

*REALISING THE ROLE OF  
BASIC SCIENCE*  
IN THE  
TRANSLATIONAL RESEARCH CENTRES:

# ARE WE THERE YET?

**Workshop | 17 May 2017**

# ALEXANDER ENGEL



## IN THE TRANSLATIONAL RESEARCH CENTRES:

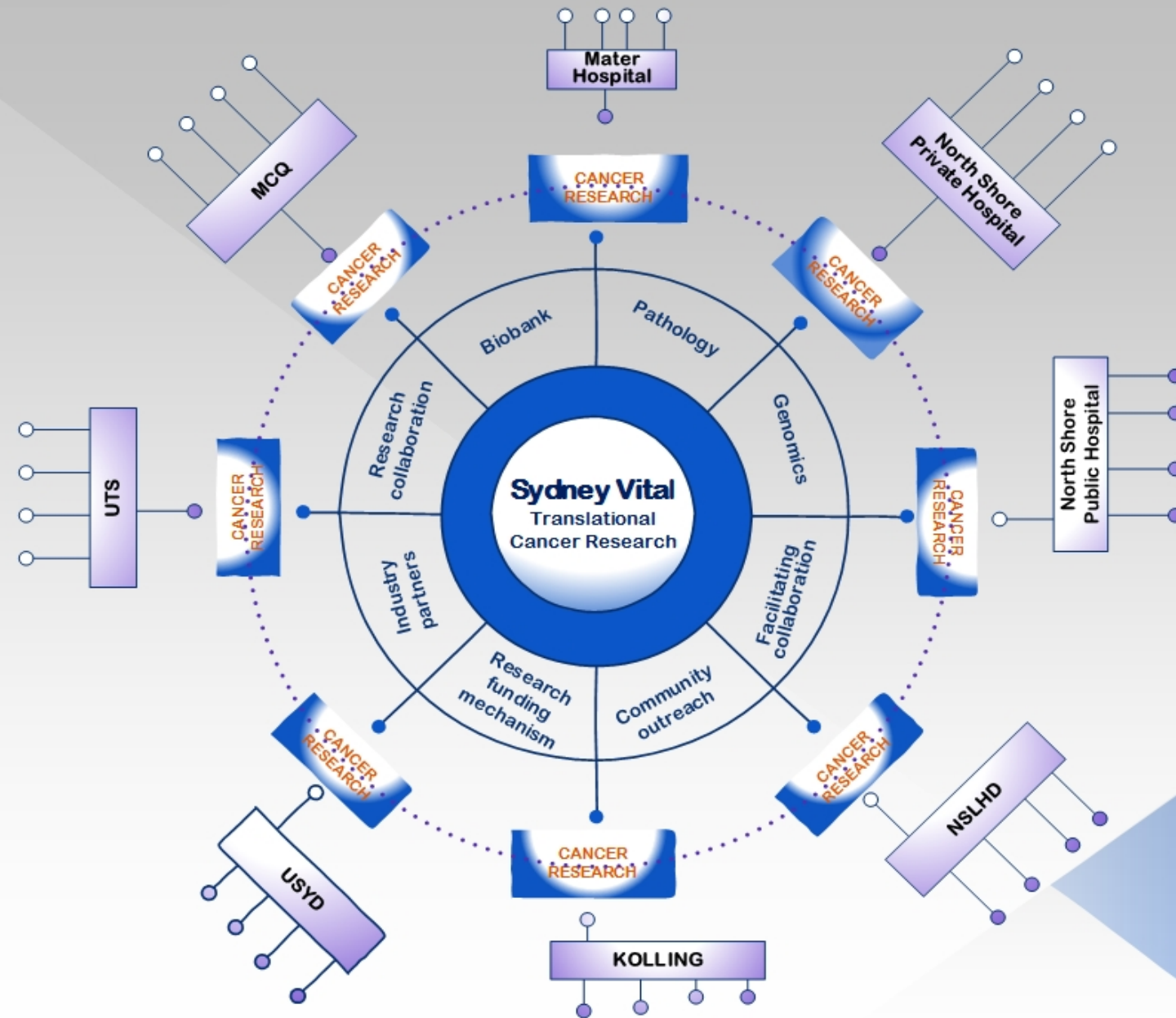
# ARE WE THERE YET?

# Environment



## Location Characteristics

- Northern Sydney Local health District has 12% of NSW cancer patients by incidence and 12% of cancer deaths.
- NSLHD has the vision to integrate clinical services, teaching and research.
- NSLHD has >4,500 new cancer patients MDT predominantly through RNSH and Mater hospital.
- The mixture of public and private treatment facilities characterises the NSLHD





# Overview of Sydney Vital

- **Vision:** Establish Sydney Vital as a competitive network of excellence in conducting collaborative translational research to improve patient outcomes.
- **Mission:** Encourage and promote innovation and collaboration among preclinical and clinical researchers to support cancer research across the translational research pipeline.
- **Objectives:**
  - Enhance collaborations.
  - Build a supportive governance structure.
  - Develop and maintain essential research infrastructure.
  - Build a process to link the right people to do research.
  - Standardize process to identify right questions that align with health priorities.
  - Facilitate comprehensive research training and educational programs.
  - Identify process disseminate research findings and support the implementation of evidence into practice in an efficient manner.

# Key achievements

- **Facilitate evidence into practice**

- Screening of colon cancers and gynaecological cancers for Lynch Syndrome
- PETNET grading system
- Virtual MDTC
- Implementing change through MTDs
- Online risk tool for lymphnode-involvement in malignant colorectal polyps

- **Enhance collaborations**

- Links with other TCRCs
- Links with SPARC
- NSPHN
- SHP (Sydney Health Partners)
- Links with industry partners (Sirtex, AINSE, ANSTO, Ipsen, PETNET, Novartis, EnGeneIC...)



# Key achievements

- **Research infrastructure**
  - Global Informed Consent
  - Biobank pilot
  - Surgical pathology
- REG 2014 NanoString platform (NATA accreditation)
- REG 2015 Mass spectrometry
- REG 2016 Animal Irradiator
- REG 2017 (x2)



# Key achievements

- **Research dissemination**

- Website
- Social medias
- Community events
- GPs events
- Educational events
- Research conferences
- Research symposiums





# Key achievements

- **Membership:** 250 members (40% increased from 2014)
  - 24 PhDs existing + 12 new PhD students,
  - 6 Postdoc Fellows ( 4 existing + 2 new)
- **Leveraged funding:** Increase leveraged funding to \$24.9 million in 2015
- **Publications:** 225 Cat I and II publications in 2015 (40% increased). 282 publications for 2016



# Key achievements

- **Building research capacities**

- Awarded PhD scholarships to students from UTS, MCQU, USYD.
- Awarded Postdocs
- Increased leveraged funding

- **Governance**

- TOR Executives
- TOR for Administration
- CaRE
- Membership recruitment
- Fellowship funding agreement
- Scholarship funding agreement
- Real time Financial report







Liver Cancer Meeting 2016

Lymphoedema with Patie



NETs Charity Event 2016



Cancer Meeting 2016

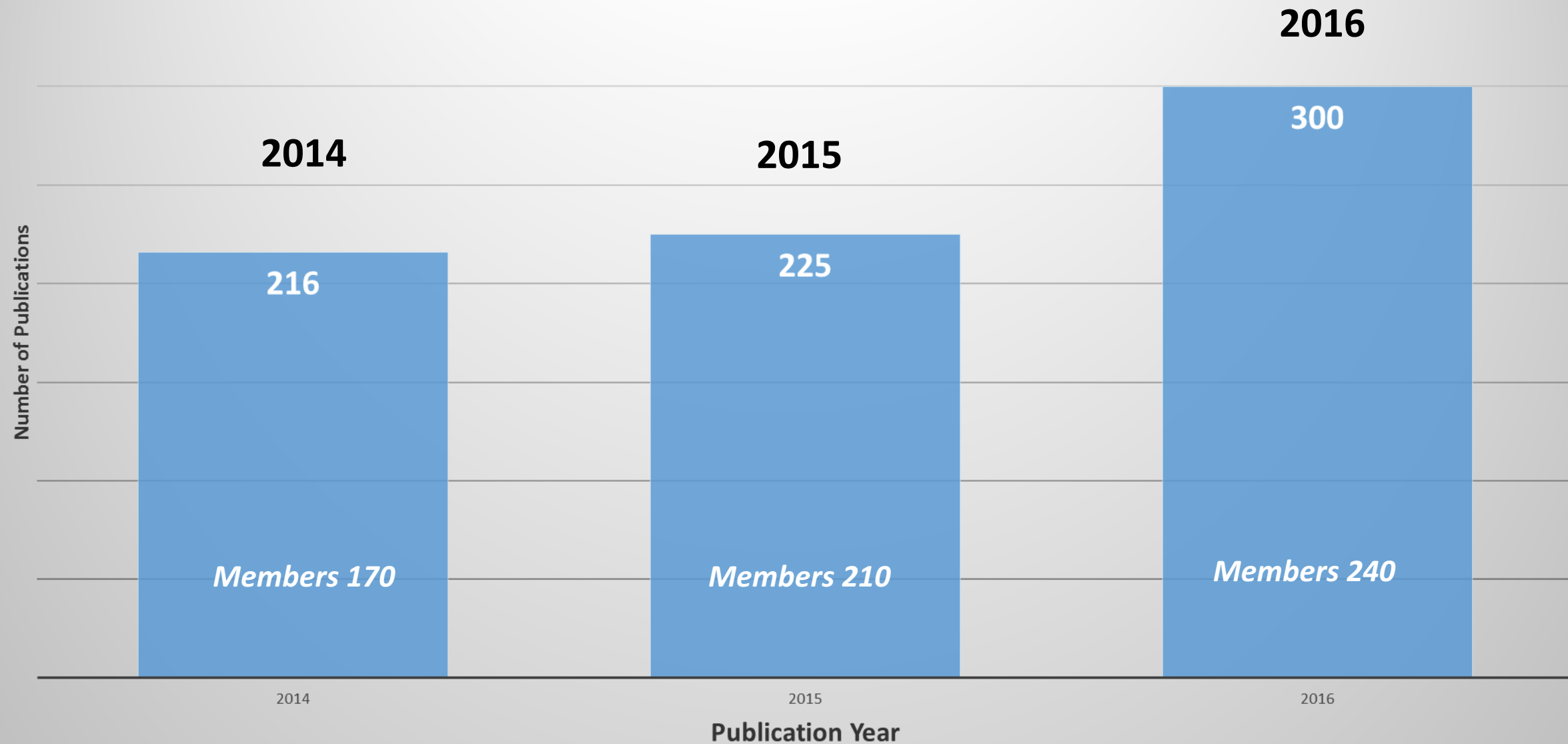


Cancer Meeting with Community 2015



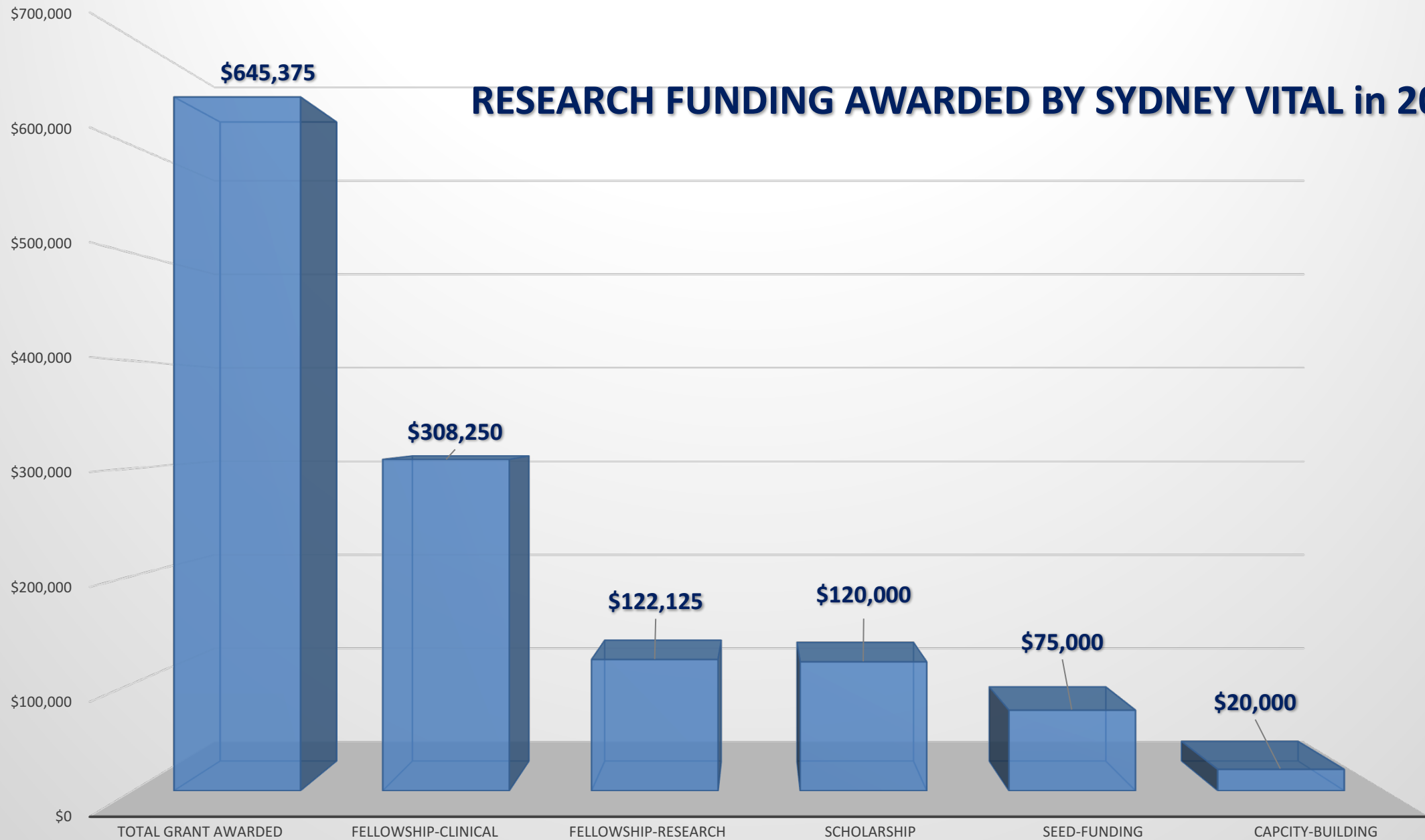
NET Q&A with Patients & Community 2016

# SV Publications





## RESEARCH FUNDING AWARDED BY SYDNEY VITAL in 2015



# Developing theranostic Superparamagnetic Iron Oxide Nanoparticles (SPIONs) for PET/MR and Targeted Radionuclide Therapy (TTR) of lymphatic micrometastases

Presented by

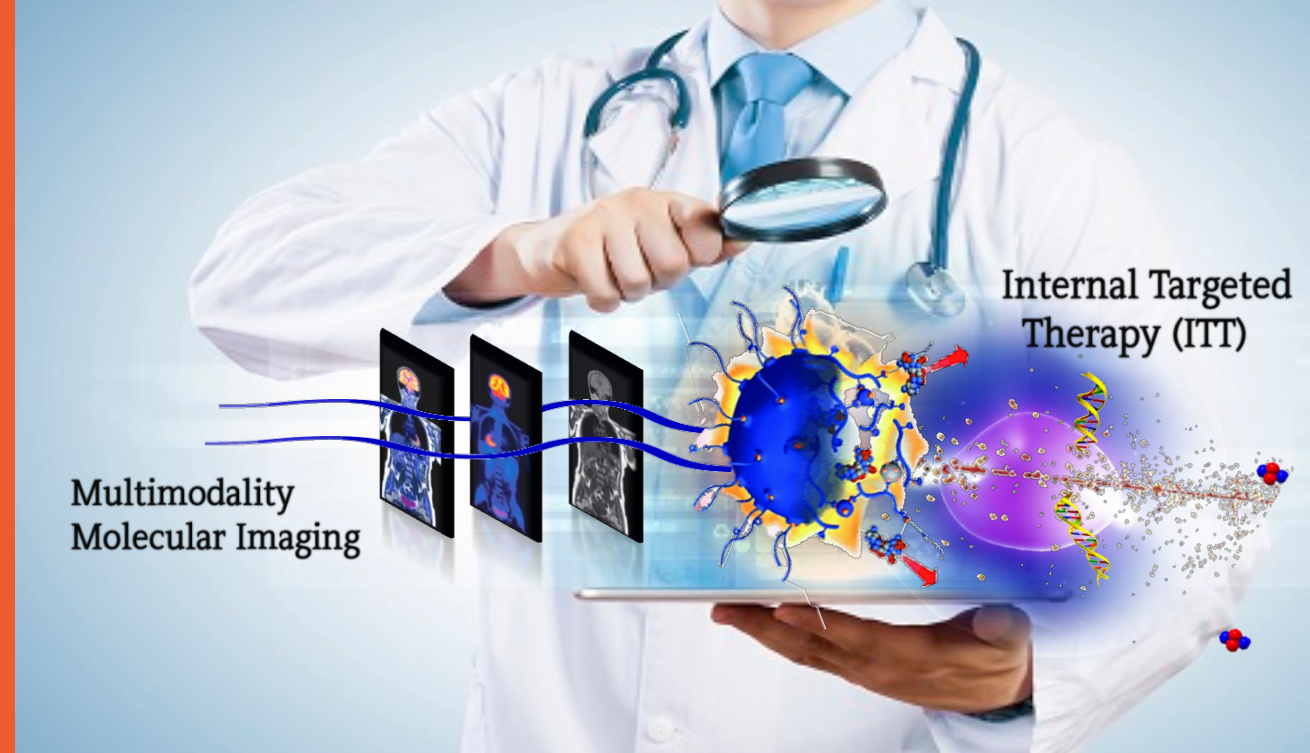
Yaser Hadi Gholami

PhD candidate

29/11/2016

Sydney

CINSW meeting



# Acknowledgement

## ➤ **Sydney Investigators:**

Zdenka Kuncic, PhD, FAIP, University of Sydney

Dale Bailey, PhD, Royal North Shore Hospital and University of Sydney

Steve Meikle, PhD, University of Sydney

Roger Fulton, PhD, Westmead Hospital and University of Sydney

Alexander Engel, MD, PhD, Kolling Institute of Medical Research and University of Sydney

Viive Howell, PhD, Kolling Institute of Medical Research and University of Sydney

Rozelle Harvie, PhD, Kolling Institute of Medical Research and University of Sydney

Brian S. Hawkett, Dr Binh Pham and Dr Nguyen Pham (School of chemistry, University of Sydney).

Richard Thomas Maschmeyer, Honours student, University of Sydney

Nidhi Singla, PhD, Senior Project Officer for the AINST, University of Sydney

## ➤ **MGH Investigators:**

Georges El Fakhri, PhD, DABR

Lee Josephson, PhD

Moses Wilks, PhD

Marc Normandin, PhD

One day it will happen  
©

# Sydney 1000 CRC Study Collaborative Network

University of Sydney with clinical collaborations from Sydney Health Partners hospitals

- Have consolidated a unique multi-disciplinary translational cancer research collaboration
- We are world leaders in cancer research and patient treatment
- We have access to large patient populations
- We possess the ability to translate research findings into new treatments to improve outcomes



# Current researchers in the network

## **Clinical research**

Prof Alexander Engel – Surgery

Prof Anthony Gill – Anatomical Pathology

Prof Stephen Clarke, Prof Nick Pavlakis, Dr Connie Diakos – Medical Oncology

A/Prof Andrew Kneebone, Dr George Hruby – Radiation Oncology

Prof Rod McLeod – Palliative Medicine

## **Translational research**

Dr Kellie Charles – Pharmacology, Immunology, Diet

Dr Haryana Dhillon, Prof Madeleine King – Psychology, QoL, survivorship

Prof Margaret Allman-Farinelli – Diet and nutrition

Prof Adrian Bauman – Physical Activity

Prof Nicholas King, Prof Derek Hart, Prof Barbara Fazekas de St Groth – Immunology

A/Prof Andrew Holmes – Microbiology of gut

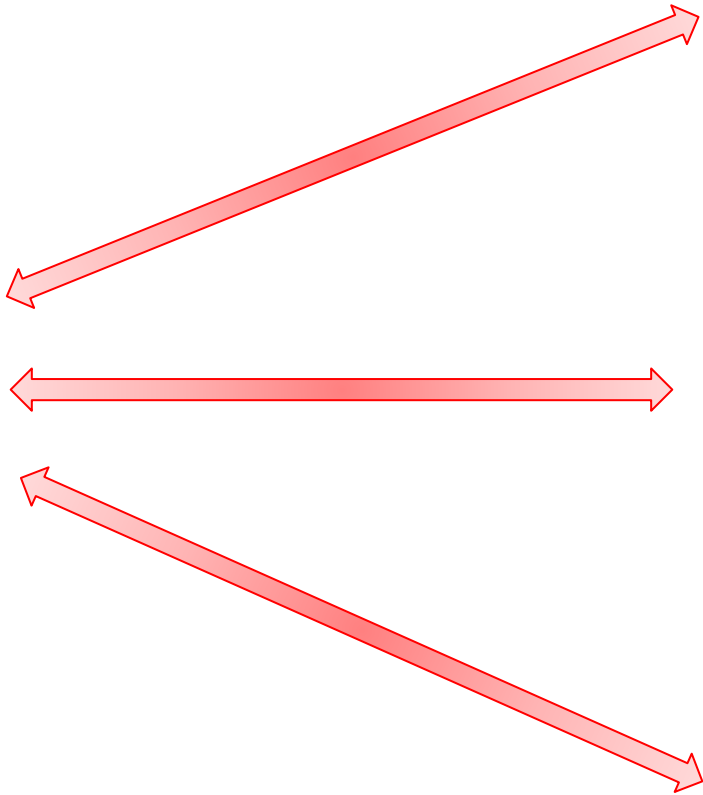
Dr Fatameh Vadee – Bioinformatics

A/Prof Anne Cust – Public Health, cancer epidemiology

New interactions



Kolling  
Tumour  
Bank



**INOVATe**

Individualised Ovarian Cancer Treatment through Integration of Genomic Pathology into Multidisciplinary Care

**Sydney 1000 Bowel Cancer Study**

Transforming the way we treat, care and support bowel cancer patients for future generations



**Health  
Pathology**

# KOLLING REVIEW

## STRENGTHS



7 April 2017

A/Prof Alexander Engel  
Director, Sydney Vital  
Level 8, Kolling Building  
Royal North Shore Hospital  
ST LEONARDS, NSW 2065

Deb Willcox  
Interim Chief Executive  
Northern Sydney Local Health District  
PO Box 4007, Royal North Shore Hospital LPO,  
St Leonards NSW 2065

**Re: The Kolling Institute Strategic Review**

Dear Ms Willcox,

Please find below Sydney Vital's response to the request for a written submission for the Kolling Strategic Review.

What is your relationship with the Institute?

Sydney Vital is a Translation Cancer Research Centre funded by, and answering to, the Cancer Institute NSW for a 5yr period (2014-19). It is co-funded by the University of Sydney, Macquarie University and is based at the Kolling Research Institute. We represent over 250 Cancer Researchers across the University of Sydney, Royal North Shore Hospital, North Shore Private, Kolling Institute, Macquarie University and the University of Technology Sydney. In 2016 SV's Cat I and II members produced some 300 scientific papers (including 16 guideline papers) and leveraged approximately \$17 million dollars in research grants.

What do you think are the Institutes present strengths and weaknesses?

**Strengths**

The Kolling's proximity to a quaternary referral teaching hospital and private hospital provides opportunities for multidisciplinary collaboration. Access to biological specimens, pathology and clinical data is the cornerstone of any translational research program. RNSH has leading Australian expertise in the treatment of certain types of malignancy which has evolved from the close relationships between basic research and clinicians. Some of the strengths noted by our members are;

- NSLHD has second largest incidence of cancer patients in NSW with state of the art treatment and excellent clinical outcomes
- State of the art building with some established core facilities
- Experienced researchers
- Quality undergraduate (MD program) and postgraduate education
- Access to key opinion leaders
- Global consent across public and private
- Access to clinical data, mature biobank facility and surgical pathology

T: (02) 99264726

[sydneyvital.admin@sydney.edu.au](mailto:sydneyvital.admin@sydney.edu.au)

[www.sydneyvital.org.au](http://www.sydneyvital.org.au)

- Second largest incidence of cancer patients in NSW
- State of the art clinical facilities and outcomes
- Experienced researchers
- Quality undergraduate (MD) and postgraduate education
- Access to key opinion leaders
- Global consent across public and private
- Mature biobank facility and extensive surgical pathology resource

# KOLLING REVIEW

## WEAKNESSES



7 April 2017

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Director, Sydney Vital  
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ST LEONARDS, NSW 2065

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- Isolation from University Sydney campus (deliberate?)
- Local health district clinical and research agenda are not aligned
- Lack of integration between clinical data, biospecimens and surgical pathology
- Dilution of resources due to trying to encompass "all" research within the LHD
- Lack of transparency in philanthropic funding
- No strategic vision to invest and divest
- Inadequate infrastructure support for core facilities
- Inadequate administrative support
- Differences related to IT, HR and financial management between LHD and University Sydney



# KOLLING REVIEW

## SOLUTIONS



7 April 2017

A/Prof Alexander Engel  
Director, Sydney Vital  
Level 8, Kolling Building  
Royal North Shore Hospital  
ST LEONARDS, NSW 2065

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- Build synergy between University and LHD based on strengths ie. Research based on clinical questions
- Strong and budgeted commitment from University and LHD
- Attract health economics, epidemiology and bioinformatics at the Kolling
- Financial support for tenured research positions, infrastructure and facility management
- Transparent process to disperse philanthropic funding
- Develop the Kolling brand and promote our successes to the wider community
- Foster community engagement (fundraising)
- Promote interaction and collaboration between disciplines
- Adopt an operational attitude

# Translational Research Capacity



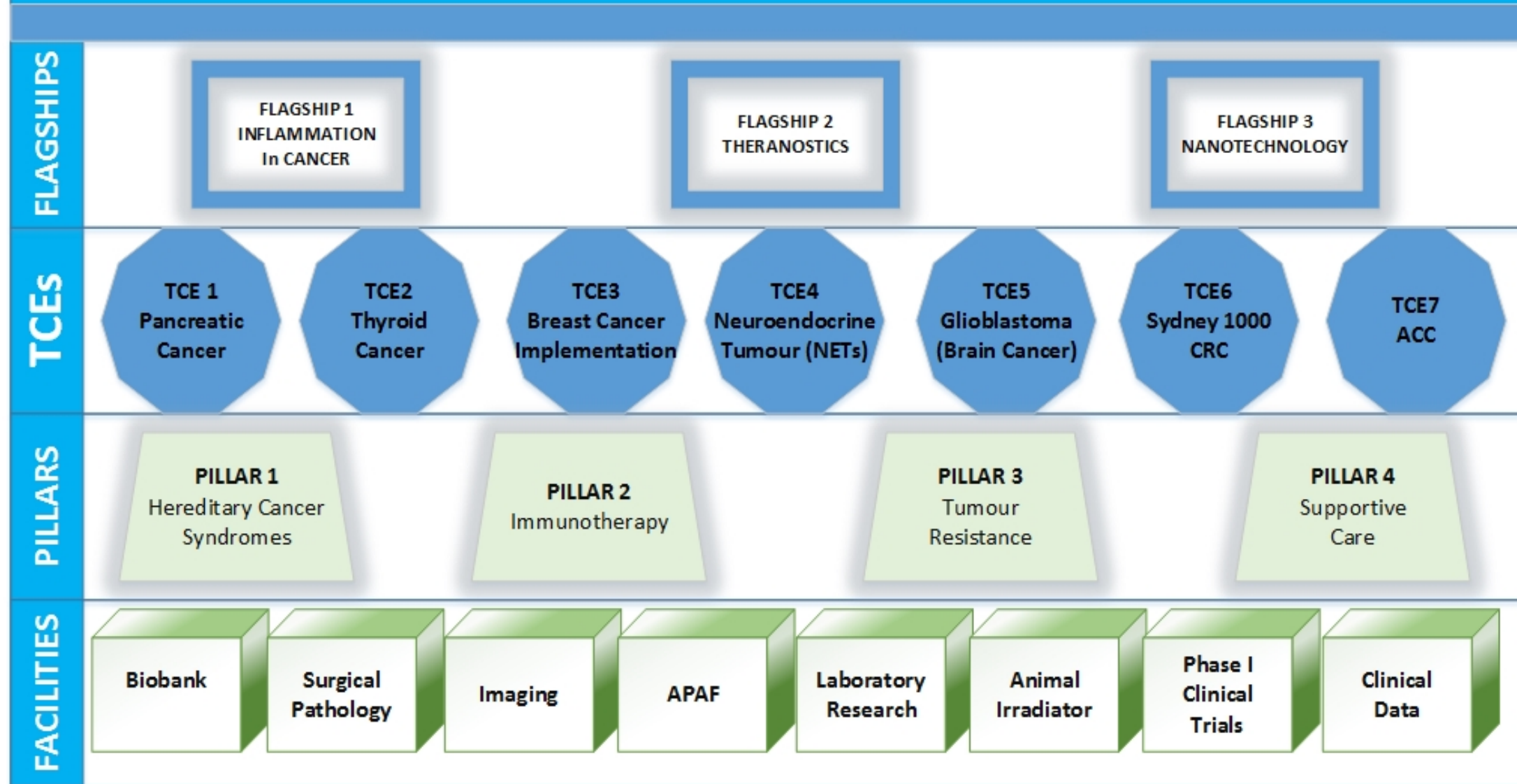
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graph TD; A[Translational Research Capacity] --> B((Clinical Centres of Excellence)); A --> C((Biospecimens)); A --> D((Surgical Pathology));
```

Clinical  
Centres of  
Excellence

Biospecimens

Surgical  
Pathology

# SYDNEY VITAL RESEARCH PLAN 2017-19



# WHAT DO HEALTHCARE PROVIDERS WANT?



## KEY NOTE

**NIK ZEPS**

GROUP DIRECTOR  
OF RESEARCH,  
EPWORTH HEALTHCARE

# Why do Health and Medical Research?



**Effective and efficient Healthcare is founded upon evidence created by research**

**Improvements in healthcare delivery can only be achieved through research**

**Research is therefore integral to healthcare delivery**

**14. Accelerate Health System Innovation.** Accelerate research translation and health system innovation.

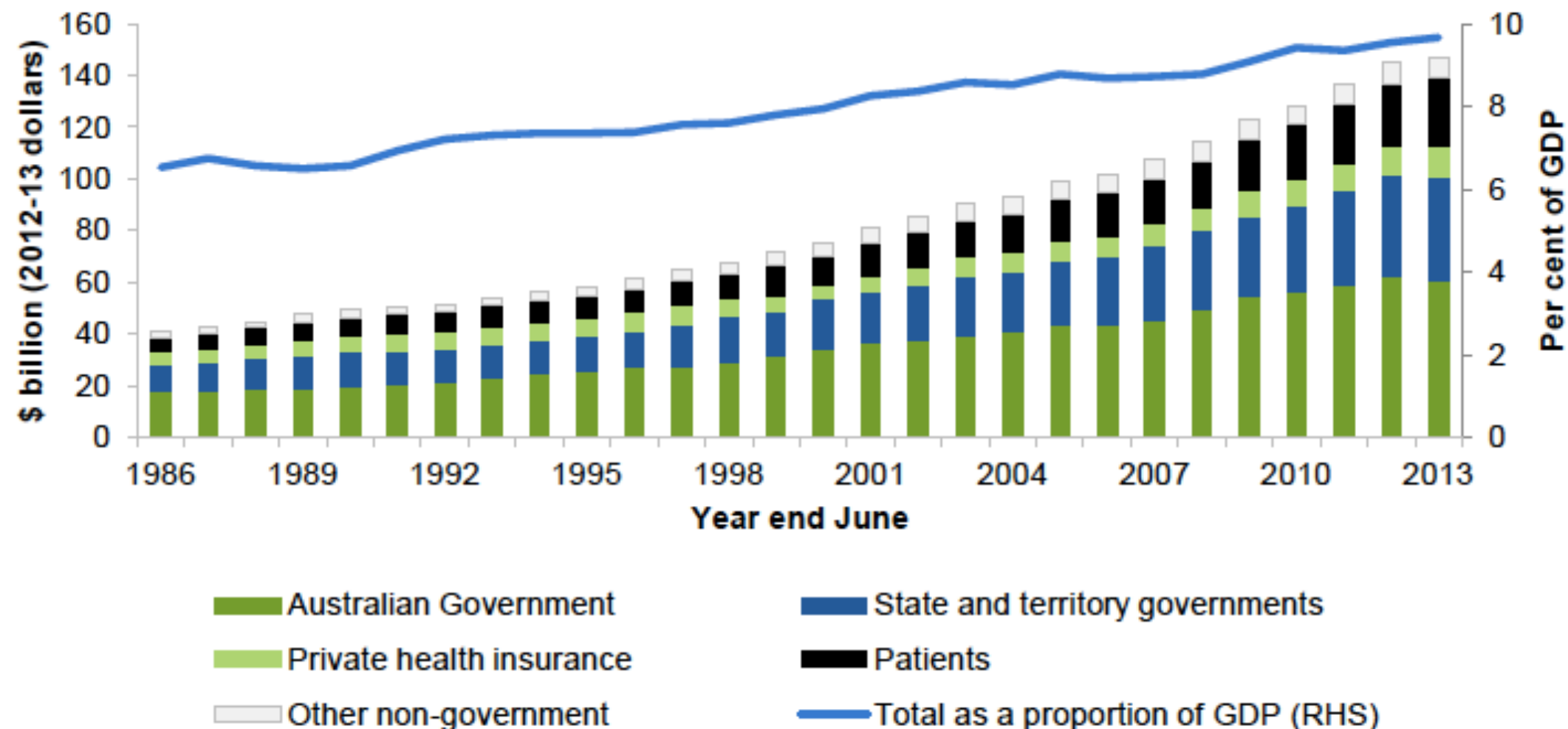
- a. Provide incentives to generate clinically-relevant research.
- b. Ensure guidelines have an implementation plan and encourage wider communication.
- c. Provide funding for non-commercial clinical trials based on potential to deliver impact.

**15. Inform Policy with Evidence.** Inform health policy and practice with research evidence.

- a. Enhance the capability of NHMRC and researchers to support policy makers.
- b. Encourage the embedding of researchers within government policy departments.
- c. Conduct research on gaps between health policy and practice, and the evidence base.



Figure 1.1 Australia's health expenditure



Data source: AIHW (2015a).





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Australian Government  
Productivity Commission

## Efficiency in Health

Productivity Commission  
Research Paper

April 2015

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## Opportunities for efficiency gains in the Australian health care system

<i>Opportunities, reform actions and responsibilities</i>	<i>Timeframes</i>	<i>Outcomes</i>
<b>Health technology assessment</b>		
<b>Australian Government Minister for Health to:</b>		
<ul style="list-style-type: none"> <li>• accelerate work to review existing MBS and PBS items — giving priority to high-cost items that have not been subject to economic evaluation, or for which the benefits are relatively uncertain — reduce or remove subsidies where appropriate, and report on progress annually</li> <li>• review and revise Australia's system for health technology assessment (HTA), with a focus on reducing unnecessary duplication and fragmentation, improving disinvestment mechanisms (giving consideration to the merits of an independent decision maker), and deterring clinicians from using MBS and PBS items in circumstances where they are not clinically and cost effective</li> <li>• share Australian Government HTA assessments with the states and territories</li> </ul>	<ul style="list-style-type: none"> <li>• Immediate</li> <li>• Within 1 year</li> <li>• Immediate</li> </ul>	<ul style="list-style-type: none"> <li>• Treatments that are not clinically or cost effective — or that are harmful to patients — are not subsidised</li> <li>• Patients potentially have greater access to higher-value health interventions</li> <li>• HTA processes achieve objectives at least cost</li> </ul>
<b>Evidence-based guidance for clinicians</b>		
<b>Australian Government Minister for Health</b> to establish expert panels of clinicians to assess and endorse clinical guidelines, and to advise on dissemination, implementation and review	<ul style="list-style-type: none"> <li>• Within 1 year</li> </ul>	<ul style="list-style-type: none"> <li>• Better informed health professionals, fewer adverse events and less waste</li> </ul>
<b>Provider payment models</b>		
<ul style="list-style-type: none"> <li>• <b>Independent Hospital Pricing Authority</b> to introduce a quality and safety dimension to pricing within activity-based funding, subject to current work confirming the feasibility of doing so</li> <li>• <b>Australian, state and territory health ministers</b> to trial and evaluate new payment models</li> <li>• A comprehensive review of the Australian health care system — instigated by the <b>Australian Government Minister for Health</b> — would provide an opportunity to investigate ways to better align financial incentives with health policy objectives</li> </ul>	<ul style="list-style-type: none"> <li>• Within 2 years</li> <li>• Ongoing</li> <li>• Review can commence immediately</li> </ul>	<ul style="list-style-type: none"> <li>• Safer and higher quality hospital services</li> <li>• More coordinated patient care, especially in primary care</li> </ul>
<b>Preventive health</b>		
<ul style="list-style-type: none"> <li>• <b>Australian, state and territory governments</b> to routinely trial and evaluate prevention initiatives</li> <li>• Options to strengthen incentives for cost-effective investment in preventive health to be considered as part of a comprehensive review of the health care system</li> </ul>	<ul style="list-style-type: none"> <li>• Ongoing</li> <li>• Review can commence immediately</li> </ul>	<ul style="list-style-type: none"> <li>• Cost-effective investment in preventive health</li> </ul>

(continued next page)



# Exploring Healthcare Variation in Australia:

Analyses Resulting  
from an OECD Study





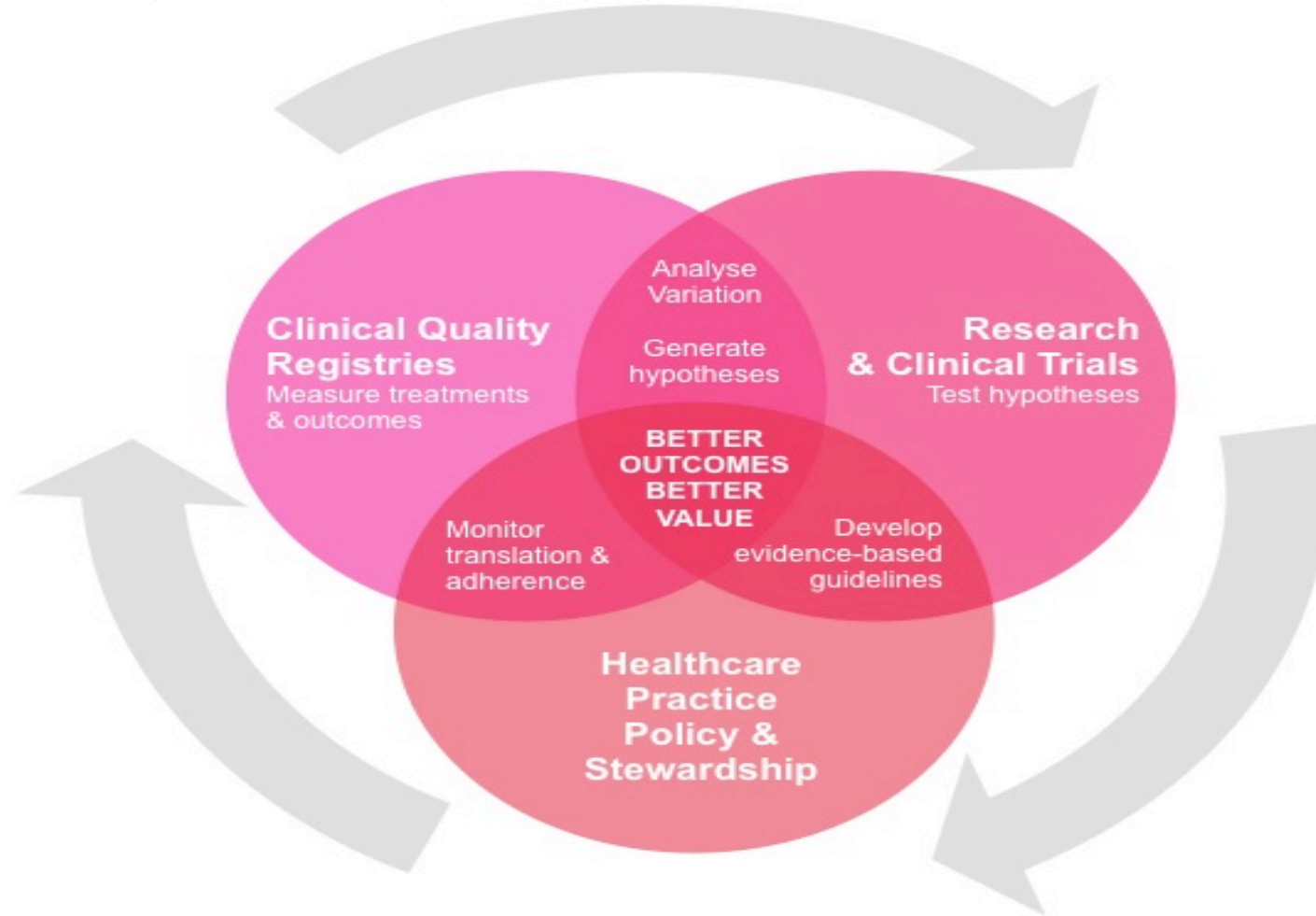
# Key Points

- Addressing the silent and prohibitively expensive epidemic of unwarranted variation in healthcare, is an urgent imperative for Governments and for the payers and providers of healthcare.
- The strategy to reduce unwarranted variation in healthcare must include the infrastructure necessary to *systematically*
  - IDENTIFY unwarranted variation
  - INTERPRET unwarranted variation
  - RESPOND to unwarranted variation

- The systematic identification, interpretation and response to unwarranted variation requires a 'self-improving' healthcare system. Such a system combines
  - - the accurate collection of treatment and outcome data,
  - - the capacity to analyse these data to provide meaningful feedback to clinicians and providers, and
  - - the capacity to undertake robust clinical trials that provide definitive answers to important clinical questions that arise from understanding these variations



# Inter-disciplinary Approach



With permission- Steve Webb. Blood CRE



Australian Government



Medical Research  
**Future Fund**



**AUSTRALIAN MEDICAL RESEARCH  
AND INNOVATION STRATEGY  
2016-2021**

**FIGURE 1. BUILDING BLOCKS FOR THE AUSTRALIAN HEALTH AND MEDICAL RESEARCH AND INNOVATION STRATEGY**

**CURRENT CHALLENGES**

Facilitate the translation of research into health outcomes	Research universally embedded across the health system	Maximise productivity within the health and research system	Reduce barriers to collaboration	Support research and innovation from concept to delivery	Enhance and sustain research enabling technologies, infrastructure and workforce	Continuous improvement and efficiency in healthcare delivery
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**AIMS AND OBJECTIVES**

An excellent and responsive health and medical research system that improves lives.

Preventions and cures of tomorrow	Leveraging and enhancing collaboration and integration	A balanced and appropriately skilled workforce
Economic benefits	A translation pathway that maximises opportunities for success	A research engaged workforce
Sustainable, high-quality, cost-effective health care	Healthcare policy and delivery have a strong evidence base	Contemporary infrastructure that meets research needs

**MANDATORY CONSIDERATIONS**

Burden of disease on the Australian community	How to deliver practical benefits from medical research and medical innovation to as many Australians as possible	How to ensure that financial assistance provides the greatest value for all Australians	How to ensure that disbursements complement and enhance other assistance provided to the sector
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**KEY INTERACTIONS AND STAKEHOLDERS**

National Health and Medical Research Council	Industry, philanthropy, the taxation system and other grants	National Innovation and Science Agenda	National Science and Research Priorities	State and territory health and medical research initiatives	The health system - medical workforce, hospitals	Commonwealth Health Portfolio priorities	Health and medical researchers	Consumers
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## THE STRATEGY

The Medical Research Future Fund (MRFF) is a \$20 billion vehicle for investment in health and medical research. It represents the single largest boost to research funding in Australia's history. The net earnings from the MRFF will serve as a permanent revenue stream, which when fully capitalised, is expected to disburse around \$1 billion annually, effectively doubling the Australian Government's direct investment in health and medical research and innovation.

This first five-year *Australian Medical Research and Innovation Strategy 2016-2021* (the Strategy) prepared by the Australian Medical Research Advisory Board (Advisory Board) sets out the vision, aims and objectives for the MRFF. It identifies a

series of strategic platforms that, if funded, have potential for greatest impact. These platforms will serve as a framework for the two-yearly identification of the *Australian Medical Research and Innovation Priorities* (the Priorities), the first of which accompany this Strategy.

In accordance with the *Medical Research Future Fund Act 2015* (the Act), the Australian Government must take into account the Priorities that are in force at the time of making disbursements from the MRFF. The Advisory Board has constructed the Priorities as a document that should be read and considered in conjunction with the Strategy as there is alignment with the strategic platforms.

### Vision

A health system fully informed by quality health and medical research.

### Aim

Through strategic investment, to transform health and medical research and innovation to improve lives, build the economy and contribute to health system sustainability.

### Objectives

- Create health and economic benefits from research discoveries and innovations
- Embed research evidence in healthcare policy and in practice improvement
- Drive collaboration and innovation across the research pipeline and healthcare system
- Strengthen transdisciplinary research collaboration
- Provide better access to research infrastructure
- Maximise opportunities for research translation by engaging with consumers

- Position the research sector and health system to tackle future challenges
- Facilitate the commercialisation of great Australian research
- Demonstrate the value and impact of research investment

### Strategic platforms

- Strategic and international horizons
- Data and infrastructure
- Health services and systems
- Capacity and collaboration
- Trials and translation
- Commercialisation

### Impact measurement

- Better patient outcomes
- Beneficial change to health practices
- Evidence of increased efficiency in the health system
- Commercialisation of health research outcomes
- Community support for the use of and outcomes from funding

## Research in practice

There are barriers and disincentives that impede research within the healthcare sector itself. Historically, teaching, training and research resources have been block funded, with their utility neither measured nor fully appreciated. Research is frequently viewed as an 'added cost' easily redirected towards

urgent activity demands.<sup>17</sup> Often, ability and reputation of an institution to undertake world-class research depend on the administration appreciating the benefits for patients, for staff recruitment and retention, and for health outcomes more broadly. Similar experience is evident in the primary care sector, where private business models based on care transactions have limited capacity to embed research in practice. These pressures must be addressed so that the potential for research translation is realised.



**OVARIAN CANCER:  
BASIC RESEARCH  
EMBEDDED IN  
MULTI-DISCIPLINARY  
CANCER CARE**



**CASE  
STUDY**

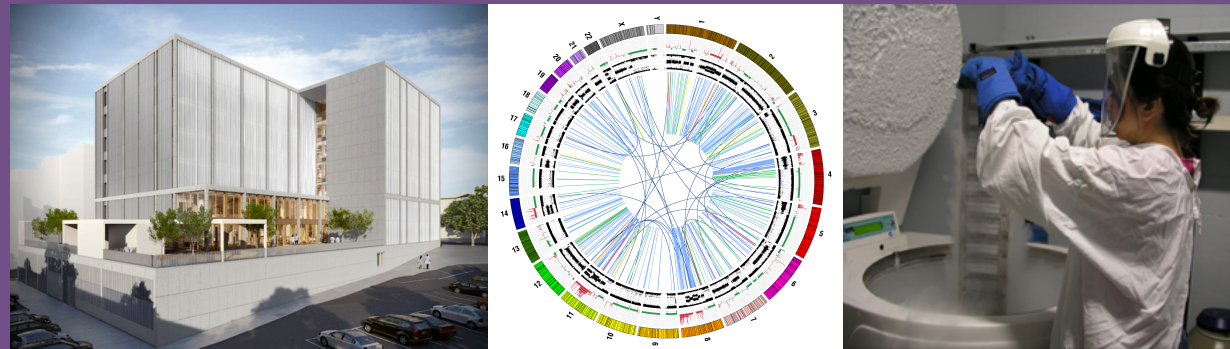
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**ANNA DeFAZIO**

**SYDNEY WEST CHAIR IN  
TRANSLATIONAL CANCER  
RESEARCH**

# Ovarian Cancer:

*Basic research embedded in multi-disciplinary cancer care*



SYDNEY MEDICAL SCHOOL

Anna DeFazio

*Cancer Implementation Science Community of Practice  
17 May, 2017*



THE UNIVERSITY OF  
**SYDNEY**



THE CROWN PRINCESS MARY  
CANCER CENTRE, WESTMEAD



The  
Westmead  
Institute  
FOR MEDICAL RESEARCH







THE UNIVERSITY OF  
**SYDNEY**

# Gynaecological Cancer Research at Westmead



## Patient Care, Clinical Trials

Crown Princess Mary Cancer Centre  
Westmead Hospital

## Laboratory Research

Westmead Institute for Medical Research  
University of Sydney

Multicentre studies:  
AOCs, ICGC, INOVATe



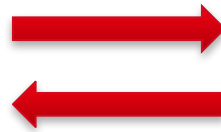
# Translational cancer research

*Translational research through embedding research in multi-disciplinary cancer care*  
**- the experiment.....**

## Hypothesis

Embedding basic research in clinical care will lead to

- translation of significant clinical problems into research questions
- rapid translation of research results into improved clinical care

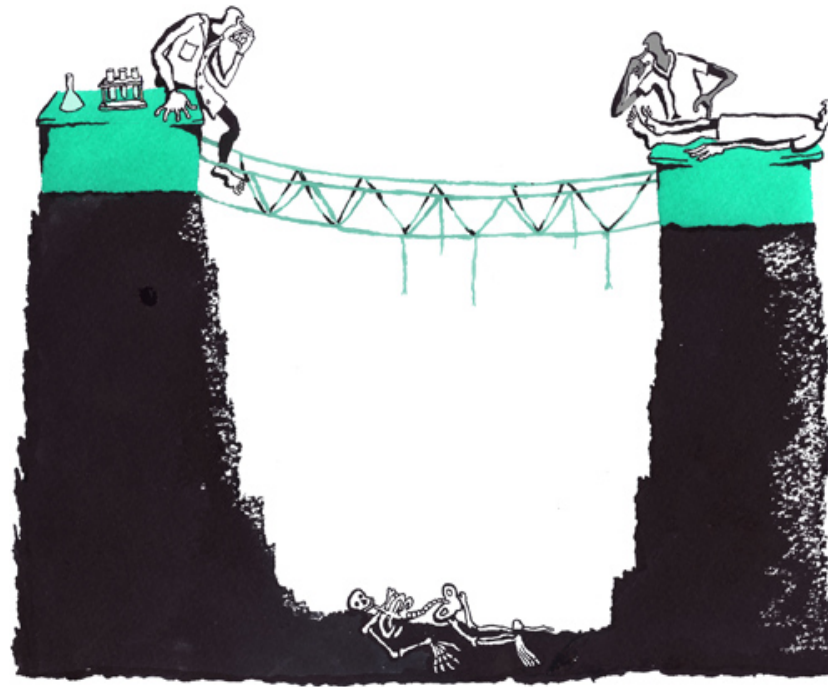




## *Translational cancer research*

*Translational research through embedding research in multi-disciplinary cancer care*  
**- the experiment...**

### **Background**



*Translational research - the valley of death!*



## *Translational cancer research*

*Translational research through embedding research in multidisciplinary cancer care*  
**- the experiment...**

### **Aim**



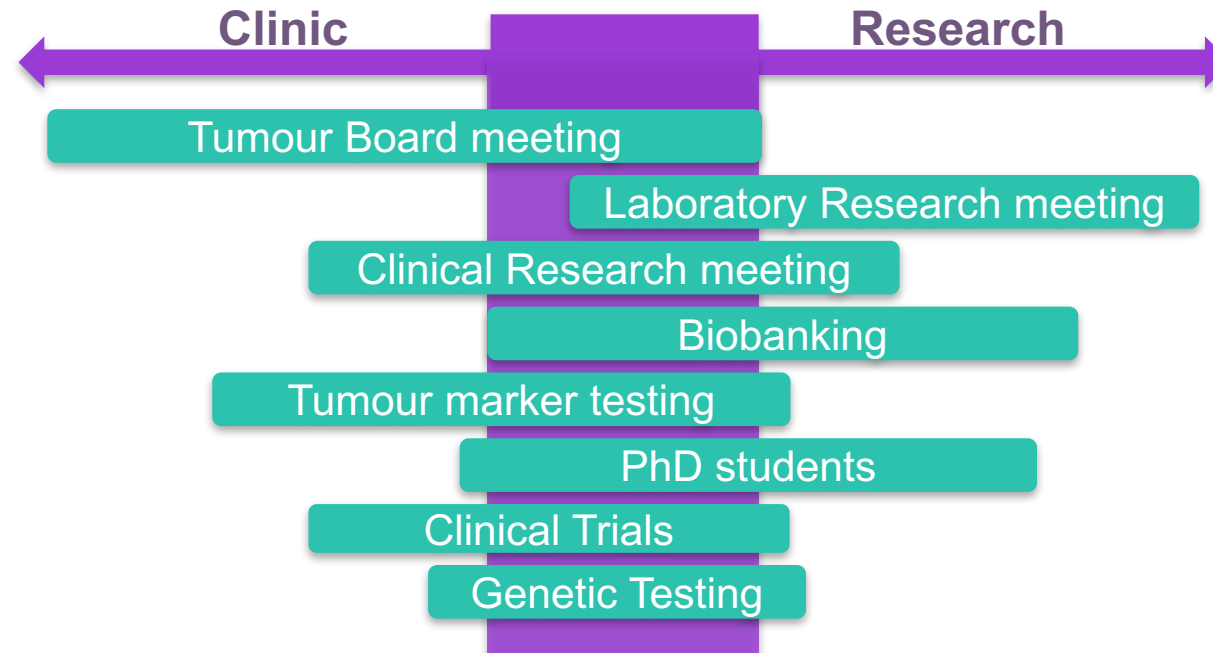


# Translational ovarian cancer research

*Translational research through embedding research in multidisciplinary cancer care  
- the experiment...*

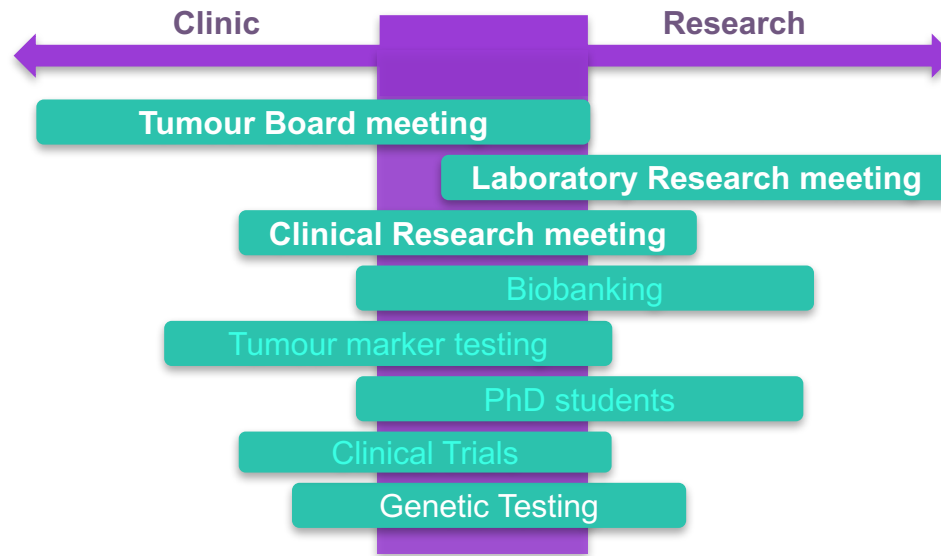
## Methods

1. **Recruit participants:** willing researchers, willing clinicians
2. Spectrum of research, interwoven with clinical care





# Collaboration between the laboratory and the clinic



## Tumour Board Meeting

- Significant research questions
- Contribute additional clinical information
- Patient recruitment, biobanking, clinical data collection
- *Challenges:* time frames, terminology
- Molecular Tumour Board



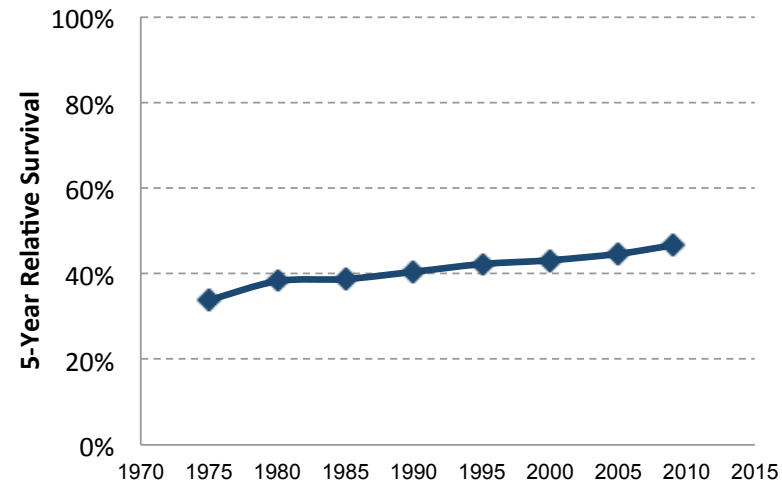
Surgeons  
Pathologists  
Medical Oncologists  
Radiation Oncologists  
**Research staff**  
Nursing staff  
Social worker  
Psychologist  
Familial cancer team  
Clinical trials coordinator





# Ovarian cancer

- Most often advanced, widespread disease at diagnosis
- Most women (~70%) are initially responsive to treatment, but development of acquired resistance is common
- Survival is slowly increasing, but remains <45%

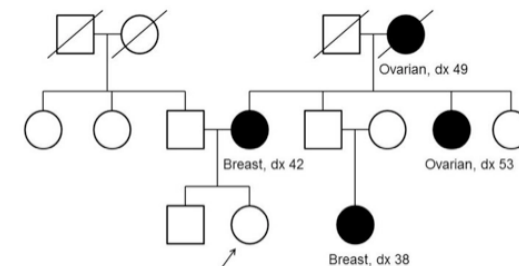


# Ovarian Cancer Risk

## Background

- Inherited mutations in *BRCA* genes and mismatch repair genes increase ovarian cancer risk - 1994
- 5-10% of ovarian cancer were thought to be familial
- Recommendation for referral to Familial Cancer Clinic for genetic testing: women with a family history of breast or ovarian cancer
- Actual rate of *BRCA1/2* mutation in Australian women was not known
- Why is it important? - prevention, treatment

Classic *BRCA1* Pedigree





## Translational research: *BRCA1/2 mutation testing*

2012  
*BRCA* mutation  
frequency - basic  
lab research

- *BRCA1/2* mutation frequency in >1,000 women in the Australian Ovarian Cancer Study
- Overall mutation frequency of 14.1% in the Australian ovarian cancer population
- 16.6% of patients with serous cancer (**17.1%** high-grade serous cancer)
- **44%** of mutation carriers had no evidence of a family history



# Translational research: *BRCA1/2 mutation testing*



- New EviQ Screening Guidelines: referral for almost all women with ovarian cancer regardless of family history ( $\leq 70$ )
- Rapid translation - Familial Cancer Clinics, clinicians as well as researchers involved from inception

## Genetic Testing for Heritable Mutations in the BRCA1 and BRCA2 Genes



ID: 000620 (V.4) Approved: 13 Aug 2010 Last Modified: 10 Mar 2017 Review Due: 03 Mar 2017

### c) based on ovarian cancer characteristics

- individuals with isolated high grade (grades 2 & 3), invasive, non-mucinous epithelial ovarian, fallopian tube or primary peritoneal cancer diagnosed  $\leq 70$  years
- individuals with invasive high grade (grades 2 & 3), non-mucinous epithelial ovarian, fallopian tube or primary peritoneal cancer diagnosed at any age when there is a family history of breast or ovarian cancer in a close relative\*
- individuals with invasive epithelial ovarian, fallopian tube or primary peritoneal cancer that has high grade (G2/3) serous histology or a high grade (G2/3) serous component AND meets [MBS criteria](#) for BRCA1/2 testing

Alsop *et al* J Clin Oncol 2012; 30: 2654-63

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

### *BRCA* Mutation Frequency and Patterns of Treatment Response in *BRCA* Mutation-Positive Women With Ovarian Cancer: A Report From the Australian Ovarian Cancer Study Group

Kathryn Alsop, Stan Fereday, Cliff Meldrum, Anna deFazio, Catherine Emmanuel, Joshy George, Alexander Dobrovic, Michael J. Birrer, Penelope M. Webb, Colin Sewart, Michael Friedlander, Stephen Fox, David Bowtell, and Gillian Mitchell



# Translational research: *BRCA1/2* mutation testing



- Practice changing internationally
- Uptake not equivalent in all centres
- Implementation strategies needed - Spaced education for clinicians, referrals at MDTs, Mainstreaming, Traceback





# Translational research: *BRCA1/2* mutation testing



- Practice changing internationally
- Uptake not equivalent in all centres
- Implementation strategies needed - Spaced education for clinicians, referrals at MDTs, Mainstreaming, Traceback



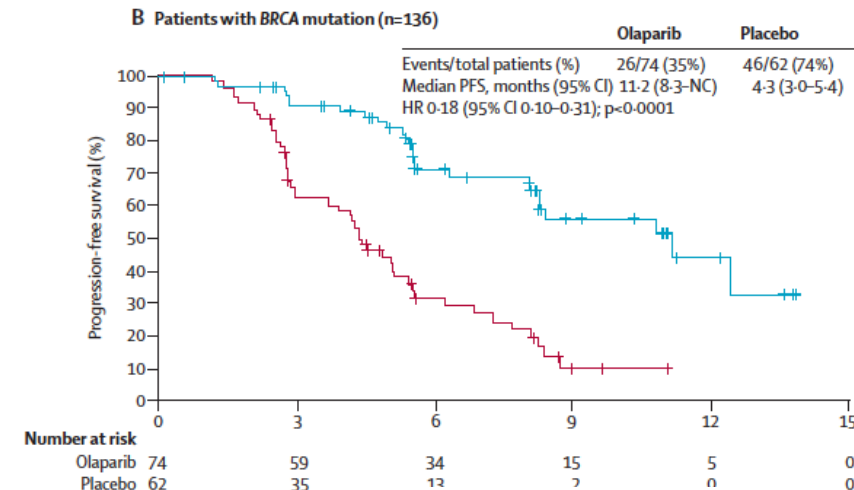
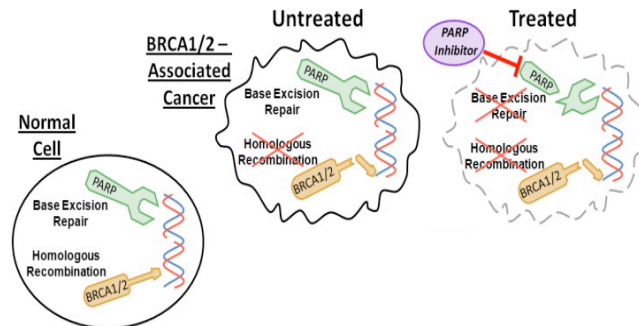




# Translational research: *BRCA1/2* mutation testing



- *BRCA1/2* carriers: response to platinum-based chemotherapy - eg carboplatin, mainstay of ovarian cancer treatment
- New treatment options - PARP inhibitors



Lancet Oncol 2014; 15: 852-61



# Translational research: *BRCA1/2* mutation testing



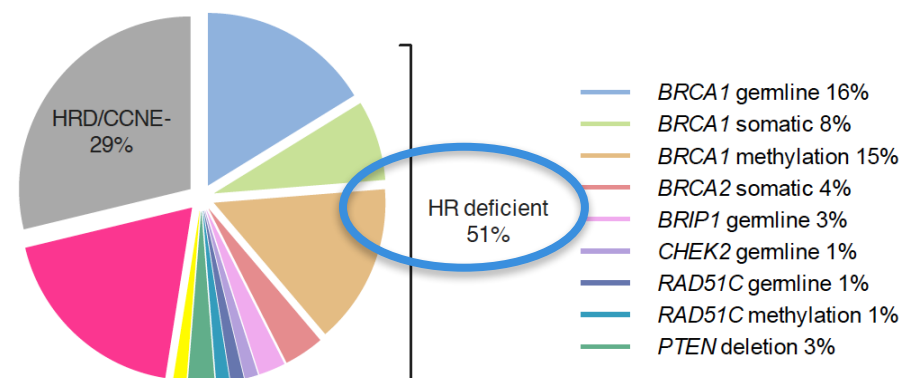
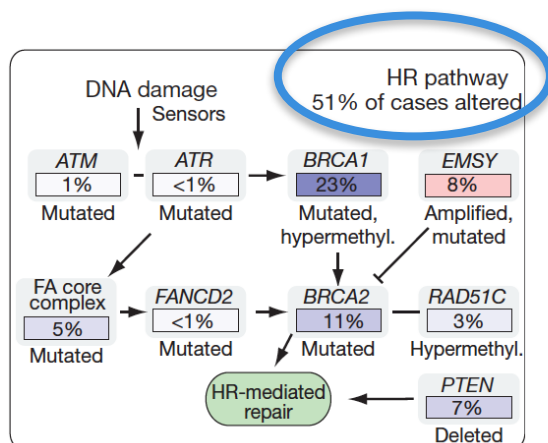
2017 - Olaparib now available on the Australian Pharmaceutical Benefits Scheme for *BRCA*-germ-line carriers with platinum-sensitive relapsed disease - AOCS data

Back to basic research

- Resistance mechanisms
- Beyond *BRCA*

# High-grade serous ovarian tumours - homologous repair (HR) pathway

*BRCA1/2* and homologous repair pathway dysfunction ~50% in high-grade serous cancer: sensitivity to platinum and PARP inhibitors



**The Cancer Genome Atlas (TCGA) 2012**  
*Nature*; Ciriello *et al.*, 2013 *Nat Genetics*

**Whole genome sequencing: International Cancer Genome Consortium (ICGC)** Bowtell, deFazio and Grimmond labs. Patch *et al Nature* 2015

Somatic panel mutation testing / HRD assays to predict response

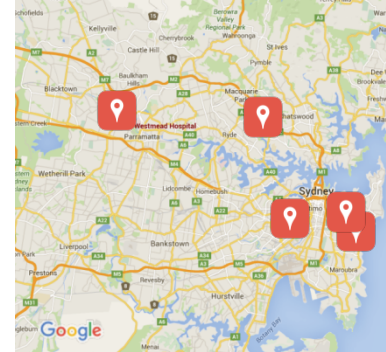


# INOVATe

## Individualised Ovarian Cancer Treatment Through Integration of Genomic Pathology into Multidisciplinary Care

### Westmead / Blacktown / Nepean

**Anna deFazio, Rosemary Balleine, Paul Harnett, Alison Brand, Yoke-Eng Chiew, Bo Gao, Catherine Kennedy, Kristina Lindemann, Cristina Mapagu, Oksana Mirochnik, Pamela Provan, Robyn Sayer, Raghwa Sharma, Annie Stenlake, Dashni Srirangan, Jessica Boros, Casina Kan, Nikilyn Nevins, Svetlana Pianova, Ying Lei, Amy Jamieson, Cecile Bergzoll, Jenny Shannon, Amanda Stevanovic, Amir Hadji ...**



### Royal North Shore / North Shore Private

**Deborah Marsh, Sally Baron-Hay, Gregory Gard, Russell Hogg, Jayne Maidens, Sue Valmadre, Connie Diakos, David Nevell, Kat Phillips...**

### Royal Hospital for Women / Prince of Wales

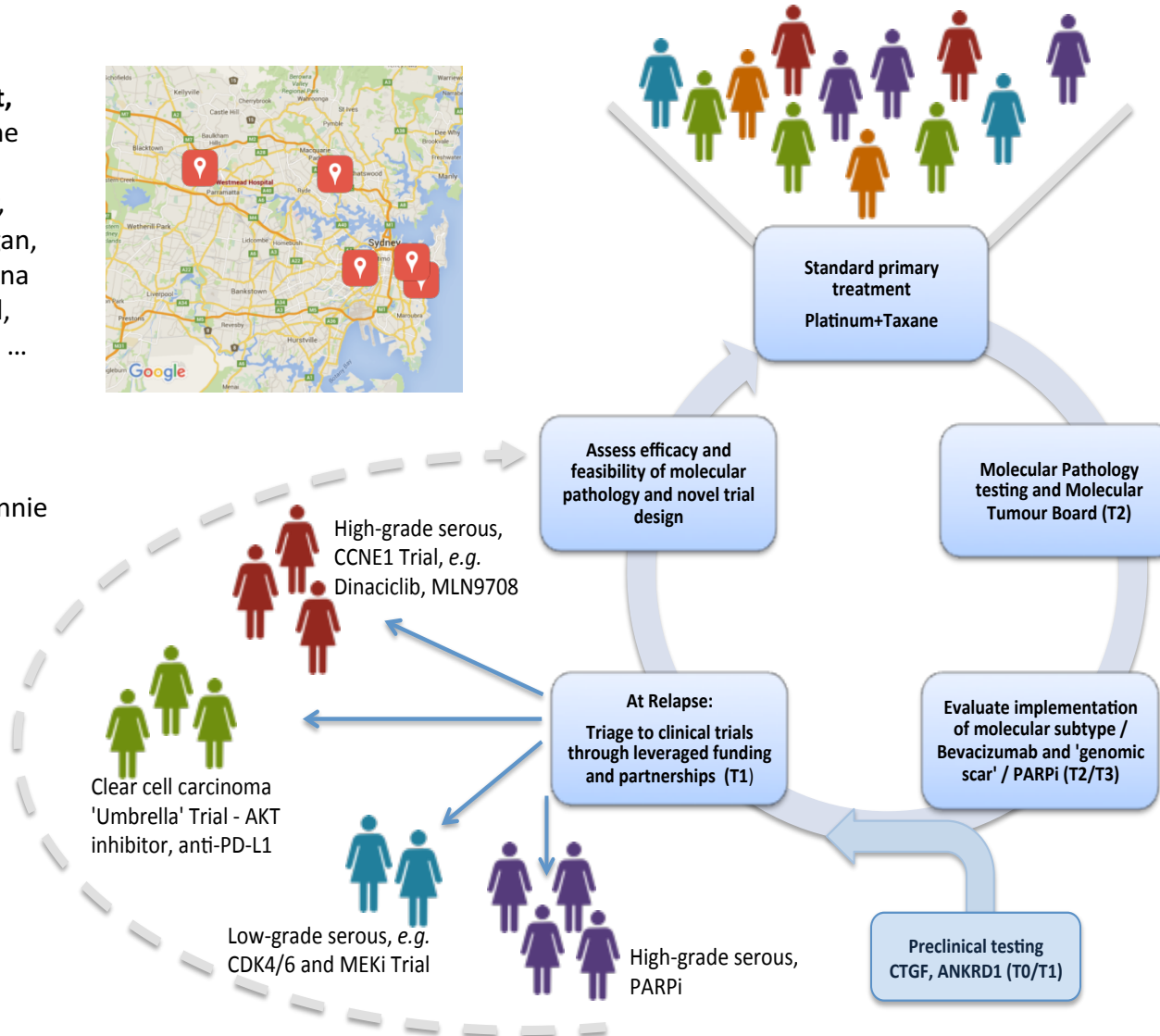
**Michael Friedlander, Neville Hacker, Rhonda Farrell, Archana Rao, Greg Robertson, Kate Webber, Christie Norris, Emma Newton ...**

### Royal Prince Alfred / Chris O'Brien Lifehouse

**Philip Beale, Lyndal Anderson, Samir Saidi ...**

### Peter MacCallum / Garvan / NIH

**David Bowtell, Goli Samimi, Sian Fereday, Nadia Traficante....**



## Conclusions - *the role of basic science in the translational research centres: Are we there yet?*

- › It takes a 'village', with complementary skills and commitment to transform scientific discoveries into improvement in patient care
  - Successful Translational Research is not always linear - can move between 'basic', 'clinical' and 'implementation' and back again
  - Its not always possible to know which basic research will lead to translation
  - Continued investment is needed in all parts of the translation spectrum.

*1980 - 2007 NIH grants: 8.4% led to a patent, but >30% led to publications that were cited in patents (Li et al Science, 2017)*



## Our Patients

### AOCS Study Group

#### Westmead

Paul Harnett, Yoke-Eng Chiew  
Catherine Kennedy, Ying Lei  
Catherine Emmanuel, Bo Gao, Jillian  
Hung, Cristina Mapagu, Tania  
Moujaber, Annie Stenlake, Rosemary  
Balleine, Alison Brand, Raghwa  
Sharma

#### Funding

NH&MRC  
Cancer Australia  
Cancer Institute NSW  
Australian State Cancer Councils  
U.S. Army Medical Research and Materiel Command, DAMD17-01-1-0729



#### Peter MacCallum Cancer Centre

**David Bowtell**, Sian Fereday, Joshy George,  
Nadia Traficante, **Kathryn Alsop**, Dariush  
Etemadmoghadam, Elizabeth Christie,  
Dale Garsed

#### QIMR Berghofer Medical Research Institute

**Georgia Chenevix-Trench**, **Penny Webb**,

#### IMB/QCMG/QIMR

Sean Grimmond, Ann- Marie Patch, Nicola  
Waddell and the ICGC Ovarian team



# TARGETING CANCER CELL METABOLISM OF GLUCOSE

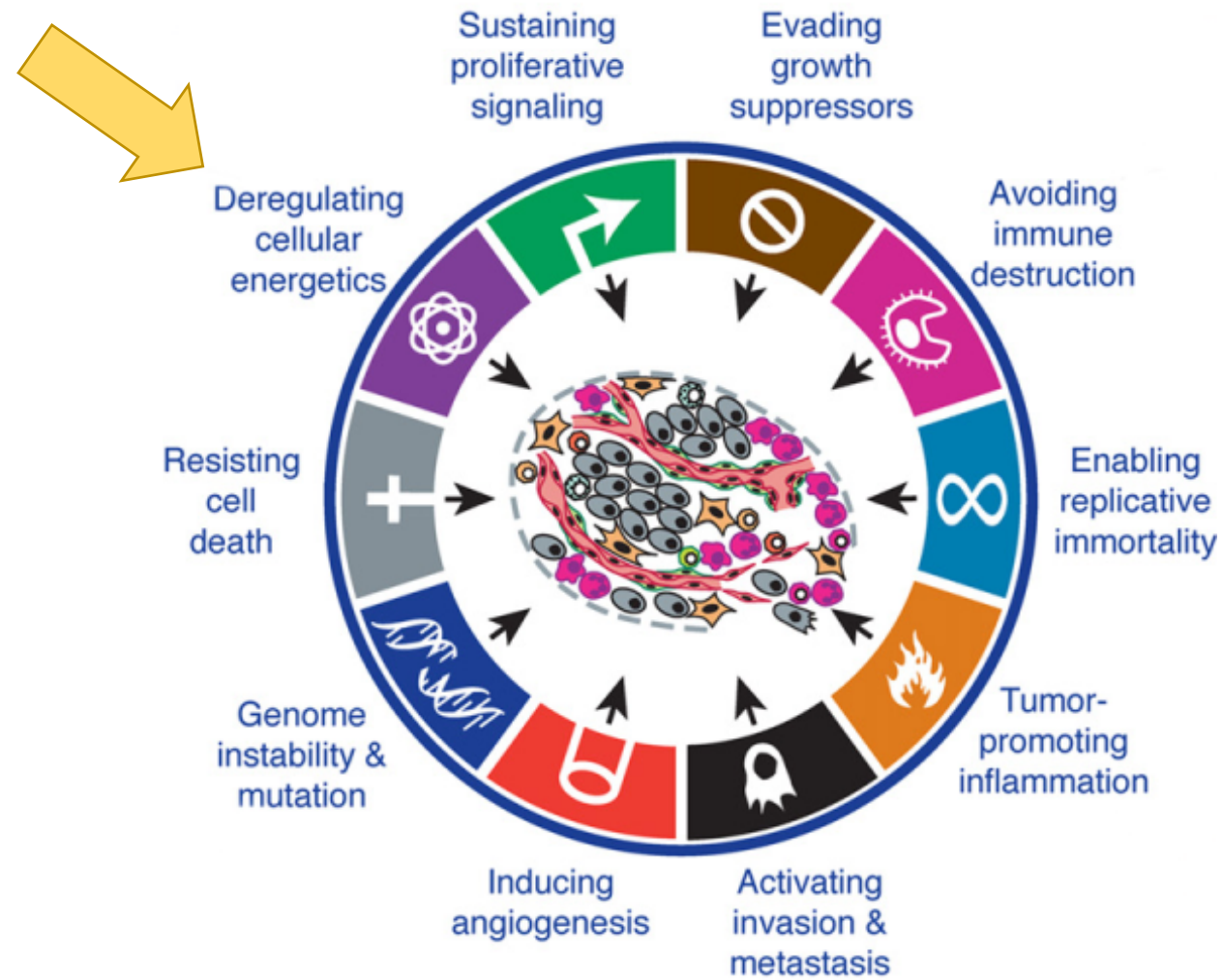
# CASE STUDY

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**PHIL HOGG**

DIRECTOR,  
ACRF CENTENARY CANCER  
RESEARCH CENTRE

# One of the hallmarks of cancer



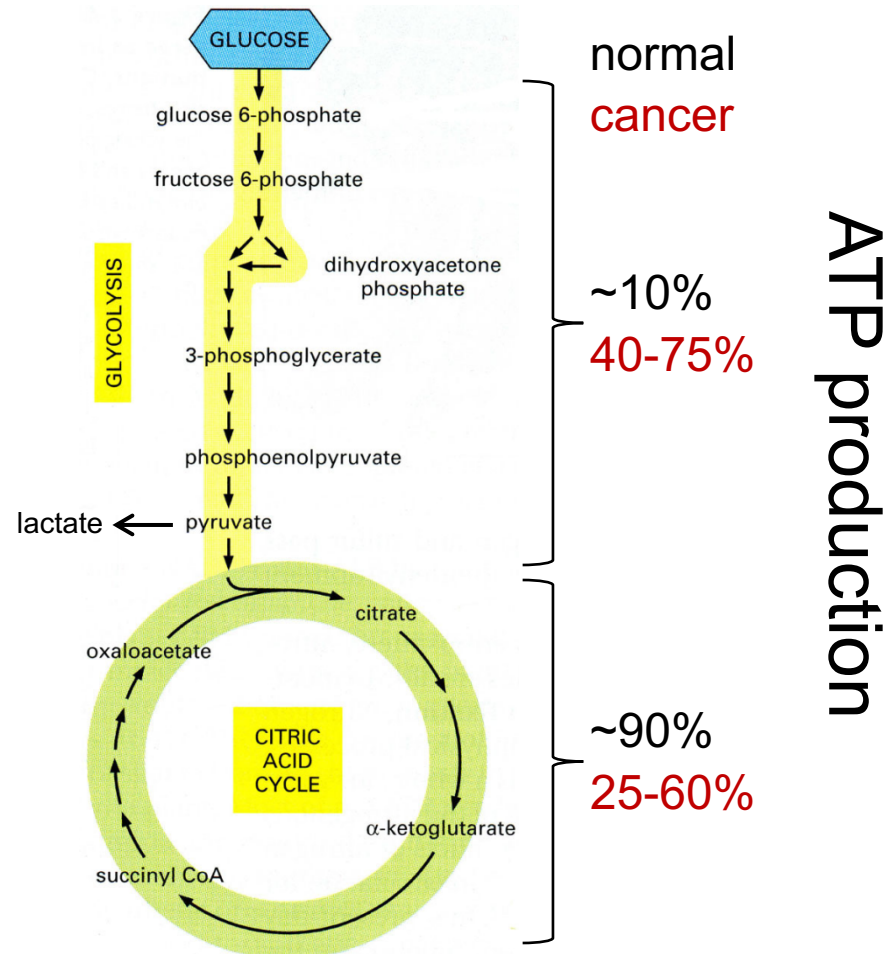
# Cancer cell metabolism

cancer cells convert  
glucose to lactate in  
normoxia



Otto Warburg

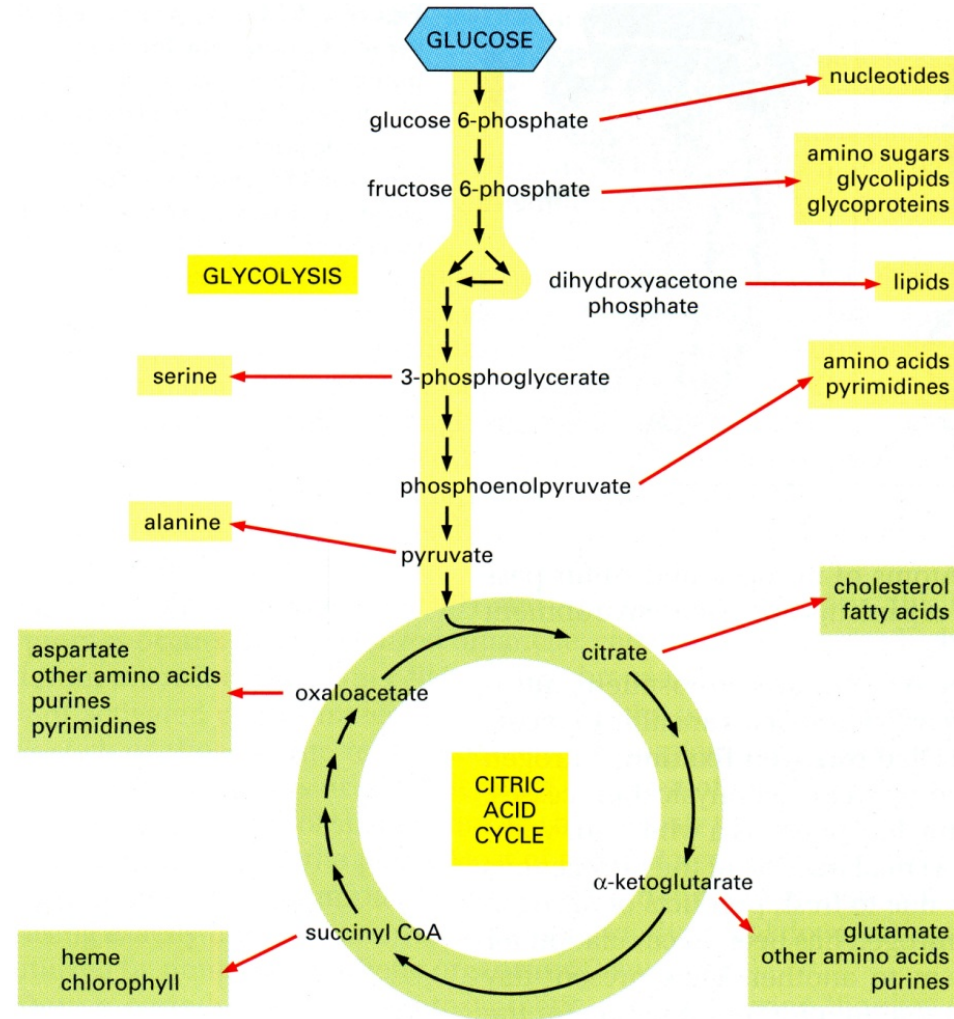
## aerobic glycolysis



# Aerobic glycolysis

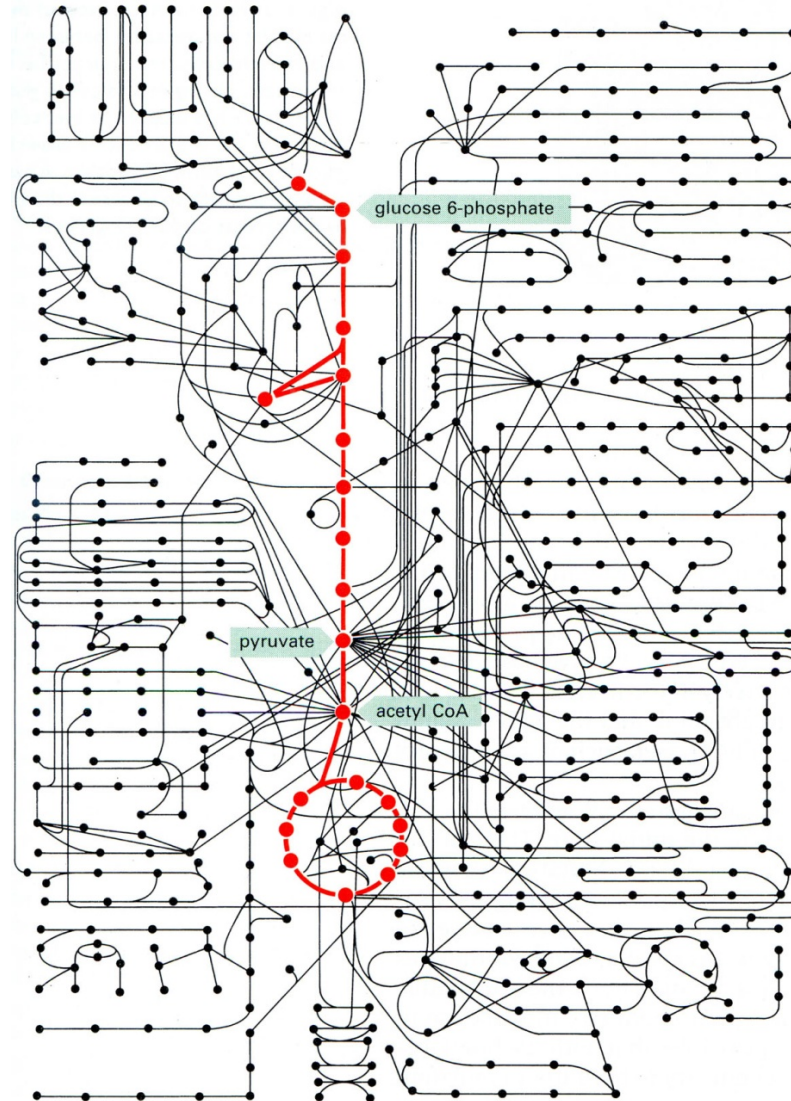
## Current understanding:

- increased biosynthesis required by rapidly proliferating cells is more efficiently supplied by aerobic glycolysis than oxidative phosphorylation
- glycolysis intermediates are siphoned out of the pathway and into alternative pathways to supply the anabolism of DNA, lipids and proteins

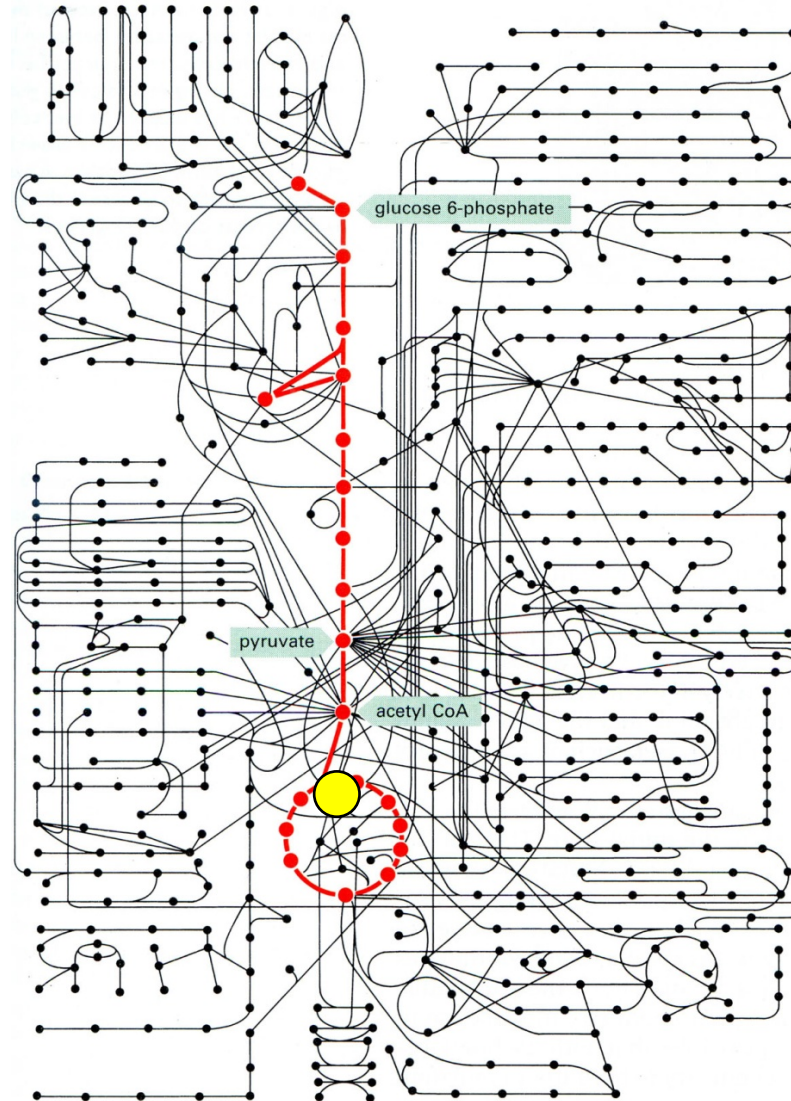




The expression and activity of many metabolic enzymes is changed in tumours to meet their metabolic demand



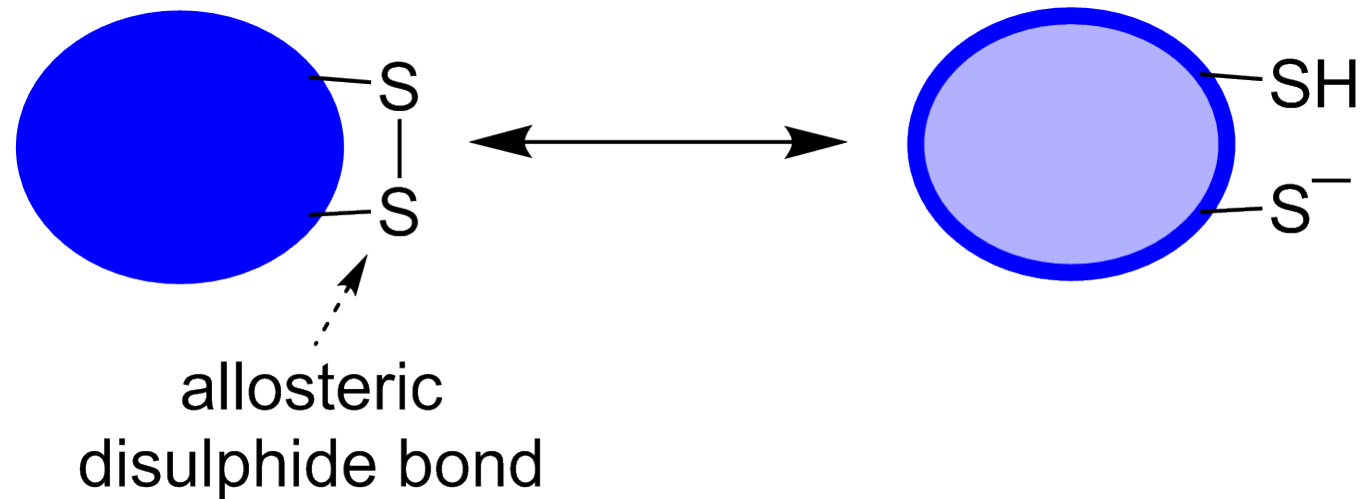
Our particular focus is an aspect of mitochondrial metabolism



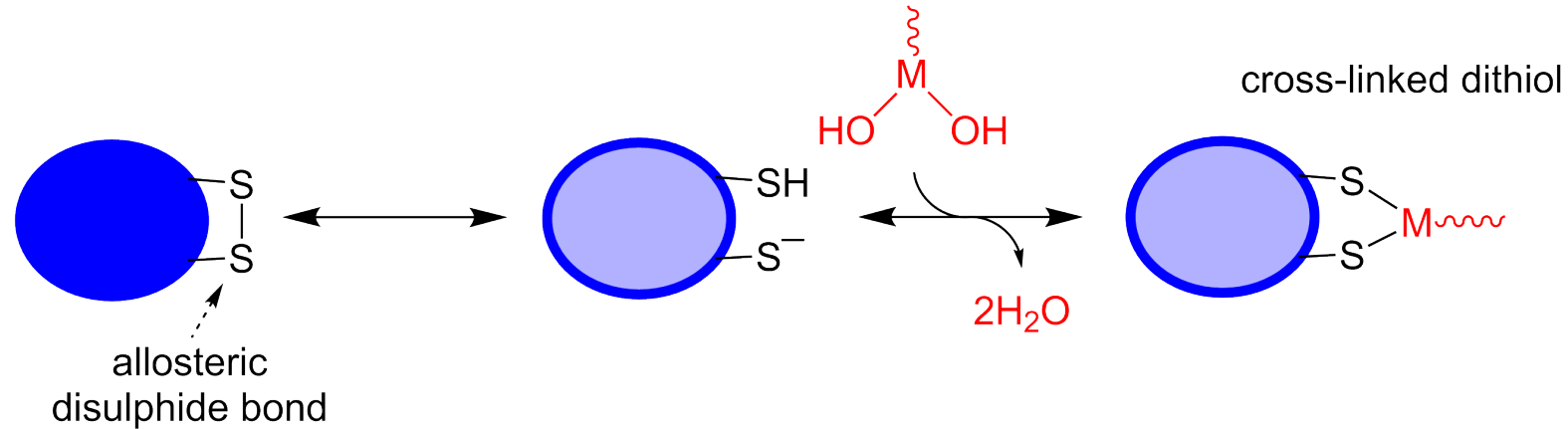


# Allosteric disulphide bonds

control the function of the mature protein in which they reside by being cleaved in a regulated way



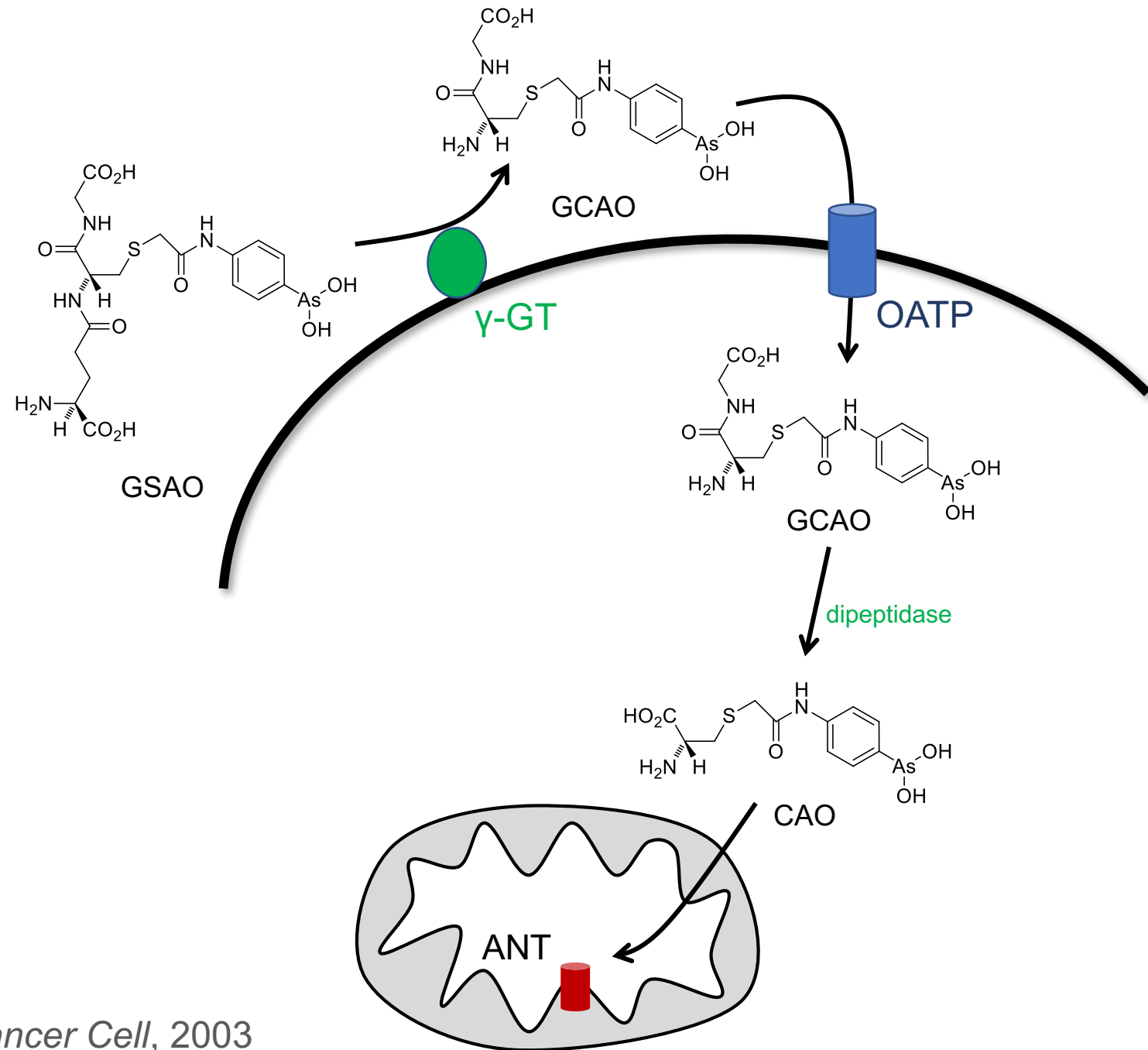
# Targeting the reduced form of allosteric disulphides using metalloids



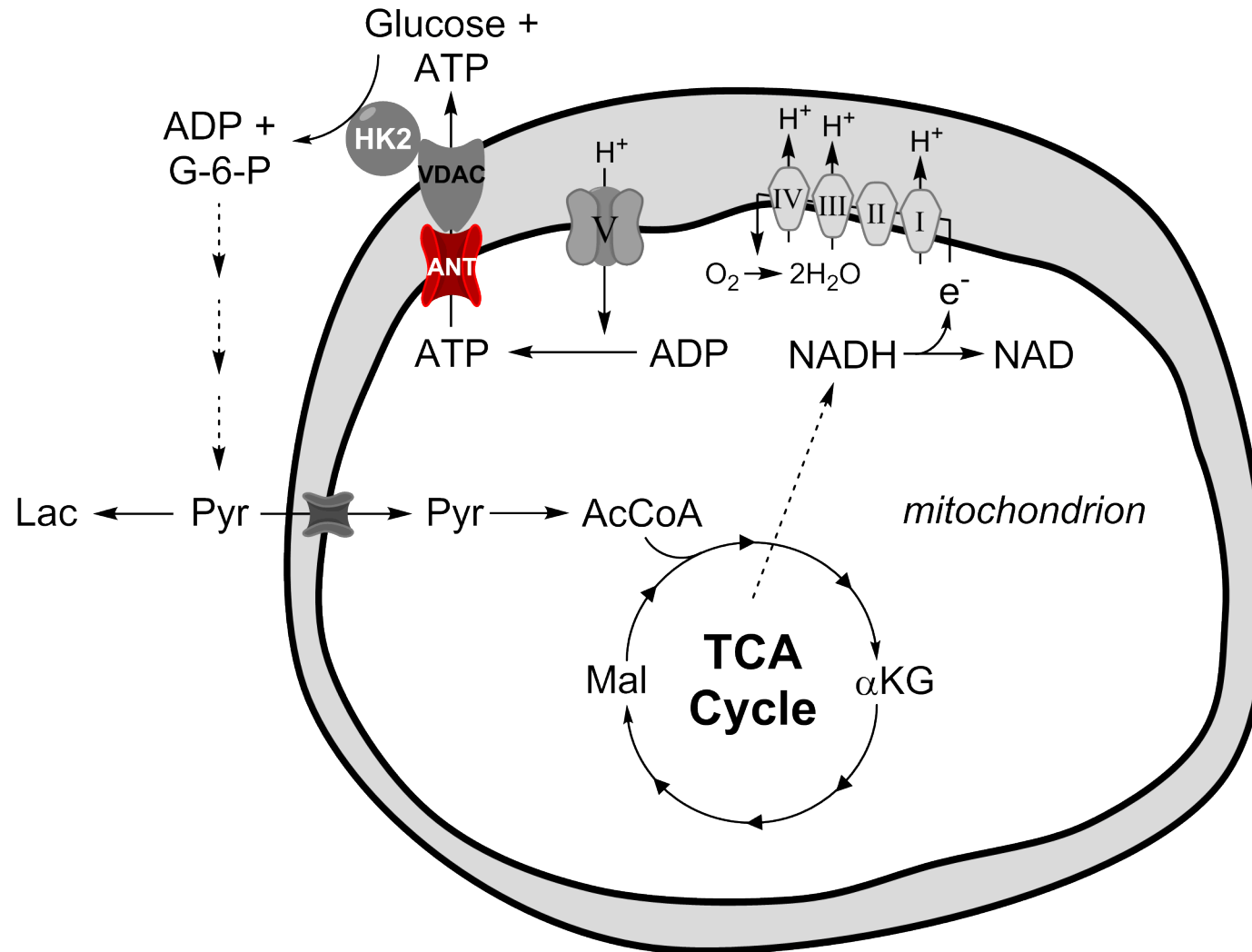
1 H																	2 He
3 Li	4 Be											5 B	6 C	7 N	8 O	9 F	10 Ne
11 Na	12 Mg											13 Al	14 Si	15 P	16 S	17 Cl	18 Ar
19 K	20 Ca	21 Sc	22 Ti	23 V	24 Cr	25 Mn	26 Fe	27 Co	28 Ni	29 Cu	30 Zn	31 Ga	32 Ge	33 As	34 Se	35 Br	36 Kr
37 Rb	38 Sr	39 Y	40 Zr	41 Nb	42 Mo	43 Tc	44 Ru	45 Rh	46 Pd	47 Ag	48 Cd	49 In	50 Sn	51 Sb	52 Te	53 I	54 Xe
55 Cs	56 Ba	57-71	72 Hf	73 Ta	74 W	75 Re	76 Os	77 Ir	78 Pt	79 Au	80 Hg	81 Tl	82 Pb	83 Bi	84 Po	85 At	86 Rn
87 Fr	88 Ra	89-103	104 Rf	105 Db	106 Sg	107 Bh	108 Hs	109 Mt	110 Ds	111 Rg	112 Cn	113 Uut	114 Fl	115 Uup	116 Lv	117 Uus	118 Uuo
57 La	58 Ce	59 Pr	60 Nd	61 Pm	62 Sm	63 Eu	64 Gd	65 Tb	66 Dy	67 Ho	68 Er	69 Tm	70 Yb	71 Lu			
89 Ac	90 Th	91 Pa	92 U	93 Np	94 Pu	95 Am	96 Cm	97 Bk	98 Cf	99 Es	100 Fm	101 Md	102 No	103 Lr			

# GSAO

targets  
proliferating  
endothelial  
cells

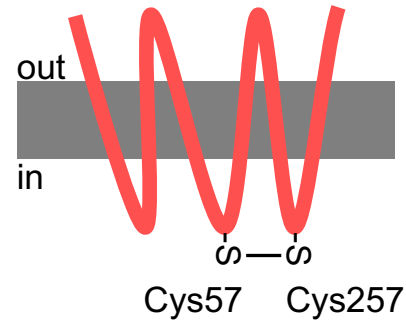


# GSAO/CAO reacts with mitochondrial adenine nucleotide translocase (ANT)



# CAO cross-links Cys57 and Cys257 of reduced ANT

quiescent cells

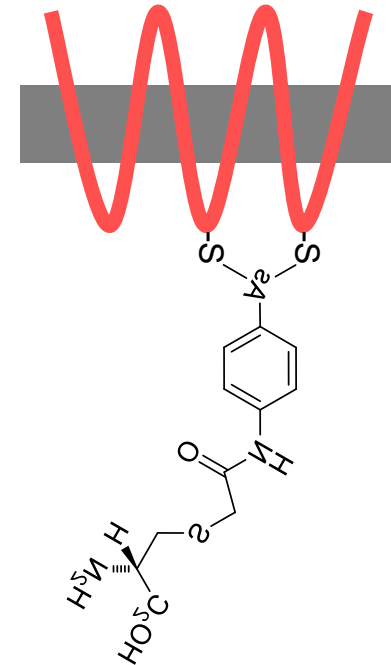
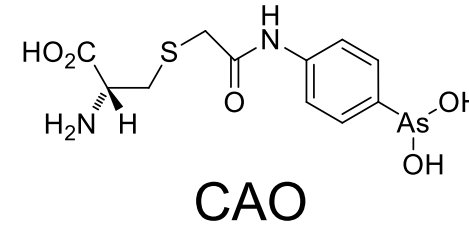
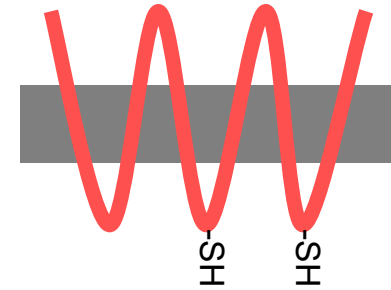


ANT

Thioredoxin



proliferating cells



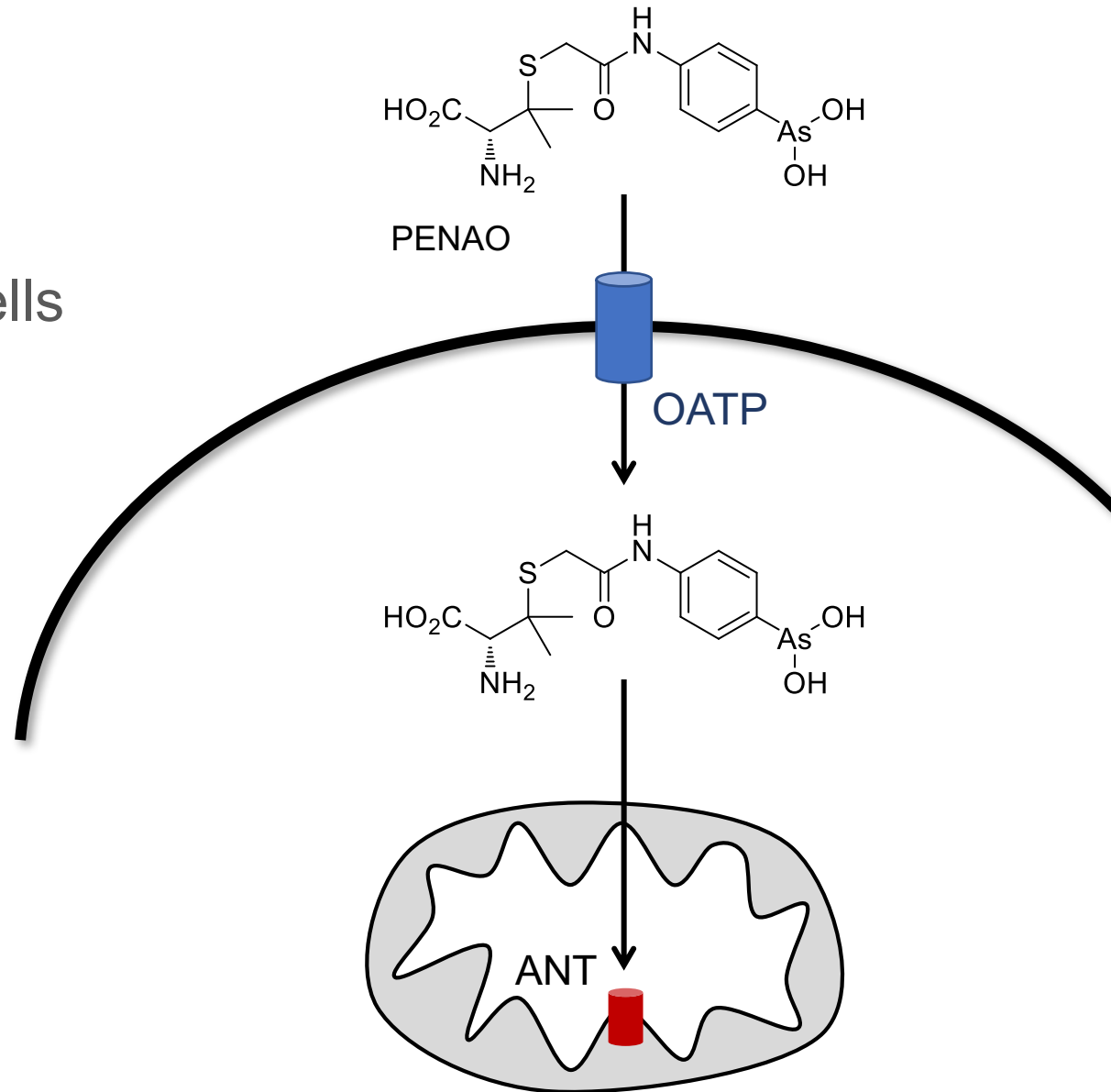
# First patient to receive GSAO





# PENAO

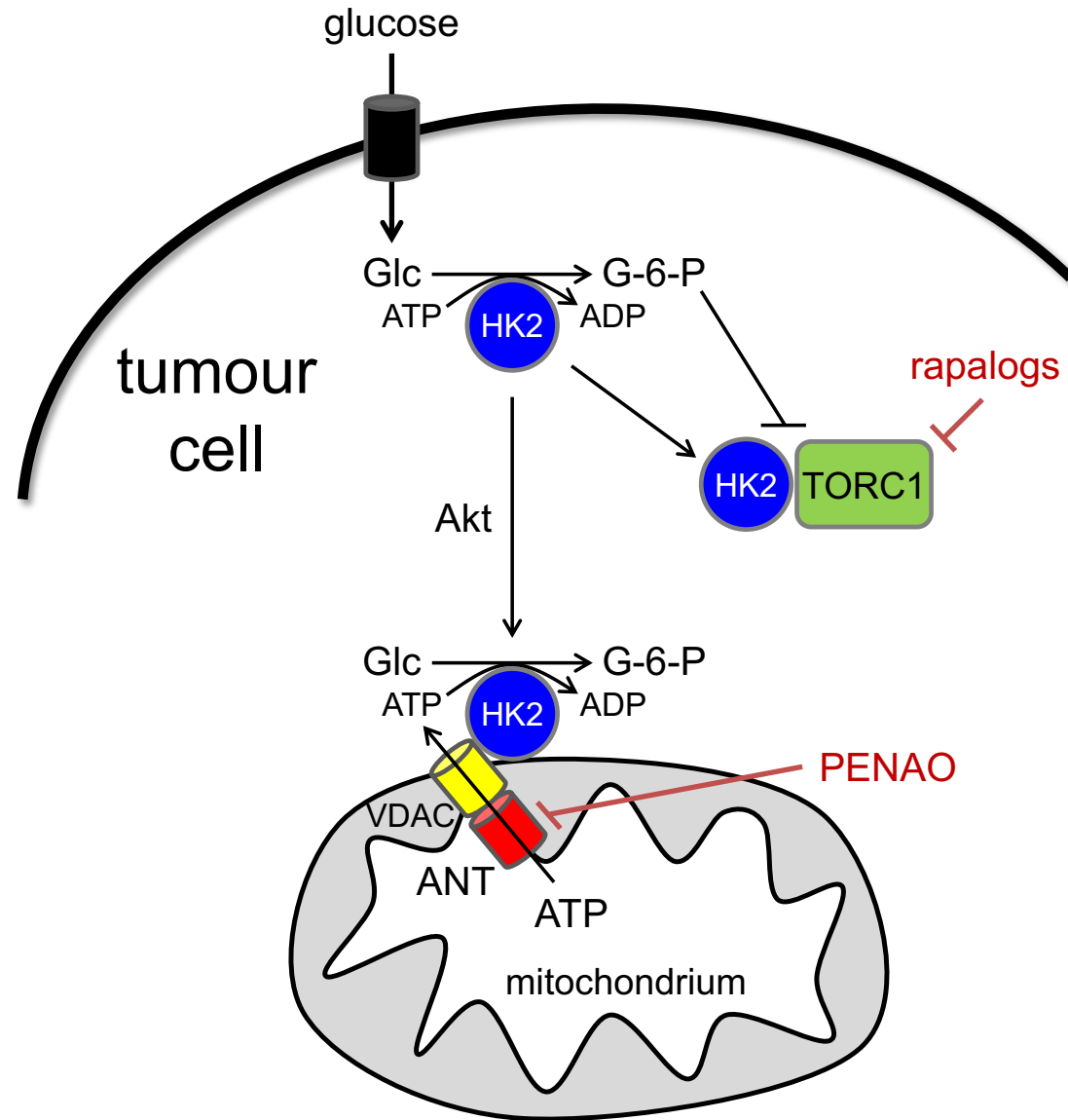
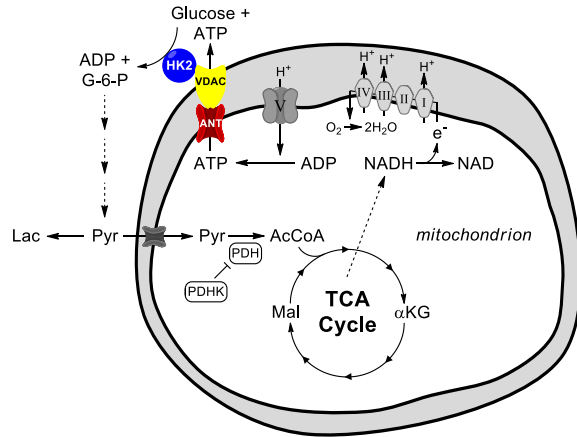
targets  
proliferating  
tumour and  
endothelial cells



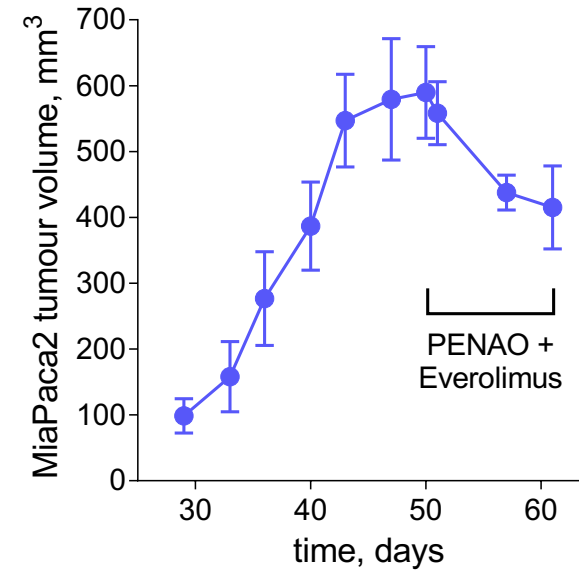
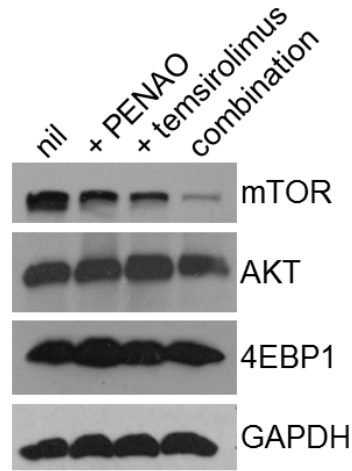
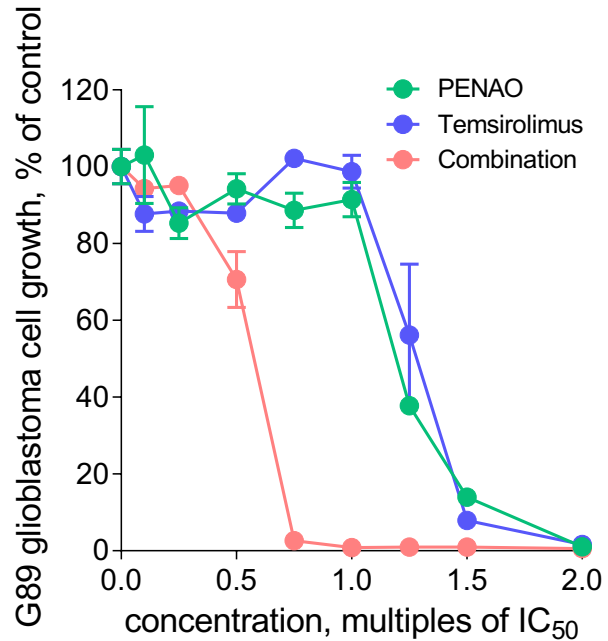
# First patient to receive PENAO



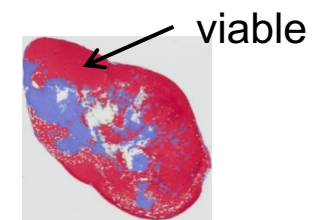
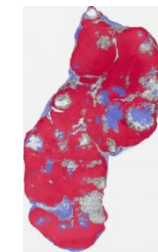
# Regulation of ANT function by HK2



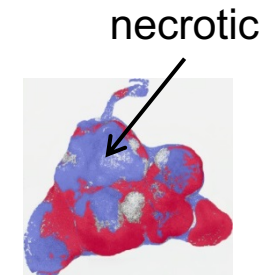
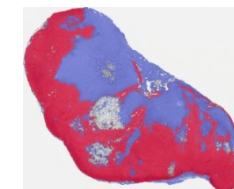
# Combination anti-ANT and anti-HK2 (via mTORC1) therapy



untreated tumour



treated tumour



ACRF-Centenary Cancer Research Centre, USyd

Jason Wong

Bryan Schmidt

Pierre Dilda

Danielle Park

Joyce Chiu

Stephanie Decollogne

Sylvia Chung

Han Shen



Sydney Children's Hospital, Sydney

Maria Tsoli

David Ziegler



Peter MacCallum Cancer Centre, Melbourne

Anne Hamilton

Danny Rischin

Royal Melbourne Hospital, Melbourne

Jayesh Desai

Chris O'Brien Lifehouse, Sydney

Lisa Horvath

# GROUP DISCUSSIONS

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TOPICS:



1. WHAT ARE THE BARRIERS?
2. WHAT ARE THE ENABLERS  
AND HOW DO WE ENGAGE  
THEM?
3. WHAT IS THE ROLE OF THE  
TCRC?



# EXPERT PANEL DISCUSSION

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**SPEAKERS:**



- **TIM SHAW, CHAIR**  
with
- **ALEXANDER ENGEL**
- **NIK ZEPS**
- **ANNA DeFAZIO**
- **PHIL HOGG**

# NETWORKING + REFRESHMENT

5-6PM

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thank you for completing your  
evaluation form