Cross-Species Models of Human Melanoma

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UV light

Melanocytes

Epidermis
Dermis
Blood vessels
Squamous cells
Basal cell
Melanocyte
Melanin
Vein
Artery
Hair shaft
Oil gland
Epidermis
Dermis
Subcutaneous tissue
Lymph vessel
Nerve
Fatty tissue
Sweat gland
Melanocytes

Iris of the eye

In mucosal tissues

In the nail bed
Dramatic increase in melanoma rates
Superficial spreading melanoma

Most common

Often on the trunk in men
Legs in women
Nodular melanoma

Prof. Julia Newton-Bishop
Acral lentiginous melanoma

Prof. Julia Newton-Bishop

Two tumours which were particularly advanced at presentation
Other forms

Desmoplastic melanoma

Mucosal melanoma

Uveal melanoma
Where are we with understanding the somatic genetics of melanoma?
C>T mutations

Alexandrov et al., Nature 2013
What mutations drive melanoma development?

Watson et al., Cell 2015
* BRAF V600/K601 mutations
** RAS G12/G13/Q61 mutations
*** Not including the TERT promoter mutations (65% N=115)
Defining significantly mutated genes

Zhang et al., PCMR 2016
Are there more drivers to find?

BRAF inhibitor resistance mediated by the AKT pathway in an oncogenic BRAF mouse melanoma model

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Transposon mutagenesis identifies genetic drivers of \textit{Braf\textsuperscript{V600E}} melanoma

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Questions still to be answered

Why do some patients get SSM, others nodular or desmoplastic melanoma?

- Cell of origin? Location of the cell?
- Somatic mutations?

What genetic alterations can be exploited therapeutically?
Questions still to be answered

What mutations drive disease phenotype?
Therapy for melanoma

Ugurel *et al.*, Eur J Cancer 2016

Which treatment for which patient?
BRAF resistance in melanoma

Before therapy

15 weeks of therapy

23 weeks of therapy

![Chemical structure of BRAF inhibitor](attachment:image.png)