

Introduction to Physiomics

BioTrinity
London, 30 April 2019

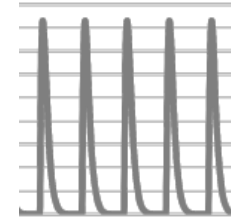


Physiomics is a consultancy focused on modelling cancer



Knowledge of
cancer

PK/ PD modelling
using Virtual Tumour™



Ability to access
and curate data

Understanding of AI/
machine learning



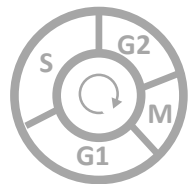


Dual company focus

Supporting oncology R&D



- Analytical and modelling support for oncology pre-clinical development



- **Virtual Tumour™** in-silico platform predicts tumour regression
- Focus on optimisation of combination regimes including iOnc, DDR agents, radiation

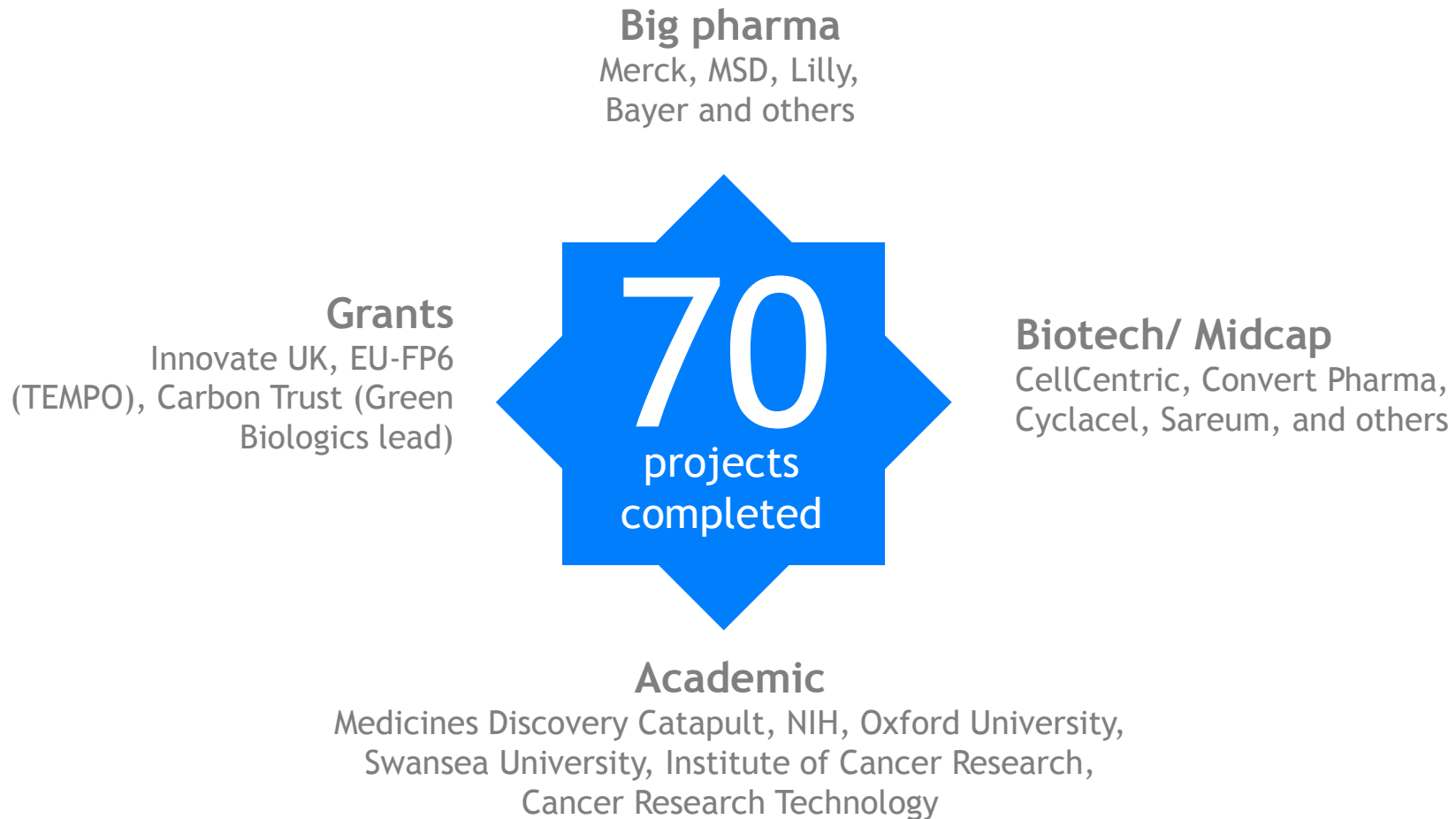
Personalised oncology



- Grant funded by Innovate UK
- Potential to predict toxicity and response to treatment for individuals or groups
- Potential applications in real world or trials
- Feasibility project competed



Completed over 70 commercial and grant funded projects





How we support development

- Recommend **efficacy/ toxicity** trade-offs ✓
- Recommend additional experiments to **confirm and refine hypotheses** if desired ✓
- Recommend **combination partner agent** for proprietary in-house asset ✓
- Assess efficacy of existing assets in **new indications** ✓
- Predict **biologically effective dose in humans** to support translation to clinical ✓
- Help build **causal chain story** for investors/ partners ✓



Case study: Physiomics supports CellCentric first in man studies

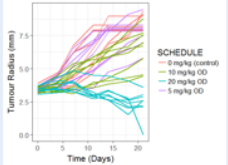
- CellCentric is developing a novel small molecule for prostate and other cancers
- Physiomics supported CellCentric with modelling and analysis in support of FIM dosing and scheduling
- Further supported FIM dosing and scheduling for a second indication in haematological cancer
- Physiomics analysis and modelling used in interactions with regulatory agency and protocol was approved

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Case study:
Supporting the use of a drug in a new indication: CellCentric

SITUATION

- CCS1477 is a novel small molecule discovered by CellCentric with potential applications in prostate and other cancers
- Having already worked with Physiomics on its Ph1 trial in prostate cancer, CellCentric wanted to choose an appropriate dose/schedule to support dose-escalation in haematological cancer

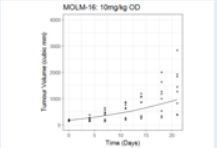


TASK

- Develop pre-clinical model of efficacy in haem cancer
- Swap mouse PK for human PK from Ph1 in prostate cancer
- Assess dosing/ scheduling to determine whether efficacy would be expected

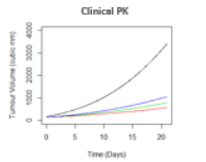
ACTION

- Built preclinical PK-Efficacy models for two relevant cell-lines
- Swapped out preclinical PK for clinical PK and simulated various dosing schedules




RESULT

- Provided client with simulations to support initial dosing/scheduling options for dose-escalation study in a new indication which were used in interactions with local regulatory agency/clinicians
- Clinical protocol approved by regulatory agency



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Case study: Using Virtual Tumour™ to model response rates following radiotherapy

- Physiomics developed a sophisticated model of radiotherapy combination treatment in clinical setting with an undisclosed client
- Poster based on use of model with literature data for combination RT/ cisplatin treatment of H&N cancer was accepted for presentation at AACR 2019
- Model can be used to predict tumour regression, response and regrowth rates

Physiomics

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Modelling the effect of Radiotherapy on tumour growth inhibition: the head and neck tumour case

Abstract No **680**
AACR Meeting 2019
Atlanta, GE, USA

Physiomics' Virtual Tumour™ technology

Physiomics' key technology is Virtual Tumour, which provides a platform for identifying, ranking and optimizing anti-cancer treatments, and in particular combination regimens [1,2]. Virtual Tumour (Figure 1) is a computer model that simulates tumour cell division and the effect of antineoplastic agents, taking into consideration the differences between proliferative cells and those that are part of the necrotic core. The complexity of the model is deliberately constrained so that it can be parameterized with data that are usually produced during drug development. These data include PK data for the drug, biomarkers showing the cell population response, and growth measurements showing how tumour growth is affected. This technology provides a rationale for designing an appropriate schedule, and allows our partners to prioritize the most effective drug combinations.

Aims and objectives

We have previously developed models that replicate and predict the effect that radiation (RT) has on tumour growth inhibition in several preclinical studies. These studies involve different RT doses and regimens as well as combinations with therapeutic agents with disparate mechanism of action. These encouraging results in the preclinical space led us to develop an enhanced strategy for modelling RT treatments using a tumour model that can predict tumour shrinkage and long-term regrowth in clinical setting (squamous cell carcinoma of the head and neck).

Data sets

- Phase 3 randomized trial of concomitant radiation and cisplatin in patients with advanced head and neck cancer. A dose of 70 Gy in 35 fractions over 7 weeks was delivered. Cisplatin (100 mg/m²) was administered over 1 hour on day 1 of weeks 1, 4 and 7. (ClinicalTrials.gov Identifier: NCT00094081) [3]
- Phase 3 randomized study of cisplatin in patients with recurrent or metastatic head and neck cancer. A dose of cisplatin (75 mg/m²) was administered on day 1 every 21. (ClinicalTrials.gov Identifier: NCT00415194) [4]

Characterisation of clinical head and neck tumour dynamics

- The initial rate of SLD (sum of longest diameter) shrinkage depends on the SLD before treatment. The tumour with the largest initial SLD shows the fastest initial tumour shrinkage rate (Figure 2 and 5).
- The magnitude of the tumour shrinkage can not be explained only by depletion of proliferative layer of the tumour.
- Many tumours remained suppressed for several years and a wide range of times to regrowth were observed (Figure 3).

Implementation of tumour growth model

We adapted our Virtual Tumour™ model to enable it to capture the experimental findings noted above.

- We assumed that the mechanism of action of RT and cisplatin at the cell cycle level in the clinical model is similar to the previously developed preclinical model.
- We hypothesized that the proliferative layer status plays a role protecting the physical integrity of the necrotic core and preventing it from being degraded by biological or physical processes. Reducing the growing layer width by depleting the number of viable cells therefore contributes to the tumour size shrinkage via necrotic core material leakage.
- As it has been shown that cell cycle doubling time was a strong prognostic factor for RT response, we estimated the tumour cell doubling times by calibrating the tumour regrowth to match locoregional control probability curves [5,6].

Virtual Tumour clinical model for cisplatin

Cisplatin mode of action. It damages DNA during S and G2 phases. It also delays G2 phase.

Virtual Tumour clinical model for RT & cisplatin

Radiation (RT) mode of action. It damages DNA in all phases.

Conclusions

Starting with a model that explained and predicted the effect of cisplatin/radiotherapy on tumour growth inhibition in the preclinical space we were able to extend it to one that describes both tumour growth inhibition and regrowth in the clinical space. Thus, we have developed a platform for head and neck cancer that could be used to predict the effects of radiotherapy alone or in combination with other procedures on tumour shrinkage and locoregional control. This approach can also be implemented to model other tumour types.

References:
[1] Ferraro, et al. (2011) Modeling the response to cisplatin-based combination using the Virtual Tumour. AACR 2011 Annual Meeting, Orlando, FL, April 2-6, 2011. [2] Ferraro, E. et al. Modeling and predicting head and neck radiation therapy in all three levels: in vitro, in vivo and clinical. PLoS One, 6(12):e28141. doi:10.1371/journal.pone.0281414 [3] Cancer, et al. Preclinical doubling time in head and neck tumors treated by primary radiotherapy: prognostic evidence for a prognostic significance in local control. International Journal of Radiation Oncology Biology Physics. Volume 57, Issue 5, 1180 - 1192 (2003). [4] Ferraro, et al. Cell kinetics of head and neck cancers. Clin Cancer Res 7: 1987-1993 (2001).

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Case study: Innovate UK funded personalised oncology project

- Literature describes ‘underdosing’ and ‘overdosing’ of various cancer drugs due to inter-patient variability
- Focusing on docetaxel in prostate cancer Physiomics developed a personalised treatment tool to support dosing decisions
- Relies only on blood tests already in common use (vs expensive assays that other companies sell)
- Provides guidance on both toxicity and efficacy at current and modelled alternative dose
- Currently engaging with clinicians before determining how to progress

Note: Tool is in development and will require regulatory approval prior to use

Physiomics
A Precision Dosing Application For Advanced Prostate Cancer Chemotherapy
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Abstract No 677
AACR Meeting 2019
Atlanta, GA, USA

Introduction

The therapeutic window of chemotherapy drugs is commonly established at a population level and patient dose selection is often simply scaled with Body Surface Area (BSA). Due to large inter-individual physiological variability, this leads to a significant number of patients being under or over-dosed [1,2]. While a limited number of precision dosing techniques exist to tailor patient-specific treatment, they typically require costly additional tests which severely restrict their use in clinical practice.

Focusing on docetaxel for advanced prostate cancer, we have developed a demonstrator for precision dosing which requires a single weekly classical blood test in the first chemotherapy cycle. It will fit within the current clinical practice to improve patient outcome at low cost.

[1] Guiney, M. (2002). British Journal of Cancer, 86(8), 1297.
[2] Engels, F.A., et al. (2011). Clinical Cancer Research, 17(12), 353-362.

Role of the App within the standard of care pathway

Figure 3 illustrates how the App fits within the current standard of care pathway.

- In the current standard of care, the first docetaxel dose is selected based on patient BSA. A blood sample is routinely collected on the day of first injection and sometimes on the first day of each subsequent cycle. If clinical toxicity is observed, the next dose is reduced or the treatment terminated. Docetaxel is administered in 3 week cycles until switch to another line of treatment, unacceptable toxicity or death.
- Our precision dosing App requires two additional blood tests during the first chemotherapy cycle around day 7 and day 14, just before selecting the second chemotherapy dose. Patient characteristics (age, height, weight) and blood tests results are entered into the App which outputs an evaluation of neutropenia and patient median survival probability relative to the general population under the current dose (Figures 4 and 5). Simulations of dose changes can be run in seconds.
- Toxicity information provided by the App may help clinicians to identify effective, under or overdosing and modulate the dose accordingly.

Results

- Concordance levels of 0.69 and 0.6 were obtained for the overall and progression-free survival models, respectively.
- Significant predictive variables include docetaxel exposure, Prostate Specific Antigen (PSA) as well as other biochemical markers.
- Patients with low estimated hematologic toxicity (neutrophil count not dropping under 0.5 billion/L) presented a median overall survival time of 480 days, against 625 days for patients with higher hematologic toxicity.
- Patients with low estimated docetaxel exposure (<3 µg h/mL) presented a median overall survival time of 450 days, against 580 days for patients with higher estimated docetaxel exposure.

Clinical question in a nutshell

50+ k	Prostate cancer diagnoses each year in the UK	20%	Patients may be overdosed [1]
3 weeks	Cycle length for docetaxel treatment	30%	Patients may be underdosed [2]

Docetaxel as chemotherapy in advanced stage
Docetaxel dose commonly guided by BSA
Main docetaxel toxicity is neutropenia

Methods

- The demonstrator App was developed using publicly available data from the comparator arm of a phase III clinical trial for metastatic hormone-resistant prostate cancer (clinical trial number NCT00617689 [3]). This cohort includes 412 patients who were treated with docetaxel between 2008 and 2011 in cycles of 3 weeks with weekly blood tests in the first cycle.
- A population PK/PD model and neutrophil population was assembled based on the literature [4, 5].

- Individual patient PK/PD parameters including docetaxel clearance were estimated by calibrating the population model with weekly measured blood count using a combination of Bayesian and machine learning approaches.
- Cox models were developed using estimated patient PK/PD parameters which relate docetaxel exposure and biomarker levels to overall and progression free survival.

[3] Phase, K., et al. (2013). Journal of Clinical Oncology, 31(14), 1742-1747.
[4] Friberg, L.E., et al. (2002). Journal of clinical oncology, 20(24), 4713-4721.
[5] MacLeod, W.L., et al. (1996). Cancer chemotherapy and pharmacology, 42(2), 159-199.

Illustrative underdosing case

Fig 4: Screenshot of the App 'analysis' tab. Overall and progression free survival models (top), neutropenia model for last (left) and upcoming (right) cycles. Patient models (blue) are compared to population models (grey) for administered 'Tommy's' dose.

Fig 5: Screenshot of the App 'dose refinement' tab. Simulation of survival probability and neutropenia in upcoming cycle for current (blue) and increased dose of 115 mg/m² (yellow). Estimated increase in median overall survival time from 440 days to 550 days.

Conclusion

We have developed a precision dosing App for Docetaxel in advanced prostate cancer which requires a single weekly standard blood test in the first chemotherapy cycle. Next stages include a validation clinical trial. This App has the potential, if approved by regulators, to significantly improve patient outcome and toxicity risk at low cost without disrupting the clinical treatment pathway.

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