PPGL research update

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Disclosures

- Speaker fees from Eisai, Bayer, Amgen, Novo Nordisk, Ipsen

- Ad boards: Eisai, Amgen, Ipsen
Overview: research agenda

1. To determine **drivers** of pheo development

2. To develop new **targeted** therapies

3. To **prevent** metastatic PPGL (identify PPGL early)
Agenda #1: Determining **drivers** of pheo development

1. Genetic information
   - Hypoxia-inducible factors
   - Telomeres

2. Metabolomics
Pheo-Para genes classify in 3 clusters

- Most of these genes are ‘tumor suppressors’ (e.g. SDHB)
- A few however are ‘oncogenes’
  - it is easier to develop inhibitor therapies against these

<table>
<thead>
<tr>
<th>Cluster 1 “pseudo-hypoxia”</th>
<th>Cluster 2 “kinase”</th>
<th>Cluster 3 (or 2B) “Wnt altered”</th>
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<tbody>
<tr>
<td>VHL</td>
<td>RET</td>
<td>MAML3</td>
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<tr>
<td><strong>EPAS1</strong></td>
<td>NF1</td>
<td>CSDE1</td>
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<tr>
<td>PHD1</td>
<td>TMEM127</td>
<td>TP53</td>
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<td>IRP</td>
<td>MAX</td>
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<tr>
<td>SDHD</td>
<td>KIF1B</td>
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<td>SDHB</td>
<td>HRAS</td>
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<tr>
<td>SDHC</td>
<td><strong>MET</strong></td>
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<tr>
<td>SDHA</td>
<td>MERTK</td>
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<td>SDHAF2</td>
<td>DNMT3A</td>
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<tr>
<td>FH</td>
<td><strong>FGFR1</strong></td>
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<td>MDH2</td>
<td><strong>BRAF</strong></td>
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<td>SLC25A11</td>
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<td>GOT2</td>
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<tr>
<td>IDH1, 2</td>
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Fishbein et al Cancer Cell 2017;31:181-193
Nobel Prize in Physiology/Medicine 2019

“for their discoveries of how cells sense and adapt to oxygen availability”
Hypoxia Inducible Factors (HIFs)

NORMOXIA

HYPOXIA

HIF

Ubiquitinated and degraded

Hypoxia-response gene (e.g. VEGF)

Hypoxia
EPAS1

- Encodes HIF2α
- First associated with PGL in 2012
- Mutations occur ~5-10% of pheos

*EPAS1* (HIF2) is overexpressed in Cluster 1 PPGLs

Even when *EPAS1* gene is not mutated, it is often overexpressed in pheos.

Qin et al Int J Cancer 2014;135:2054-2064
HIF2α inhibitors

- PT2385 in phase 1 trial for renal cancer:
  - Prolonged response in one pt

### Pheo-Para gene clusters

#### Cluster 1
- **“pseudo-hypoxia”**
- VHL
- EPAS1
- PHD1
- IRP
- SDHD
- SDHC
- SDHA
- SDHAF2
- FH
- MDH2
- SLC25A11
- GOT2
- IDH1, 2

#### Cluster 2
- **“kinase”**
- RET
- NF1
- TMEM127
- MAX
- KIF1B
- MET

#### Cluster 3
- **(or 2B) “Wnt altered”**
- MAML3
- CSDE1
- TP53
- HRAS
- MET
- DNMT3A
- BRAF

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**SDHB** accounts for approximately 10% of all PPGL. However, about 40% of metastatic cases involve SDHB.

**SDHB alone is not sufficient for progression**

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**Sporadic**

- Age: 35, 40, 45, 50

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Hamidi et al. JCEM 2017;102:3296–3305
Hescot et al. JCEM 2019; 10.1210/jc.2018-01968
Crona et al. ERC 2019; pii ERC-19-0024.R2
American Australian Asian Adrenal Alliance (A5)
A5 SDHB Genomics Study

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University of Melbourne
A/Prof Oliver Hofmann  
University of Melbourne

A5 Chairs: Gary Hammer and Tobias Else
University of Michigan
Telomere maintenance

- **Telomerase**: enzyme that adds telomeric repeats (TTAGGG) to the 3’ end of chromosomes

- In PPGLs associated with *SDHB*:
  - TERT promoter activation or chromosomal translocation in ~20%
  - alternative lengthening of telomeres (ALT) in ~5%
  - Strong association with metastatic disease

Tothill et al, in preparation
Why are telomere maintenance mechanisms activated by *SDHB* mutations?

- **HIF stabilization**
  - succinate to fumarate
  - Electron transport chain
  - reactive oxygen species
  - SDHA, SDHB, SDHC, SDHD
Connecting SDHB with telomeres

- Understanding **how** *SDHB* is linked to telomere maintenance will identify **targeted** approaches for new treatments
Connecting SDHB with telomeres

- Understanding how $SDHB$ is linked to telomere maintenance will identify targeted approaches for new treatments.
Not just succinate: extending the metabolomic signature of SDHB pheos

- Increase in polyamines
- Blocking these with DENSPM reduced cell growth in vitro and in xenografted mice

Rai et al. Metabolism 2020;110:154297
Agenda #2: Developing **new targeted therapies**

- Slow progress due to:
  - lack of preclinical models
  - Heterogeneity of disease
  - Scarcity
**Existing therapies**

<table>
<thead>
<tr>
<th>Radionuclides</th>
<th>Complete/partial response</th>
<th>Stable disease</th>
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<tr>
<td></td>
<td>Horm</td>
<td>Tumor</td>
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<tr>
<td><strong>131-MIBG</strong></td>
<td>51%</td>
<td>30%</td>
</tr>
<tr>
<td><strong>HSA-MIBG</strong></td>
<td>25%</td>
<td>23%</td>
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<tr>
<td><strong>Lutathera</strong></td>
<td>57%</td>
<td>29%</td>
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<table>
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<tr>
<th>Chemotherapy</th>
<th>Complete/partial response</th>
<th>Stable disease</th>
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<tr>
<td></td>
<td>Horm</td>
<td>Tumor</td>
</tr>
<tr>
<td><strong>CVD</strong></td>
<td>54%</td>
<td>41%</td>
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<tr>
<td><strong>TMZ</strong></td>
<td>-</td>
<td>36%</td>
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<tr>
<td><strong>Sunitinib</strong></td>
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</tbody>
</table>

*not FDA approved

- Most studies retrospective
- **Gene dependent** response to therapy
  - Tailor therapy for *SDHB* patients

References:
- Van Hulsteijn et al Clin Endocrinol 2014;80:487-501
- Niejmeyer et al Clin Endocrinol 2014;81:642-651
- Hadoux et al Int J Cancer 2014;135:2711-2720
- Kong et al JCEM 2017;102:3278-3287
- Fishbein et al Endocr Relat Cancer 2017;24:L51-L55
- Jawed et al Cell Mol Neurobiol 2018;38:1099-1106
- Asai et al Horm Cancer 2017;8:108-118
- Hadoux et al Int J Cancer 2014;135:2711-20
Phaeochromocytoma vs paraganglioma

Phaeochromocytoma

Thoracoabdominal paraganglioma

Head and neck paraganglioma

PGL of organ of Zuckerkandl
Peptide receptor radionuclide therapy in pheo-paras

- Overall results for PRRT in paraganglioma and pheochromocytoma are promising with response rates (SD and PR) of over 60% and long term survival

- $^{177}$Lu-DOTATATE has a favorable risk profile

Kong et al J Clin Endocrinol Metab 2017;102:3278-3287
Lutate in head and neck paragangliomas

- Retrospective analysis of 7 pts with HNPGLs treated with Lutate

- After treatment, all had stable disease; four had reduced tumor

- May be suitable for HNPGLs refractory or unsuitable to surgery and/or radiosurgery
Agenda #3: Detecting PPGL early

- Tumor size is strongly related to risk of metastases
- Detecting PPGL early gives best possible chance of cure

1. Genetic testing of those families at risk
2. Pro-active follow-up of those family members carrying genetic mutation
   - annual biochemical measurements
   - bi-annual rapid whole-body magnetic resonance imaging and/or $^{68}$Ga-DOTATATE-PET imaging
Overview: ticking genetic time bombs

- Hereditary paraganglioma syndromes due to mutations in >12 different genes

- Bespoke care:
  1. Tailored information about personal risk
  2. Early identification of tumours
These ‘rare’ syndromes are more common than we expected

- Using large genetic databases, it is possible to estimate the prevalence of specific genetic conditions

- ~4,000 Australians have hereditary pheochromocytoma (Pheo) mutations
Positive impact of genetic test on the patients outcome

Patients with up to 5 metastases at diagnosis of malignancy

Survival after the diagnosis of first metastasis

Slide courtesy of A-P Gimenez-Roqueplo Buffet et al JCEM 2019;104:1109-1118
Logistic problems of screening

1. Timely diagnosis of heritable basis of PPGL
2. Capture of all family members at risk
3. Regular follow-up for carriers
   1. Cost, radiation, reminders
   2. Action on positive results
4. Evolution of screening protocols

○ PATIENT ENGAGEMENT: avoid “loss to follow-up”
Conclusions

1. Drivers of pheos: **HIFs and telomeres** important targets to inhibit HIFs, telomerase

2. Therapy development: extensive pipelines exist

3. Detecting PPGLs early: feasible in **hereditary** disease

Radionuclide therapy holds promise

Patient engagement Screening protocols
Collaborations and Funding

**Peter Mac**
- Rod Hicks
- **Richard Tothill**
- Aidan Flynn
- Alison Trainer

**QUT**
- Emma Duncan

**SEALS**
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- Talia Novos
- Chris White

**NIH (USA)**
- **Karel Pacak**

**Europe**
- Graeme Eisenhofer
- Mercedes Robledo, M Mannelli

**NZ**
- Mike Croxon, Marianne Elston

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**Hillcrest Foundation**

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**PheoPara Alliance**

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**NHMRC**

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**PARADIFFERENCE Foundation**