Melanoma PDX

Table 1: Success rate PDX platform

<table>
<thead>
<tr>
<th>Tumor samples</th>
<th>Number</th>
<th>Xenografted</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRAF&lt;sub&gt;V600E/K&lt;/sub&gt;</td>
<td>86</td>
<td>73 (85%)</td>
</tr>
<tr>
<td>NRAS&lt;sub&gt;Q61&lt;/sub&gt;</td>
<td>10</td>
<td>10 (100%)</td>
</tr>
<tr>
<td>BRAF&lt;sub&gt;WT&lt;/sub&gt;NRAS&lt;sub&gt;WT&lt;/sub&gt;</td>
<td>7</td>
<td>6 (85%)</td>
</tr>
<tr>
<td>Total</td>
<td>103</td>
<td>89 (86%)</td>
</tr>
</tbody>
</table>

Whole exome sequencing | 13
360-cancer gene panel  | 47

Kemper et al., Cell Rep. *In press*
Studying resistance mechanisms with PDX

Research Article

Intra- and inter-tumor heterogeneity in a vemurafenib-resistant melanoma patient and derived xenografts

Kristel Kemper1,†, Oscar Krijgsman1,†, Paulien Cornelissen-Steijger1, Aida Shahrai1, Fleur Weeber1, Ji-Ying Song2, Thomas Kuilman1, Daniel J Vis3, Lodewyk F Wessels3, Emile E Voest1, Ton NM Schumacher4, Christian U Blank4, David J Adams5, John B Haanen4 & Daniel S Peeper1,†

Published online: June 23, 2015
Questions still to be answered?

What mutations drive disease phenotype?
A cross-species study for the discovery of genes involved in melanoma metastasis

**Leeds cohort FFPE samples 222 patients**

**Lund cohort FFPE samples 223 patients**

**Melanoma-specific survival analysis**
Cox proportional HR

**Overall Survival**
Cox proportional HR

**Comparison**

**Microarray Expression Data**

**Genes Assessed**

**RNA-seq**
5 cell-lines, 5 Biol. replicates per line

**Differential Expression analysis**
High VS Low metastatic lines

414 under-expressed genes & 464 over-expressed genes
(93% have orthologous gene in human)

**18 genes (FDR<0.1) with concordant expression change associated with risk (Hazard Ratio>1)**
Low LFNG expression is predictive of a poor outcome in melanoma

Melanoma Specific survival

Hazard Ratio: 1.66
g2d1 clones carry a 1bp frameshift mutation in Lfng
Dog melanoma
Dog mucosal melanoma

Spontaneous model

Dog trials
Mucosal Melanoma

Small numbers of mutations

No *KIT/GNAQ* mutations

No *BRAF* mutations

But some *K-RAS* and *N-RAS*

Some *p53*

MAPK therapies??
Zebrafish melanoma

$\text{BRAF}^{V600E}$
Horse and pig melanoma

Grey horses
Real opportunity for comparative genomics/pathology!!
Phenotype is highly associated with melanoma risk
Melanoma GWAS

Pigment and telomere genes predominate

Law & Bishop et al., 2015
What GWAS has contributed?

Pathways and processes that contribute
Reconfirmed the importance of phenotype

*MC1R* homozygote
Red head mice

Mitra et al., Nature 2012
UV melanoma models

Kannan et al., PNAS 2003
Cross-species models of human melanoma

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