Why don’t xenografted tumour models translate to patients?

Dr James Yates, Oncology DMPK Modelling and Simulation
DMLG 2017 Managers Meeting

31st May 2017
Or:
Why xenografted tumour models might translate to patients if we thought about it and did some more work…

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Why xenografted tumours might translate to patients if we thought about it and did some more work…

We use pre-clinical exposure – response relationships to predict active dose and schedule

There is very little evidence that animal models of cancer translate in a quantitative sense to the clinic

I believe that currently important differences between animal models and the human disease need to be taken into account
Motivating example 1: Tagrisso

Nonclinical PKPD-Efficacy relationship + Clinical PK to predict active clinical dose

Pharmacokinetics

Pharmacodynamics

95% Confidence intervals of efficacy
Even with variability effect saturates at low doses

1st generation TKI resistant
Activating mutant
Wild type xenograft

Response seen from 20mg up
Motivating example 2: Using pathway PKPD model to predict mouse efficacy and extrapolate to clinic

Prediction

Tumour regression
- Reduced proliferation rate
- Low apoptotic threshold = cell death
- pS6, uGSK3β

Growth inhibition
- Reduced proliferation rate
- High apoptotic threshold = cell survival
- pS6, uGSK3β

Validation

Cancer Chemotherapy and Pharmacology 76, 343-356 (2015)
The difficulty of translation

1. Pharmacokinetic differences
2. Genetics
3. Growth rate differences
4. Immune status
5. Heterogeneity

Increasing R: can some variability on y axis be explained by these factors?

A. BREAST VS BREAST

Pre-clinical Activity (mean T/C%)

Overall Phase II Activity (RR)

Theodora Voskoglou-Nomikos, Joseph L. Pater and Lesley Seymour
Evidence that animal models of cancer do not translate to the clinic

A. BREAST VS BREAST

1. Pharmacokinetic differences

2. Genetics

At AZ we’ve had similar findings.

Comparison of Human and Mouse Efficacy

Linakis et al 2015
EORTC-NCI-AACR
PK corrections don’t work for comparing schedules

- Translation appears to be drug specific.
- Useful for translating intermittent schedules?
- How can we bring in genetics, doubling time etc?

How can we increase the R-squared value of the correlation?
Challenge: Animal models grow quickly than the human disease

Fig. 1. Tumour Doubling Time by Primary Cancer Site
Why is drug effect vs tumour recovery time important?

1. Tumours are equally sensitive in terms of kill per dose

2. Red line is for slow growing tumour which “responds” to treatment

3. Green line is for fast growing tumour that is “resistant” to treatment
IR Biologically equivalent dose and repopulation

Can estimate loss of effectiveness due to tumour recovery
For Glioma $K=0.23\text{Gy per day lost}$, equivalent to 39 day doubling time
Opportunity: The theoretical treatment of IR is based upon 4 Rs. All of which have a corresponding “PKPD” terminology.

<table>
<thead>
<tr>
<th>IR</th>
<th>PKPD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Repair</strong></td>
<td>Pharmacodynamic persistence/overlap</td>
</tr>
<tr>
<td><strong>Repopulation</strong></td>
<td>Tumour volume made up during drug holiday</td>
</tr>
<tr>
<td><strong>Redistribution</strong></td>
<td>Cell cycle dependent effect. Treatment can deplete particular population of cells Can mediate combination antagonism (E.g AKTi+Taxane)</td>
</tr>
<tr>
<td><strong>Reoxygenation</strong></td>
<td>Slow onset of regrowth but can be accelerated due to larger proliferating fraction of smaller tumours</td>
</tr>
<tr>
<td><strong>Resistance</strong></td>
<td>Reversible (tolerance) vs Irreversible (clonal)</td>
</tr>
</tbody>
</table>

Note cell cycle time / proliferating fraction = doubling time
A simple mathematical model can be used to capture proliferating fraction and cell cycle time

Get sensible parameter estimates in xenografts:
1. Depth of shell is 100-300um (effective oxygen penetration). Increases to 10x this in PDX
2. Intrinsic proliferating fraction doubling time is typically 24-48hrs

Growth rate is function of proliferating fraction and intrinsic doubling time
Timescales learned from in vitro data predict combination efficacy in vivo efficacy

Confidence that mechanistic models developed using in vitro systems is predictive of in vivo
Challenge: Clinical Heterogeneity

FDA NSCLC model with different outgrowth rates

\[ T_{S_i}(t) = B_{ASE_i} \cdot e^{-SR_{i\cdot t}} + P_{R_i \cdot t}, \]

- Tumour reduction at 8 weeks shown to be predictive of OS
- Why do these treatments show different progression growth rates?
- Different resistant phenotype selected?
- But OS not impacted?

<table>
<thead>
<tr>
<th>Treatment</th>
<th>M_BASE (cm)</th>
<th>M_SR (1/week)</th>
<th>M_PR (cm/week)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCB</td>
<td>9.1 (0.33)</td>
<td>0.06 (0.004)</td>
<td>0.13 (0.02)</td>
</tr>
<tr>
<td>PC</td>
<td>8 (0.03)</td>
<td>0.038 (0.01)</td>
<td>0.14 (0.04)</td>
</tr>
<tr>
<td>DC</td>
<td>8.7 (0.31)</td>
<td>0.052 (0.01)</td>
<td>0.16 (0.02)</td>
</tr>
<tr>
<td>DCb</td>
<td>9.2 (0.38)</td>
<td>0.047 (0.005)</td>
<td>0.16 (0.02)</td>
</tr>
<tr>
<td>VC</td>
<td>8.5 (0.28)</td>
<td>0.063 (0.01)</td>
<td>0.17 (0.02)</td>
</tr>
<tr>
<td>DT</td>
<td>8.5 (0.82)</td>
<td>0.033 (0.01)</td>
<td>0.13 (0.02)</td>
</tr>
<tr>
<td>PT</td>
<td>7.4 (0.47)</td>
<td>0.023 (0.01)</td>
<td>0.25 (0.05)</td>
</tr>
<tr>
<td>PB\textsuperscript{a}</td>
<td>8.6 (0.44)</td>
<td>0.0047 slow (0.001)</td>
<td>0.20 (0.02)</td>
</tr>
<tr>
<td>ET\textsuperscript{a}</td>
<td>8.4 (0.32)</td>
<td>0.0045 slow (0.001)</td>
<td>0.058 (0.02)</td>
</tr>
</tbody>
</table>

DC, docetaxel and cisplatin; DCb, docetaxel and carboplatin; DT, docetaxel; ET, erlotinib; PB, placebo; PC, paclitaxel and carboplatin; PCB, paclitaxel, carboplatin, and bevacizumab; PT, pemetrexed; VC, vinorelbine and cisplatin.
Opportunity to Embrace Heterogeneity: N=1 mouse trials

Genetic signals and patient like variability

Develop PKPD models using such data sets and get an estimate of PD variability (cf Tagrisso example)
There is also evidence that doubling time of PDXs is an important predictor of drug sensitivity.

Can we use such datasets to build more translatable models of efficacy?

Data from Novartis (Gao et al 2015) on use of PDXs for patient selection
Y-axis is ratio of control to treated growth rate: big number=big effect
Summary: Translation via the biomarker cascade:

- **Dose**
- **Plasma / Tumour PK**
- **Target Engagement**
- **Pathway Modulation**
- **Phenotypic Response**
- **Efficacy**

**Compound properties**

**Pharmacology**

**Cancer Biology**

- **PK differences**
- **Heterogeneity of the disease**
- **Growth rate of the disease**
- **Resistance**
- **Immune component**
Conclusions

We need to take into account other things than PK

There exist data sets to investigate these differences

I haven’t even talked about the immune system

Modelling and simulation is key to take into account all of these differences
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