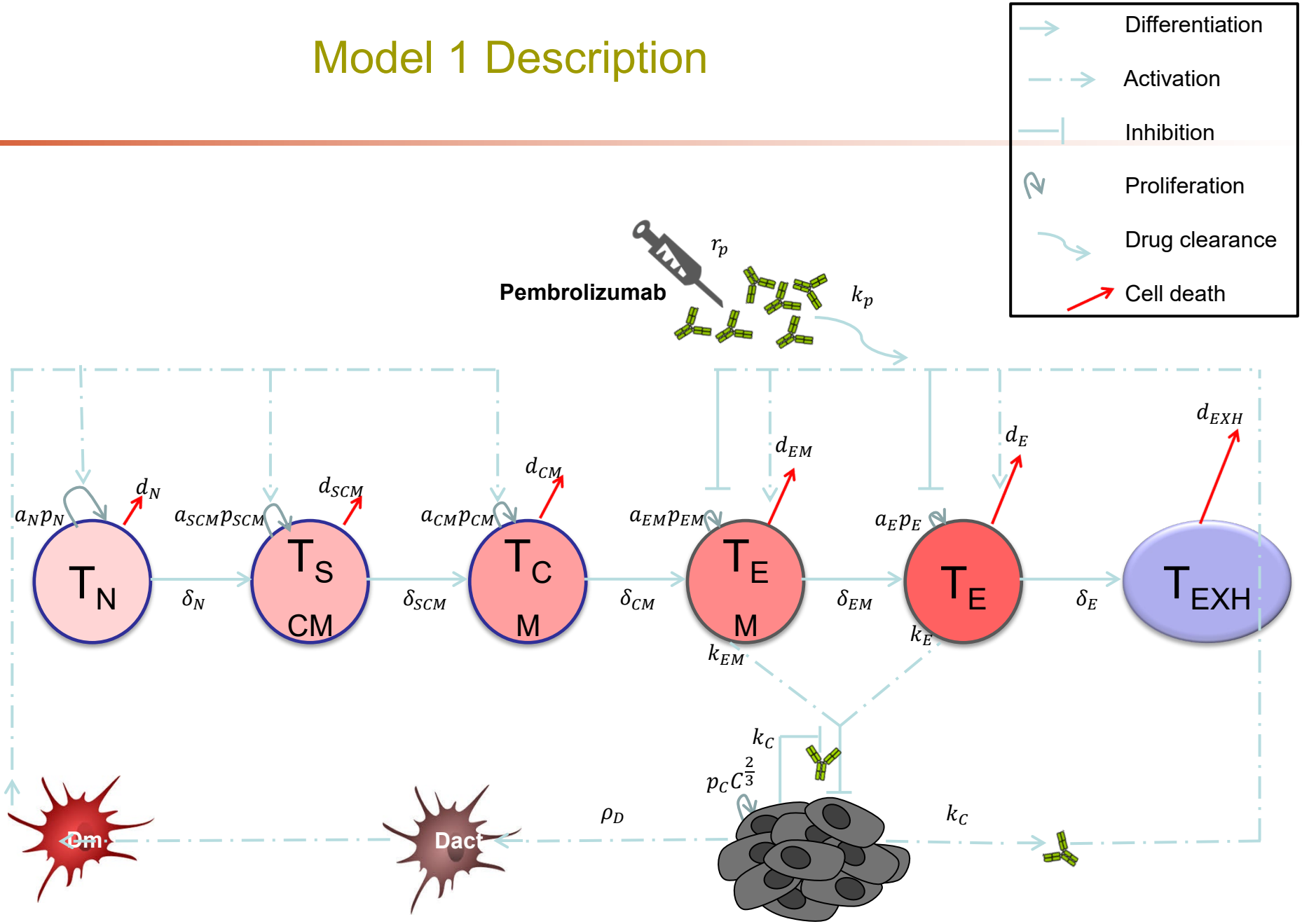
- Overall Response Rate to pembro is <50% and the drug can cause adverse events.
- There is a clinical need for new tools to predict patient response before therapy.

Need to personalize immunotherapy

Preliminary Questions

- To optimize immunotherapy, we need to model it.
- The adaptive arm of the immune system is complex
- Can we provide a **realistic** mathematical model for immunotherapy?
- Can we personalize immunotherapy?

Model 1 Description



Mathematical Mechanistic Model 1

Model characteristics:

- Mechanistic and deterministic,
- Non-spatial,
- No time delay,
- Non-linear, coupled, ODEs,
- More than twenty parameters

Model Description

Dendritic Cells

$$\dot{D}_{act} = \frac{\rho D_{act} C}{D_{act}+C} - k_D D_{act} \; ; \quad \dot{D}_m = a_l \, k_D \, D_{act} - \mu D_m \; .$$

T Lymphocytes

$$\dot{T}_{i,j} = 2a_{i,j-1}\, p_{i,j-1}\, T_{i,j-1}\, f_i + 2\left(1 - a_{i-1,j-1}\right) p_{i-1,j-1} f_{i-1}\, T_{i-1,j-1} - \left(p_{i,j}\, f_i + d_i\right) T_{i,j} - k_i^C \Gamma_{i,j}^C \; ,$$

where

$$f_i = \frac{D_m}{D_m + N + \sum_j \left(T_{1,j}+T_{2,j}\right)} \text{ for } i=1, 2 \; ; \qquad f_i = 1 \text{ for } i=3, 4 \; ; \qquad k_1^C = k_2^C = 0 \; ;$$

$$p_{1,j} = p_1^0 - j\alpha_1 \; ; \quad p_{2,j} = p_2^0 - j\alpha_2 \; ; \quad p_{3,j} = p_3^0 - j\alpha_3 - k_3^C \Omega_C \; ; \quad p_{4,j} = p_4^0 - j\alpha_4 - k_4^C \Omega_C \; ;$$

$$\Omega_C = \frac{C}{\frac{C}{\left[1 - \frac{P}{P+\sum_j \left(T_{3,j}+T_{4,j}\right)}\right]} + \sum_j \left(T_{3,j}+T_{4,j}\right)} \; ;$$

$$\Gamma_{i,j}^C = \frac{\left(T_{i,j} - T_{bi,j}\right) C}{C + \sum_j \left(T_{3,j}+T_{4,j} - \left(T_{b3,j}+T_{b4,j}\right)\right)} \; , \quad T_{bi,j} = \frac{P T_{i,j}}{P + \sum_j \left(T_{3,j}+T_{4,j}\right)} \text{ for } i=3, 4 \; .$$

Model Description

Cancer tumor

$$\dot{C} = p_C C^{0.66} - \frac{\sum_j \left(k_3^E T_{3,j} + k_4^E T_{4,j}\right) \cdot C}{C + \sum_j \left(T_{3,j} + T_{4,j}\right)},$$

where

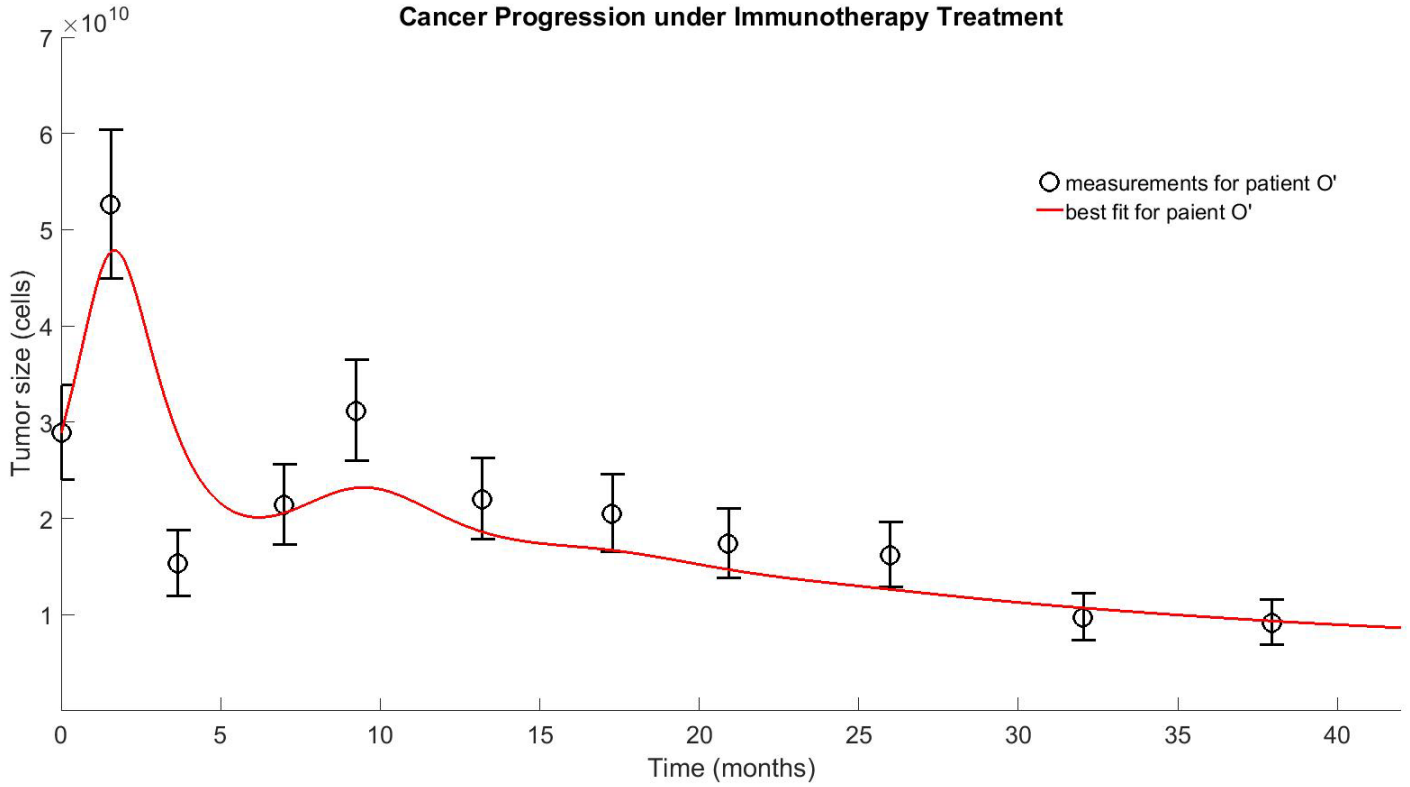
$$k_{3j}^E = z_0 k_0^E - k_3^C \Omega_3^C \; ; \quad k_4^E = k_0^E - k_4^C \Omega_3^C \; ;$$

$$\Omega_3^C = \frac{C}{C + \sum_j T_{3,j}} ; \quad \Omega_4^C = \frac{C}{C + \sum_j T_{4,j}} .$$

Pembrolizumab drug

$$\dot{P} = r_p \cdot \delta(t - 3weeks \cdot n) - k_p P \, .$$

Model Personalization - Fit the data of Patient O'



Patient O' is a 27 years old female with a histology of primary thymic metastatic melanoma

Conclusions

Conclusions

- The model can retrieve the typical non-monotonic dynamics of tumor progression under immunotherapy
- No chance of evaluating the large number of population and personal parameters in this relatively complex model
- A crucial goal is assessing how to decrease the number of parameters that must be evaluated in the clinic.

  - Simplify the model.

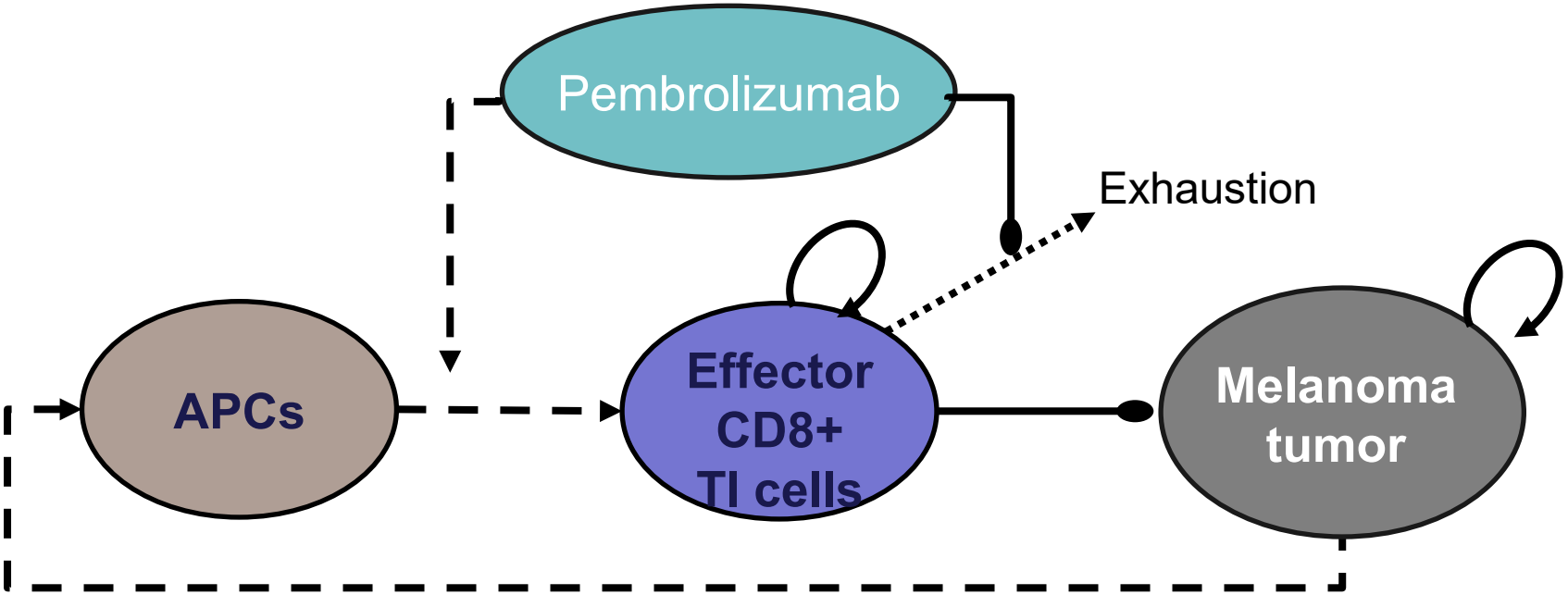
Predicting response to immunotherapy in metastatic melanoma by a personalized mathematical model

N. Tsur, Y. Kogan, E. Avizov-Khodak, D. Vaeth, N. Vogler,
J. Utikal, M. Lotem, Z. Agur

Journal of Translational Medicine 2019;17(1):338.

A Simplified Mathematical Mechanistic Model

The previous model is reduced



Activation
Exhaustion
Inhibition
Proliferation

APCs – Antigen-presenting cells

A Simplified Mathematical Model

APC activation rate

$$\frac{dA_{pc}}{dt} = \alpha_{im} \cdot \frac{M_{el}}{M_{el} + b} - \mu_{APC} \cdot A_{pc},$$

Max. pembro effect on APC activation

Max. pembro effect on T_{eff} exhaustion

$$\frac{dT_{il}}{dt} = a_{pem} \cdot \alpha_{eff} \cdot A_{pc} - b_{pem} \cdot \mu_{eff} \cdot T_{il},$$

Activation rate of naïve T cells

$$\frac{dM_{el}}{dt} = \gamma_{mel} \cdot M_{el} - \upsilon_{mel} \cdot \frac{T_{il} \cdot M_{el}}{M_{el} + g}.$$

Melanoma cell growth rate

Melanoma cell death rate

Evaluate Personal Parameters (which?)

Evaluate Personal Parameters

Correlation between clinical data and model personal parameters

- Tumor burden at baseline is significantly correlated with the effect of pembro on the activation of immune cells (a_{pem}).
- Breslow thickness and the status of nodular melanoma are significantly correlated with the tumor growth rate (γ_{mel}).

Prediction Capacity

Predicted TTP \ Observed TTP	0 - 90 days	90 - 150 days	150 - 365 days	No PD during follow-up
0 - 90 days	6	0	2	2
90 - 150 days	0	2	0	3
150 - 365 days	0	0	1	0
No PD during follow-up	4	2	2	30

- Predicted PD in 11/19 cases (8 false negatives).
- predicted no PD in the follow-up period in 30/35 of the patients (5 false positives).

Algorithm predictions of the TTP were moderately accurate

Discussion

- Personalization of a mathematical mechanistic model by clinical measurements of different metrics can serve for predicting TTP.
- Baseline tumor burden, Breslow thickness, and nodular melanoma status can be markers for TTP prediction under pembro when integrated and processed by an algorithm that implements the mechanistic model.
- Currently, the algorithm is based on its training by a small patient cohort (54 patients), partly accounting for the moderate accuracy.
- Second source of error – ignoring previous immunotherapy

Current Work

- Improve algorithm prediction accuracy, e.g., by its training by a more extensive and more diverse patient dataset and by accounting for previous drug treatment.
- Retrospectively validate the algorithm with clinical data from an independent dataset from other patient populations.
- Adapt the algorithm to other available therapies.

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Thank You

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