Principle of Cancer Modeling in Mice: How to Translate Preclinical Studies

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Relevance of mouse models to human diseases depends on the “driving factors” in common.
Irrelevance resulted from mismatch between model setting and human disease

- **Mouse**
  - Growth delay
    - Protocol-defined survival
    - Single-line treatment
    - Preventive therapy for metastatic diseases

- **Human**
  - RECIST*
    - Multiple metastases
    - Cancer-related death
    - Multiple-lines treatment
    - Intervention therapy for metastatic diseases

*response evaluation criteria in solid tumors
Disease tracking and treatment in the preclinical models need to match those in clinical situations.

Therapeutic setting
- Intervention
- Adjuvant
- Neoadjuvant
- Maintenance

Therapeutic response in the individual setting

Endpoint
Therapeutic setting
- Intervention
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Therapeutic response in the individual setting

Endpoint

Disease tracking and treatment in the preclinical models need to match those in clinical situations
Different therapeutic settings target different disease states

<table>
<thead>
<tr>
<th>Therapeutic setting</th>
<th>Targets of the treatment</th>
<th>Goals</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>Detected disease</td>
<td>Eliminating the detected disease</td>
<td>Surgical resection of tumors</td>
</tr>
<tr>
<td>Adjuvant</td>
<td>Residual disease</td>
<td>Preventing metastatic diseases</td>
<td>Chemotherapy following tumor resection</td>
</tr>
<tr>
<td>Neoadjuvant</td>
<td>Disseminating disease</td>
<td>Preventing the dissemination of the disease</td>
<td>Chemotherapy followed by tumor resection</td>
</tr>
<tr>
<td>Maintenance</td>
<td>Progressing disease</td>
<td>Slowing the progression for symptom relief</td>
<td>Palliative chemotherapy</td>
</tr>
</tbody>
</table>
Tumor models for studying adjuvant setting

Luciferase-labeled Metastatic LLC tumor

Syngeneic mice → Primary tumor → Resection of primary tumor

No treatment → Metastatic tumors in lungs

Drug treatment → Delayed onset of metastasis

Melinda Hollingshead, John Carter, Carrie Bonomi
Adjuvant setting model should allow quantitative tracking of metastatic disease

Pathological scoring

<table>
<thead>
<tr>
<th>Chest BL</th>
<th>Corresponding Lung Pathology</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>$1.5 \times 10^5 - 2 \times 10^5$</td>
<td>1-2 nodules</td>
<td>1</td>
</tr>
<tr>
<td>$2 \times 10^5 - 1 \times 10^6$</td>
<td>A few nodules</td>
<td>1-2</td>
</tr>
<tr>
<td>$1 \times 10^6 - 5 \times 10^7$</td>
<td>Mostly multifocal</td>
<td>3-4</td>
</tr>
<tr>
<td>$&gt; 5 \times 10^7$</td>
<td>Diffuse</td>
<td>4</td>
</tr>
</tbody>
</table>

Quantitation

$$y = 2.3587x + 0.15$$

$R^2 = 0.8034$
Clinically relevant readout can be generated from quantitative disease tracking in adjuvant setting model.
Models for neoadjuvant therapy should allow tracking of disseminated disease

DMBA-induced HGF-tg;CDK4^{R24} melanoma labeled with luciferase and GFP

Tumor reached 500 mm^3 and resected (Day 1)
Therapeutic setting
• Intervention
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Therapeutic response in the individual setting

Endpoint

Disease tracking and treatment in the preclinical models need to match those in clinical situations
Effects of disease stage on therapeutic response

**Ewing’s Sarcoma**

**Standard combination chemotherapy:**
- Doxorubicin
- Vincristine
- Cyclophosphamide
- Dactinomycin

**Experimental therapy:**
Combination chemotherapy alternating with courses of ifosfamide and etoposide

Comparing therapeutic responses of diseases at distinct progression stages

**Syngeneic mice**

Luciferase-labeled Metastatic LLC tumor

Resection of primary tumor

Treatment of primary tumor

Vehicle

Drug

Treatment of metastasis

Vehicle

Drug
Responses of primary and metastatic tumors to the same chemotherapeutic agent are driven by different factors.
Responses of primary and metastatic tumors to the same chemotherapeutic agent are driven by different factors.
Therapeutic responses in different settings may not be associated with each other.
Disease tracking and treatment in the preclinical models need to match those in clinical situations

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Therapeutic response in the individual setting

Endpoint
Different types of therapies require different modeling endpoints


PFS ≠ OS
Surrogate endpoint: growth rate

PFS ~ OS
Surrogate endpoint: PFS
Tumor response to immune checkpoint inhibitors is associated with effector T cell levels and growth delay

Larimer et al. (2017) Cancer Res; 77(9):2318
1. PFS and DFS are the surrogate endpoints for cytotoxic therapy study. Metastatic models could be more relevant setting.

2. Growth delay is associated with levels of infiltrated effector T cells. Subcutaneous models therefore can be used in immunotherapy study.

3. Selection of models with similar therapeutic response in growth kinetics and endpoints is critical for the clinical relevance of the model.
“Observer Effect”

measurements of certain systems cannot be made without affecting the system.
Inconsistent growth and/or labeling maintenance in a syngeneic tumor model

Day et al. (2014) PLoS ONE 9(11): e109956
Glowing head mice: GEM pre-tolerized with GFP and luciferase

Day et al. (2014) PLoS ONE 9(11): e109956
Antigenicity of labeling markers can alter disease progression

Day et al. (2014) PLoS ONE 9(11): e109956
Antigenicity of labeling markers confounded study results by altering therapeutic response of the tumor

Day et al. (2014) PLoS ONE 9(11): e109956
Transduction with control lentivirus suppresses metastasis and alters therapeutic response in the Mvt1 model

Lalage Wakefield (LCBG, NCI)

Gene integration of “control” vector can cause confounding effects
1. Effect seen with multiple independent control lentiviruses in multiple experiments.

2. Not an immune response to the lentivirus: Effect is also seen in fully immunodeficient (NSG) mouse hosts.
Relevance of Preclinical Models: Revisited

- Experimental setting
- Therapeutic response
- Endpoints
- Preclinical model
- Clinical Study
- Relevance of Preclinical Models: Revisited
  - Disease tracking
  - Technologies & Logistics
  - Experimental setting
  - Therapeutic response
  - Endpoints
  - Observer Effect
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