We know virtually nothing about host genetics and its role in melanoma development

Immune system?
Tumour microenvironment?
Microbiome?
Metabolism?

Major role for animal models
**Braf**<sup>V600E</sup> as a driver of melanoma

*BRADF*<sup>V600E</sup> is mutated in >50% of melanomas (*BRAF<sup>V600E</sup>, *BRAF<sup>V600K</sup>*)

Braf model of melanoma

\[ \text{Braf}^{V600E} \]

Tyrosinase Cre

\[ \text{MEK} \rightarrow \text{ERK} \]
Braf<sup>V600E</sup>; Tyr<sup>CreER<sub>2</sub></sup> mice develop multiple nevi
\textbf{Braf}^{V600E}; \textbf{Tyr}^{CreERt2} mice develop melanoma
Transposons for insertional mutagenesis
Transposons for insertional mutagenesis

*Sleeping Beauty* transposon
Transposons for insertional mutagenesis

Anatomy of a transposon

Promoters, stop cassettes

IR/DR 300 bp IR/DR

+ transposase

IR/DR IR/DR
Transposons can activate and inactivate genes

Profile the sites of transposon insertion using next-gen sequencing
Mouse model of melanoma

\(Tyr-Cre^{ERT2}\)  \(B-Raf^{v600E}\)  Transposons and transposase

\(Tyr-Cre^{ERT2}; B-Raf^{v600E};\) Transposons and transposase
A forward genetic screen for melanoma

Braf mice without transposons

Braf mice with transposons

Control cohort

LSL-Braf^{V619E}; R26-LSL-SB13; T2/Onc; Tyr-CreER^{T2}

LSL-B-Raf^{V619E}; T2/Onc; Tyr-CreER^{T2}

LSL-B-Raf^{V619E}; Tyr-CreER^{T2}

p<0.0001
Mouse CISs include known human melanoma genes
shRNA knock-down of \textit{Epc1} in \textit{Braf}^{V600E}/Tyr-Cre cells

\textit{shEpc1}
**Braf^{V600E} melanomas shrink in response to PLX4720 BRAF inhibitor**

**dosage scheme:** PLX4720 diet

mice T12004 and T12011 treated for 14 days, mice T12003 and T12296 treated for 5 days

Tranposons mobilizing in these tumours
Braf\textsuperscript{V600E}/drug resistance with the BRAF inhibitor

![Graph showing tumor volume over days for different treatments](image)
Eras and resistance to BRAF inhibition

Insertions drive overexpression of Eras
**ERAS** expression confers resistance to BRAF inhibition

Human melanoma cell line

LTR- **ERAS** - LTR

**PLX4720 IC50 in WM164 cells**

- Control
- ERas
- **ERas_SSVA**

Increasing drug concentration