# Modeling the Emergence of Resistance to Chemotherapeutics with Virtual Tumour

PHYSIOMICS
rational therapeutics

# Disclosure Information

**AACR Minisymposium: Novel and Integrative Analyses of Cancer Genome Data**

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**I have the following financial relationship to disclose:**

**Employee of Physiomics plc**

**and**

**I will not discuss off label use and/or investigational use in my presentation.**

# Chemotherapeutic Resistance: Background

- Major cause of treatment failure
- Arises from genetic mutations/epigenetic changes
- Intrinsic or acquired, to one drug or many simultaneously
- Inter- and intra-tumour heterogeneity compound the problem
- Personalized medicine proposed as a way to prevent and overcome resistance – the future of cancer therapy…
- Emergence of resistant disease can be delayed by novel dosing regimens

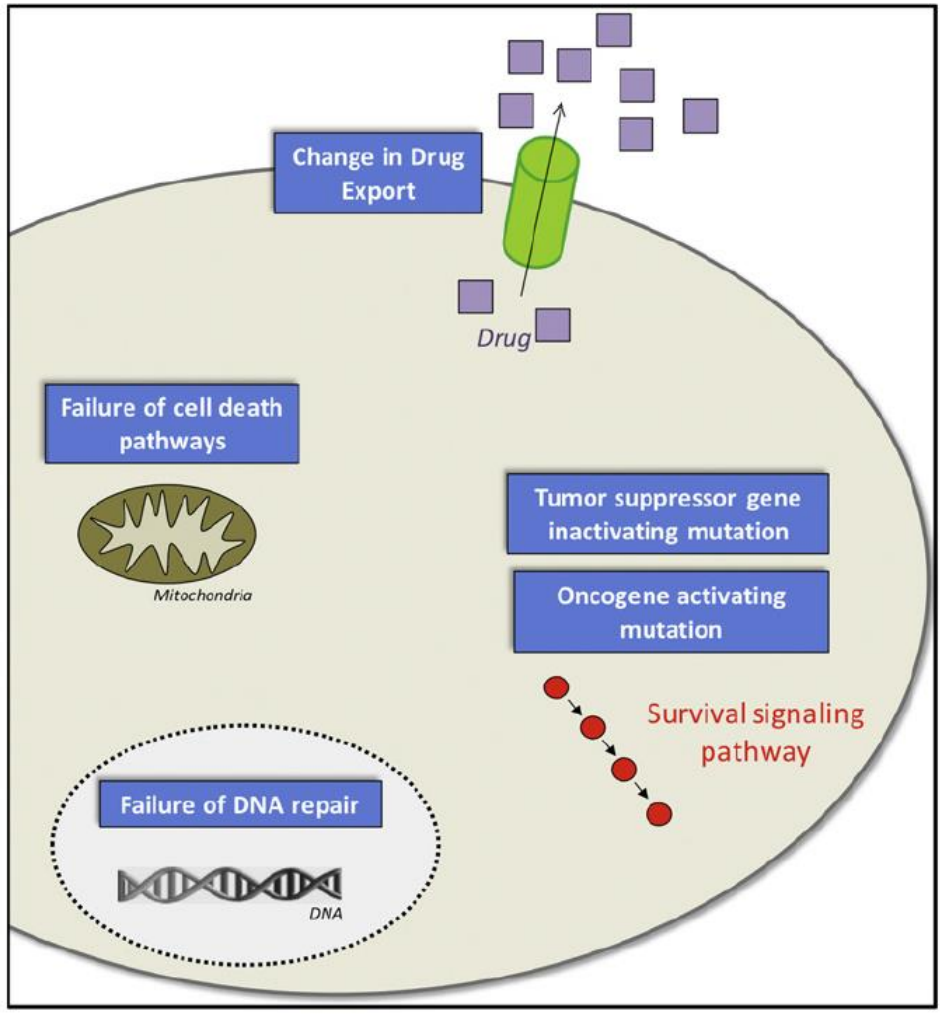
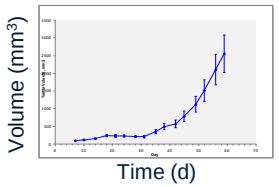



**Fig. 1.** Overview of drug resistance common mechanisms.

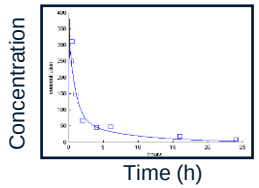
**From Rebucci and Michiels (2013) Biochem. Pharmacol. 85: 1219-26.**

# Virtual Tumour

**1) Cell line growth data:** Control xenograft growth curves

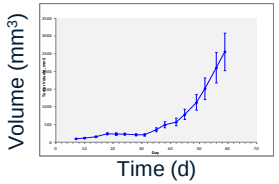



**2) Compound PK data:** Plasma/tumor time courses

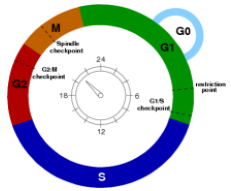



**3) Compound PD data:**

**- Xenograft inhibition data** (growth curves)

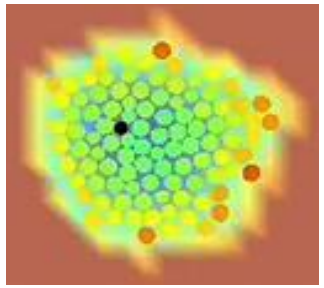



**- Biomarker data** (cell cycle, cell death, target biomarkers)



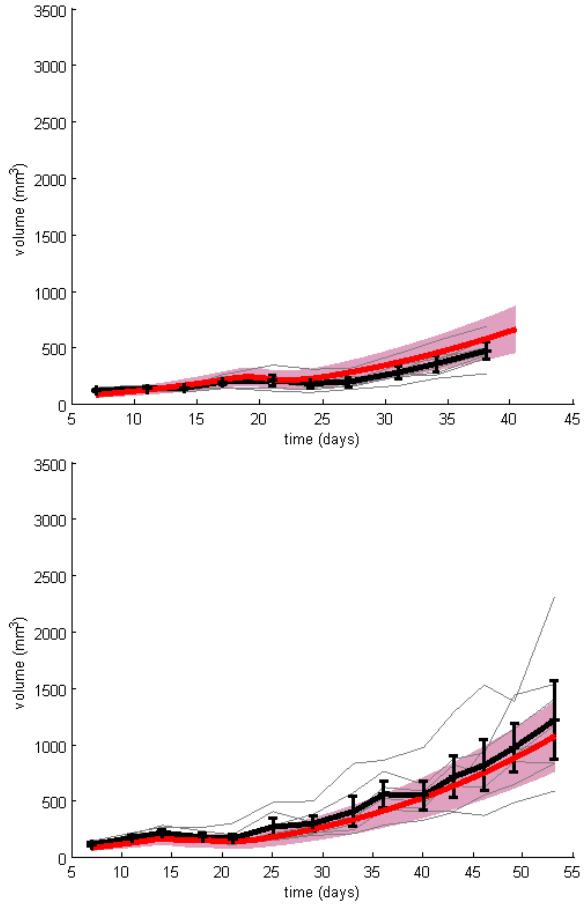

**Required data**
Optional data

## Virtual Tumour



**proprietary cell population model**

## Tumor growth inhibition for selected schedules




**Prediction**
Mean → Confidence interval

**Experiment**
Individual mice
Mean and standard error

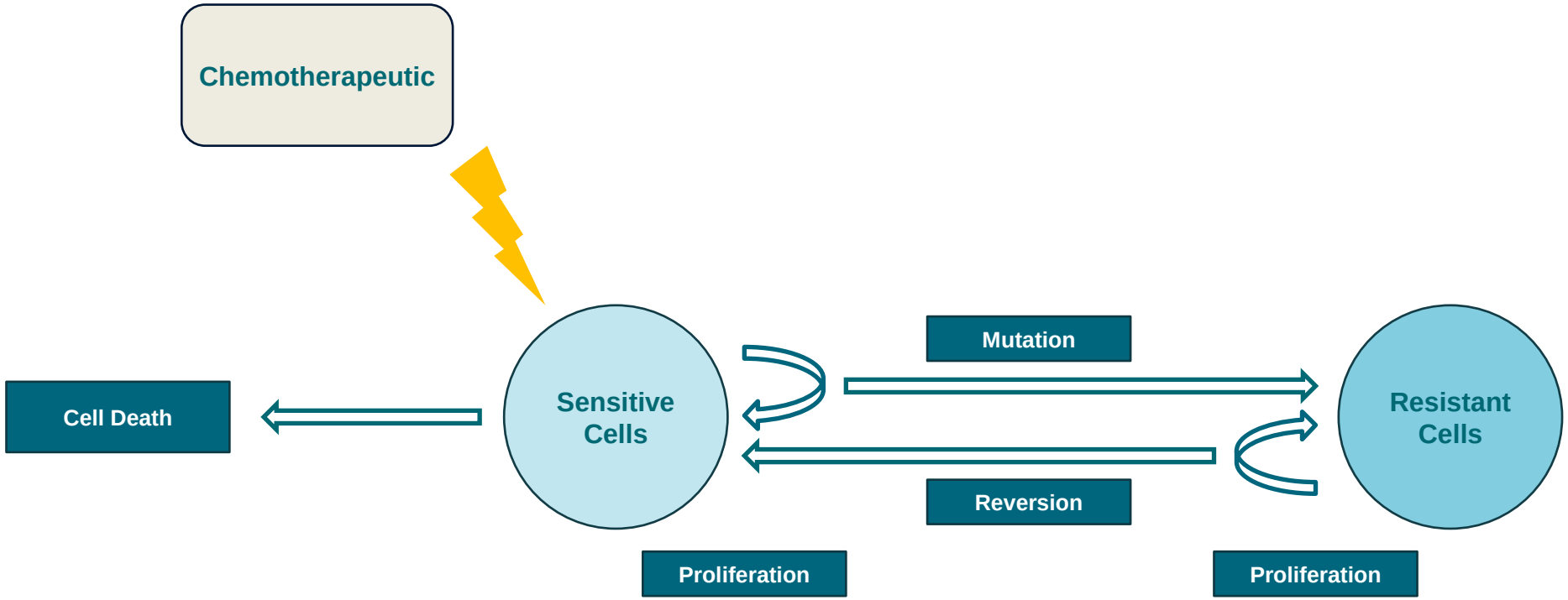
# Case Study

## Predicting the efficacy of an optimized regimen to minimize the emergence of chemotherapeutic resistance

| | |
|---|---|
| **ADVANCE:** | Validation of the VT resistance module |
| **OBJECTIVE:** | To determine whether our technology could accurately predict the efficacy of a novel dosing regimen of vemurafenib in metastatic melanoma PDX in minimizing the emergence of resistance |
| **PARTNER:** | Internal – literature based |
| **START POINT:** | Published PK and PDX growth inhibition data for calibrating the resistance module, with supportive literature data to determine the structure of the model |
| **DURATION:** | Three months |
| **OUTCOMES:** | Correctly predicted the efficacy of an optimized vemurafenib regimen for minimizing the appearance of resistance “time to regrowth” |

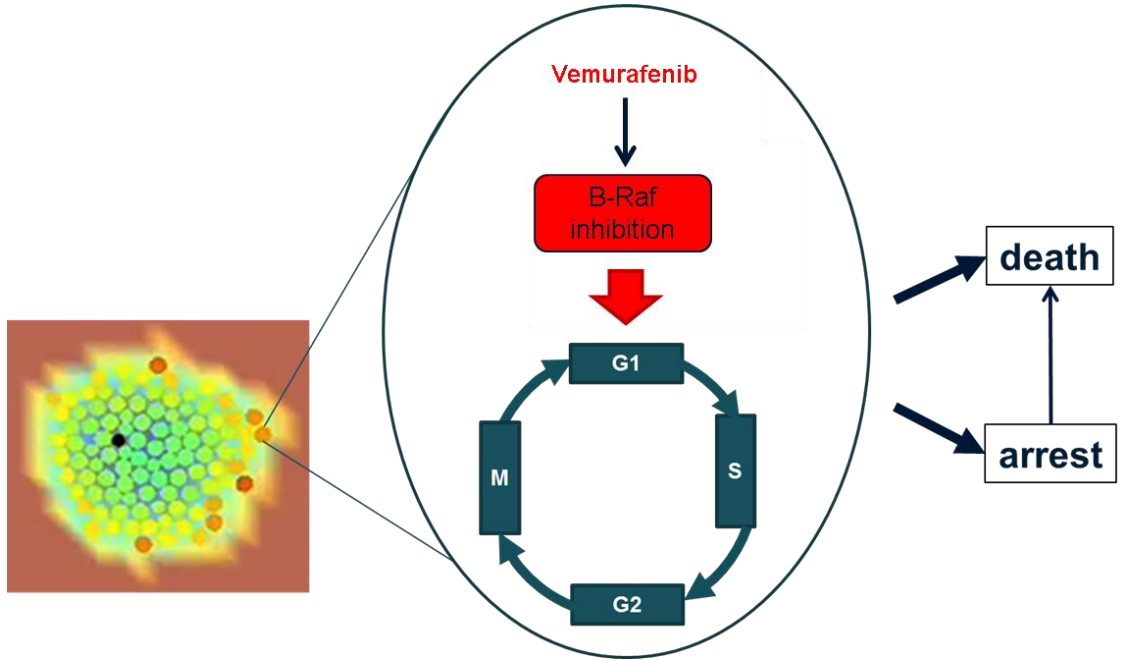
# Modeling Drug Resistance

- **A provisional model for chemotherapeutic resistance has been developed as an add-on module for the Virtual Tumour platform**



# Modeling Vemurafenib Mechanism of Action

- **Each cell in the Virtual Tumour contains set of equations that simulate:**
  - Cell-cycle phase progression and checkpoints
  - The effect of anti-neoplastic drugs/agents
- **The state-dependent effect of a drug on individual cells is modeled according to our understanding of the mechanism of action from literature and biomarker data**
- **Vemurafenib inhibits B-Raf/MEK/ERK pathway, leading to cell cycle arrest in G1 and cell death in sensitive cells**
- **Balance for cell arrest and cell death can be estimated using experimental observations and cell-cycle biomarker level measurements in treated tumors (e.g. TopoII and pRB)**

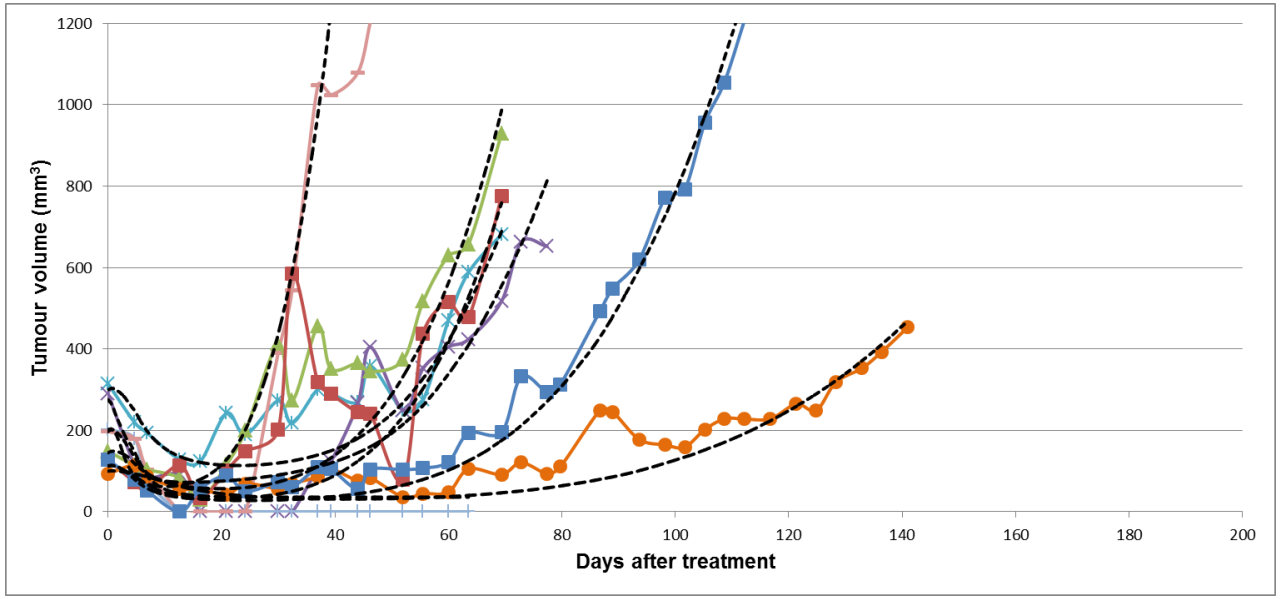


# Model Comparison with Experimental Data

- **Continuous dosing of HMEX1906 xenografts with vemurafenib results in rapid emergence of resistance (Das Thakur *et al. Modelling vemurafenib resistance in melanoma reveals a strategy to forestall drug resistance.* Nature 494, 251-5 (1013).)**

- **This effect can also be simulated using the model**

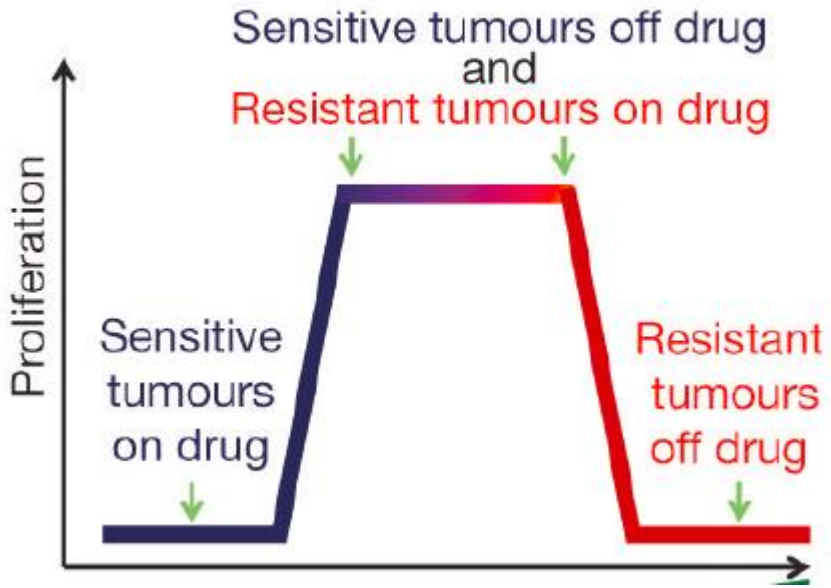
  - The pre-existing population of resistant cells was fixed, while the growth kinetics and vemurafenib efficacy were calibrated individually for each xenograft




**Tumor growth kinetics of naïve HMEX1906 xenografts dosed continuously with vemurafenib (15 mg/kg twice daily). Experimental data (coloured lines and symbols) from Das Thakur *et al*. Nature 494, 251-5 (1013), overlaid by simulation results (dashed black line).**

# How to forestall the onset of drug resistance?

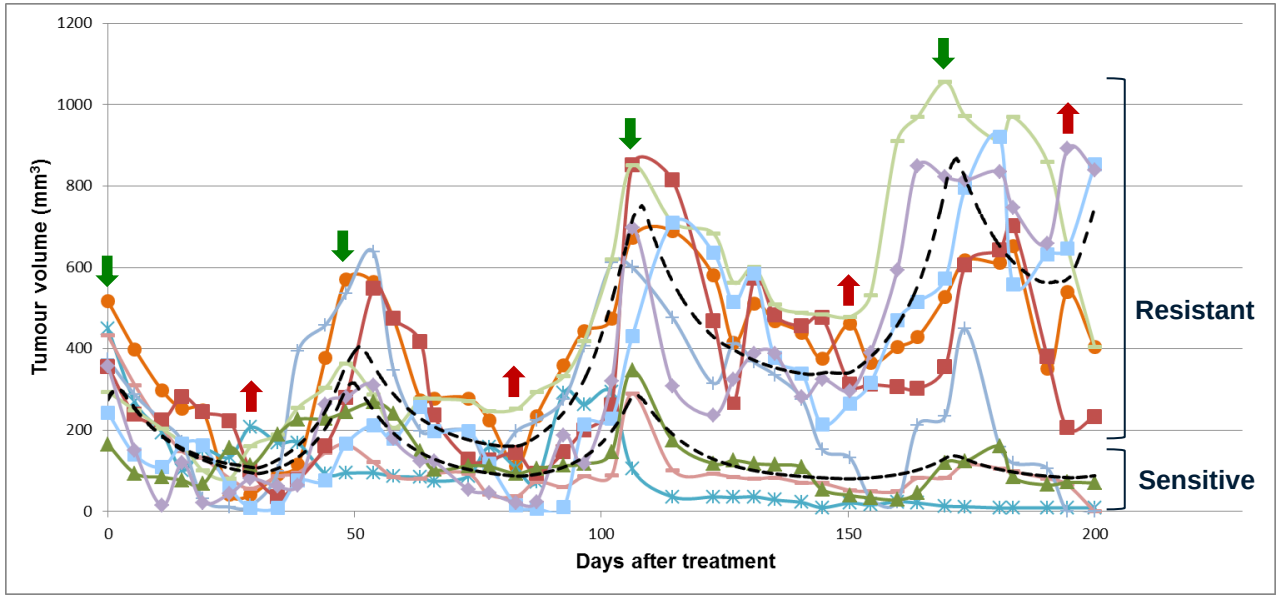
- **Das Thakur et al. suggest to use discontinuous dosing regimens**
- **Intermittent dosing significantly delays the onset of drug resistance by exploiting the fitness deficit of drug-resistant cells in the absence of the drug**




**Das Thakur *et al*. Nature 494 251-5 (1013).**

# Model Comparison with Experimental Data

- **Intermittent dosing of HMEX1906 xenografts with vemurafenib delays the emergence of resistance by exploiting the fitness deficit of drug-resistant cells in the absence of the drug**
- **The model also reflects this behaviour**
  - The model was calibrated separately for two groups of xenografts, sensitive (no resistant cells) and resistant (pre-existing resistant cells)

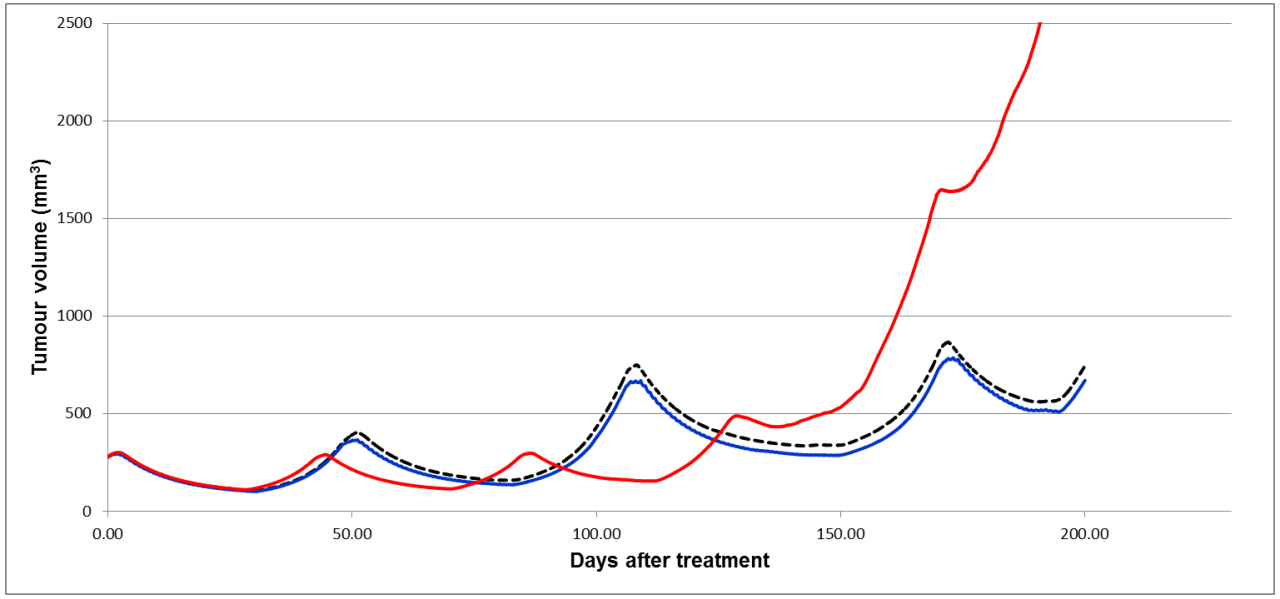



**Tumor growth kinetics of naïve HMEX1906 tumors dosed intermittently with vemurafenib (15 mg/kg twice daily, adaptive schedule). Experimental data (coloured lines and symbols) from Das Thakur *et al*. Nature 494 251-5 (1013), overlaid by simulation results (dashed black line).**

# Investigation of Optimal Dosing Schedules to Delay the Emergence of Resistance

- **The model also confirms that the 'adaptive' dosing regimen (dosing 15 mg/kg twice daily or 30 mg/kg once daily on an intermittent and adaptive on/off schedule) that was employed in the experimental study is close to optimal**

- **A strict four-week on two-week off schedule (15 mg/kg twice daily) fails to delay the emergence of resistance**




**Simulated tumor growth kinetics of naïve HMEX1906 tumors dosed intermittently with vemurafenib. Original adaptive schedule (15 mg/kg twice daily), dashed black line; (30 mg/kg once daily), blue line; strict four-week on two-week off schedule (15 mg/kg twice daily), red line.**

# Summary and Next Steps

- **Successfully validated the resistance module of our Virtual Tumour technology**
  - Using fixed, non-adaptive scheduling of vemurafenib administration leads to the risk of early onset of resistance, which eventually overwhelms the population of drug-sensitive cells
  - On the other hand, monitoring tumour growth and predicting the optimal time at which treatment should be applied or withdrawn leads to a better outcome
  - Model can be used to help design better preclinical schedules
- **Next step 1: Integrate the resistant module into Virtual Tumour Clinical**
  - Use existing validated translational Virtual Tumour for metastatic melanoma, developed in collaboration with Oxford University (Prof. Mark Middleton)
  - Accurate translation of preclinical efficacy reduces the number of clinical studies required to find optimal doses and schedules
- **Next step 2: Patient stratification with Virtual Tumour Clinical to predict time to relapse**
  - Stratify patient based of pERK expression and link it to PDX data
  - Optimize regimen for each group of patients, or individual patients

* Mistry, H. *et al*. Virtual Tumour Clinical development, part II: translational modelling of vemurafenib, selumetinib and docetaxel in metastatic melanoma, PAGE Meeting (2015), Alicante, Spain. Download poster here.

# Physiomics' People













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