Combination of Immune and DNA Damage Repair gene alteration predicts for better outcome in Malignant Melanoma.

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DNA Damage, Immunity and Cancer

- DNA damage repair is a fundamental cellular pathway with an important role in maintaining genomic integrity\(^1\).

- Malignant Melanoma is associated with high mutation rate (16 mut/Mb) and thus likely to have abnormal DNA repair pathway aberrations and these could have prognostic, predictive or therapeutic role\(^2\).

- There is increasing data supporting the interaction between DNA Damage Response and Immunity\(^3,4\).

- Immune therapy is a well established treatment option in metastatic melanoma.

\(^1\)Hannah & Weinberg, Cell 2011; 144: 646-566
\(^2\)TCGA, Cell 2015; 161:1681-96
\(^3\)McGranahan et al. Science. 2016; 35: 1463–1469
\(^4\)Snyder et al. NEJM 2014; 371: 2189-2199
Method

- A comprehensive survey of all the available data from established public data repositories, published literature and abstracts, was used to produce an unbiased assessment of the genes involved in DNA damage pathway.
• DNA Damage signature (DDS) was assessed in malignant melanoma (Epitope Generating).

• Immune genes- PD1, PDL1, CTLA4 & STAT1 (Effector).

• These two were evaluated in sequencing, copy number, and gene expression data from 287 patients from The Cancer Genome Atlas\textsuperscript{2}.

\textsuperscript{2} TCGA, Cell 2015; 161:1681- 96
Results: DNA Damage Signature and Cancer

Cancers in The Cancer Genome Atlas Data Base

- Melanoma 40%
- Ovarian Cancer 40%
- Prostate Cancer 28%
The DDS was altered in 74% (213/287) of the patients and included mutation, deletions or altered expression.

The most frequently altered genes were MDC1 (25%), RNF8 (25%), PRKDC (23%), TP53BP1 (18%) and NBN (15%).

Number of patients with Alteration in DDS & subtype

<table>
<thead>
<tr>
<th>Alteration in DDS &amp; subtype</th>
<th>Number of Melanoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRAF 78%</td>
<td>150</td>
</tr>
<tr>
<td>NRAS 89%</td>
<td>100</td>
</tr>
<tr>
<td>NF1 75%</td>
<td>50</td>
</tr>
<tr>
<td>Tri WT 60%</td>
<td>20</td>
</tr>
</tbody>
</table>

Altered

Not altered
Only DDS Altered and Overall Survival

- Altered: 74% (213/287)
- Not altered: 36% (74/287)

p = n.s.
DDS and Immune Gene Alterations: 
*Disease Free and Overall Survival*

### Table

<table>
<thead>
<tr>
<th></th>
<th>Number</th>
<th>deaths</th>
<th>Med. Survival (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Altered</td>
<td>78</td>
<td>34</td>
<td>151</td>
</tr>
<tr>
<td>No alteration</td>
<td>203</td>
<td>126</td>
<td>64</td>
</tr>
</tbody>
</table>

*p*=0.008

*p*=0.01

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**Legend**

- Blue line: Overall Survival
- Red line: Disease Free Survival
Conclusion

- This analysis shows that a significant number of malignant melanomas have an aberration in DNA Damage response pathway.

- The improved survival associated with alteration of the two pathways suggests that this might have a role in modulating the immune system.

- The significant number of patients with aberrations of both pathways could explain the significant benefit of immunotherapy in melanoma.

- This could define a group likely to benefit from immunotherapy.
Acknowledgements

Prostate Cancer Research Group, Monash University
Gail Risbriger  Carmel Pezaro
Ashlee Clark  Laura Porter
Stuart Ellem  David Pook
Luc Furic  Richard Rebello
Shelley Hedwards  Michelle Richards
Sophie Lee  Gail Risbridger
Natalie Lister  Renea Taylor
Birunthi Niranjan  Linda Teng
Daisuke Obinata  Jenna Van Gramberg
Melissa Papargiris  Hong Wang
Brooke Pereira

Funding - E.J. Whitten Foundation

Mark Frydenberg (Monash University)
Declan Murphy (Peter Mac)