Fossilised knowledge? Libraries as repositories of knowledge in biomedical research in the cyberspace era.

Ian Frazer
Diamantina Institute,
The University of Queensland, Brisbane, Australia
i.frazer@uq.edu.au
Medical instruments on a temple wall at Kom Ombo, Egypt
The great library at Ephesus
The Bodleian Library: Oxford
The National Library: Canberra
The University of Queensland from the Diamantina Institute – circa 1890

Martyn Roberts- Evening, Mount Cootha – Queensland art Gallery
The New Translational Research Institute at the Princess Alexandra Hospital
The New Translational Research Institute at the Princess Alexandra Hospital
Research institute Aims

- Generation of Knowledge
- Interpretation of Knowledge
- Application of Knowledge
- Dissemination of Knowledge
  - Other Scientists
  - Next generation of researchers
  - Public and Government
Research Challenges

• Too Much Knowledge
• Rate of change of Knowledge
• Quality of Knowledge
• Reinterpretation of Knowledge
The role of the Librarian of the 21st Century

• Catalogue ideas, not books
• Prioritise the value of sources of ideas
• Capture ideas
  – Wiki ? Or what!
Ian Hector Frazer (born 6 January 1953) is a Scottish-Australian immunologist, best known for his work on the development of a cervical cancer vaccine, which works by protecting women from Human papillomavirus (HPV). Frazer was born in Glasgow, Scotland. Frazer initially enrolled to study physics at Edinburgh University, but the emerging job prospects at that time did not appeal to him and so he switched to training as a physician, specialising in immunology. He emigrated to Melbourne in 1980 to research viral immunology at the Walter and Eliza Hall Institute of Medical Research, and moved to Queensland in 1985 where he currently heads the University of Queensland's Diamantina Institute for Cancer, Immunology and Metabolic Medicine at the Princess Alexandra Hospital.

In 2004 Ian Hector Frazer moved to Brisbane to study how to protect people from skin cancer as his wife was diagnosed with it and really wished to help her get better.

Then in 2005 Frazer and his research groups undertook clinical study of a vaccine against human papillomavirus, which was 100% effective in preventing common cervical cancers caused by the virus types covered by the vaccine. One version of the vaccine named Gardasil, has been approved by the US Food and Drug Administration and has been approved for use in the European Union. Ian Frazer personally administered the first publicly available injection of the vaccine in Australia in August 2006. He is also involved in a large clinical trial taking place in Australia and China of a therapeutic vaccine against genital warts.

In January 2006 he was named Australian of the Year. Also in that year, he received the Cancer Research Institute’s William B. Coley Award along with Harald zur Hausen. He was awarded the Florey Medal for biomedical research in March 2007. He won the Balzan Prize in September 2008 for his work developing a vaccine for cervical cancer.

In November 2008, Professor Ian Frazer is set to unveil a skin cancer vaccine that may start in human trials as early as next year.
The role of the Librarian of the 21st Century

• Catalogue ideas, not books
• Prioritise the value of sources of ideas
• Capture and preserve ideas
  – Wiki! Or what?
• Teach people how to work with ideas
  – Morals and Ethics
  – Ideas are the intellectual capital of the 21st century
I DON'T THINK YOU CAN ACCUSE ANOTHER AUTHOR OF PLAGIARISM IF THEY USE THE SAME WORDS AS YOU BUT HAPPEN TO PUT THEM IN A DIFFERENT ORDER!

I'VE GOT ALL THE WORDS I NEED FOR MY PAPER, IT'S JUST A CASE OF PUTTING THEM IN THE RIGHT ORDER NOW!
Research as the driver for sustainable health – the Virtuous Cycle

Clinical Problem

Basic Research

Observation

Education

Translational Research
Life expectancy is increasing...

“--a baby born in Australia today can expect to live for 81.4 years, with men expected to live for 79 years and women for almost 84. Australians' life expectancy is bettered only by the Japanese at 82.2 years.” Australian Institute of Health and Welfare (AIHW)

“ among Aboriginal and Torres Strait Islander peoples, life expectancy at birth is around 17 years less…..”
.... but it comes at a cost

Health Care Spending Outpaces GDP Growth

How much would you pay for an extra 3 months of life:
- At 20?
- At 80?

<table>
<thead>
<tr>
<th></th>
<th>1970</th>
<th>2004</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
<td>7</td>
<td>15.3</td>
</tr>
<tr>
<td>Canada</td>
<td>7</td>
<td>9.9</td>
</tr>
<tr>
<td>Germany</td>
<td>6.2</td>
<td>10.6</td>
</tr>
<tr>
<td>UK</td>
<td>4.5</td>
<td>8.1</td>
</tr>
</tbody>
</table>
...the cost may be less than you think!

**Rapamycin for Research** (Google Ad)
100 mg $69; 500 mg $274

Rapamycin prolongs the lifespan of healthy mid-adult mice by >30%!
Healthcare opportunities and challenges change over time!

**AGRARIAN** (botanical)
- Hyponutrition
- Infection
- Accident/Injury
- Reproduction

**INDUSTRIAL** (small drug molecules)
- Hyponutrition
- Infection
- Accident/Injury
- Reproduction

**POST INDUSTRIAL** (biopharmaceuticals)
- Hyponutrition
- Infection
- Accident/Injury
- Reproduction
- Environmental
- Malnutrition
- Ageing population
- Mental Illness
- Ageing population
- Over nutrition
- Environmental
- Alcohol and drugs
- Infection
- Epidemic
- New pathogens
- Genetic diseases
Cancer - a model to study

- In Australia cancer is now the commonest cause of death
- UICC estimates suggest that by 2050 this will be true worldwide

WHAT ARE THE SOLUTIONS

- With some effort, we can prevent over 70% of cancer (social responsibility the key)
- We can now cure over 50% of cancer (personalised medicine is a critical next step)
A short aside on the history of medical research in cancer

“The incidence of uterine cancer is not increased through the licentious practices of women; however, the risk is greater among women who are excessively sensitive morally and nervously irritable...”

“...that of the cancers of the breast.”
The global burden of cancer

All sites but non-melanoma skin, Females
Age-Standardized incidence rate per 100,000

Cervix uteri
Age-Standardized incidence rate per 100,000

ALL CANCERS

CERVICAL CANCER
Cancer control in the 21st century— for richer or for poorer?

- **Prevention**
  - Behaviour change,
  - environment change,
  - infection risk reduction

- **Early detection (screening)**
  - premalignancy,
  - early malignancy
  - Genetic risk

- **Definitive therapy**
  - Surgery,
  - Radiotherapy,
  - Chemotherapy,
  - Immunotherapy

- **Palliation, Social care**

- Smoking reduction
- Clean water (arsenic)
- Vaccination (Hep B)
- Cervical Screening
- Breast Cancer screening
- BRCA1/2
- Excision
- Cesium implants
- Taxanes
- Herceptin
- MORPHINE
Preventing cancer: Risk assessment leads to education

“Thou shalt not.....”

But the messages can be confusing
Behavior modification for cancer avoidance

• Smoking
  - globally the biggest challenge
  - about 40% of avoidable cancer
• Obesity – in the developed world
  - About 10% of avoidable cancer
• Alcohol –
  - About 10% of avoidable cancer
• Sun exposure
  - A localised problem - Europe and Australia
Research in cancer
Who is genetically at risk?
Some Genetics Terminology and Facts

- Base pairs in the human genome
  - 3 billion
- Genes in the human genome
  - 30000
- Number of SNPs with minor allele frequency >1%
  - 5-10 million
SNP genotyping
High accuracy
2 days
$500
Next-Generation Sequencing

• **1980s**
  - Autoradiographs
    • 1000 bases per plate per day

• **1990s**
  - Fluorescent Sanger sequencing
    • 10000 bases per machine per day

• **2000s**
  - Short read ‘sequence by synthesis’
    • 2,000,000,000 bases per machine per day.
Replication of Genome-Wide Association Signals in UK Samples Reveals Risk Loci for Type 2 Diabetes

Eleftheria Zeggini,1,2,* Michael N. Weedon,3,4,† Cecilia M. Lindgren,1,2,‡ Timothy M. Frayling,3,4,§ Katherine S. Elliott,2 Hana Lango,3,4 Nicholas J. Timpson,3,4 John R. B. Perry,3,4 Nigel W. Rayner,1,2 Rachel M. Freathy,3,4 Jeffrey C. Barrett,6 Beverley Shields,5 Andrew P. Morris,6 Sten Eklund,7,8 Christopher J. Groves,9 Lorna W. Harries,10 Jonathan L. Marchini,2 Katharine R. Owen,2 Beatrice Knight,6 Lon R. Cardon,6 Mark Walker,6 Graham A. Hitman,9 Andrew D. Morris,10 Alex S. F. Donn,6,9 The Wellcome Trust Case Control Consortium (WTCCC),3,4, § & Andrew T. Hattersley1,2,9

The power of genome wide SNP analysis to map disease susceptibility genes

Studies will be multinational and will need to be undertaken for many ethnic groups
Published Genome-Wide Associations through 3/2009, 10\(^{-8}\) NHGRI GWA Catalog
www.genome.gov/GWAStudies

398 published GWA at p ≤ 5 x 10\(^{-8}\)
Harnessing the immune system to control cancer

My research career journey

The Press and Journal

Saturday April 13th 1912

Aberdeen man believed lost at sea

1500 others also missing as Titanic sinks on maiden voyage
THE pioneering scientist who invented the cervical-cancer jab is working on a world-first vaccine for skin cancer. Professor Ian Frazer says human trials of the vaccine will begin next year after testing on animals proved successful. He believes the vaccine may be available in five to 10 years, with children aged between 10 and 12 being inoculated to prevent them developing skin cancers later in life. Professor Frazer will reveal his ground-breaking work at a conference in Brisbane tomorrow. Australia suffers from the highest rate of skin cancers in the world, with 1600 deaths each year.
Infection causes >20 % of cancer

<table>
<thead>
<tr>
<th>Infectious agent</th>
<th>Associated Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Viruses</strong></td>
<td></td>
</tr>
<tr>
<td>Human Papillomavirus</td>
<td>Anogenital, Oropharyngeal</td>
</tr>
<tr>
<td>Hepatitis B virus</td>
<td>Hepatocellular</td>
</tr>
<tr>
<td>Epstein Barr Virus</td>
<td>Nasopharyngeal Ca + Lymphomas</td>
</tr>
<tr>
<td>Hepatitis C virus</td>
<td>Hepatocellular Ca</td>
</tr>
<tr>
<td>HIV</td>
<td>Potentiates viral cancers</td>
</tr>
<tr>
<td>HTLV -1</td>
<td>T cell leukemia</td>
</tr>
<tr>
<td>HHV -8</td>
<td>Kaposis sarcoma</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
</tr>
<tr>
<td>H. Pylorii</td>
<td>Gastric</td>
</tr>
<tr>
<td>Parasites</td>
<td>Bladder, ?HCC</td>
</tr>
</tbody>
</table>

Vaccines to prevent HPV infection

Cancer associated Human Papillomaviruses (~1980)
- Some HPVs cause cancer
- Virus can’t be grown in the lab

Virus Like particles (~1990)
- L1 recombinant DNA
- Self assembly to VLPs
- VLPs highly immunogenic

Vaccines to prevent HPV infection

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HPV vaccines (~2005)
- Conventional vaccines
  - VLPs+ adjuvant
  - Neutralising Antibody
  - Protection > 5yrs
- Cervarix – HPV 16, 18
- Gardasil – HPV 6, 11, 16, 18

Disclosure of conflict of interest

Dr Ian Frazer and the University of Queensland benefit financially from commercial sale of the prophylactic HPV vaccines discussed in this talk.
HPV vaccines- frequently asked questions

- Do the vaccines work?
- Are the vaccines safe?
- How long should protection last?
- Who should be vaccinated?
- What do we need to know next?
# HPV vaccine Phase III trial outcomes

<table>
<thead>
<tr>
<th>Study</th>
<th>Vaccine²</th>
<th>No of subjects</th>
<th>End-points</th>
<th>Vaccine efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>% (confidence limits)</td>
</tr>
<tr>
<td>Koutsky</td>
<td>6/11/16/18</td>
<td>6087</td>
<td>6080</td>
<td>CIN 2/3 AIS</td>
</tr>
<tr>
<td>Ault</td>
<td>6/11/16/18</td>
<td>10291</td>
<td>10292</td>
<td>CIN 2/3 AIS</td>
</tr>
<tr>
<td>Garland</td>
<td>6/11/16/18</td>
<td>2241</td>
<td>2258</td>
<td>CIN 2/3 AIS</td>
</tr>
<tr>
<td></td>
<td>2261</td>
<td>2279</td>
<td>GW VIN VAIN</td>
<td>100 (94-100)</td>
</tr>
<tr>
<td>Joura</td>
<td>6/11/16/18</td>
<td>7811</td>
<td>7785</td>
<td>VIN2/3 VAIN 2/3</td>
</tr>
<tr>
<td>Parvonen*</td>
<td>16/18</td>
<td>9319</td>
<td>9325</td>
<td>CIN2,3</td>
</tr>
</tbody>
</table>


*: Phase III bivalent vaccine data from 25th IPV Malmo 2009
Protection against CIN2/3 - all HPV types (Quadrivalent vaccine - HPV Naïve population)

Residual disease due to non vaccine HPV types mandates continued screening where available, and development of broader spectrum vaccines.
Cervical cancer vaccines are not therapeutic for existing HPV infections

### Efficacy Against HPV 6,11,16, 18-Related Disease by Baseline Serostatus and PCR Status

**MITT-2 Analysis** *(Protocols 007, 013, and 015)*

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>HPV Vaccine Cases (N = 9075)</th>
<th>Placebo Cases (N = 9075)</th>
<th>% Efficacy</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sero Negative &amp; PCR Negative</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CIN (any grade)</td>
<td>16</td>
<td>309</td>
<td>95</td>
<td>(92, 97)</td>
</tr>
<tr>
<td>EGL</td>
<td>11</td>
<td>303</td>
<td>96</td>
<td>(94, 98)</td>
</tr>
<tr>
<td><strong>Sero Positive &amp; PCR Negative</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CIN (any grade)</td>
<td>0</td>
<td>7</td>
<td>100</td>
<td>(29, 100)</td>
</tr>
<tr>
<td>EGL</td>
<td>0</td>
<td>8</td>
<td>100</td>
<td>(40, 100)</td>
</tr>
<tr>
<td><strong>Sero Negative &amp; PCR Positive</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CIN (any grade)</td>
<td>83</td>
<td>101</td>
<td>22</td>
<td>(-6, 42)</td>
</tr>
<tr>
<td>EGL</td>
<td>46</td>
<td>43</td>
<td>-4</td>
<td>(-62, 33)</td>
</tr>
<tr>
<td><strong>Sero Positive &amp; PCR Positive</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CIN (any grade)</td>
<td>105</td>
<td>113</td>
<td>5</td>
<td>(-25, 28)</td>
</tr>
<tr>
<td>EGL</td>
<td>14</td>
<td>16</td>
<td>12</td>
<td>(-93, 60)</td>
</tr>
</tbody>
</table>

*MITT-2: Received at least one dose, case counting starts 30 days after dose 1

Source: ACIP website 2008/03/30
Delivering HPV vaccines in the developing world (Vanuatu/Nepal)

• Why Vanuatu and Nepal?
  - Pragmatism (they wanted us to help them!)

• The problem
  - 5% of apparently healthy 30 year old Ni-vanuatu women have CIN 2/3.
  - 1% have cervical cancer

• The challenge
  - Free vaccine from GSK available
  - Significant problems with vaccine delivery already obvious
  - New challenge: 12 year old girls the target and 3 shots required

• The hypothesis
  - A silicone wrist band with a reminder in Nepali/Bislami will be effective in achieving delivery of 3 shots of vaccine to 12 year olds
Delivery logistics: staffing, distribution and a cold chain

Vanuatu
- 50 islands
- 250,000 people
- 5 doctors
- 91 parliamentarians
- 1 vaccine fridge
- 0 reliable electricity
Education: parents, children, staff, and government

Parents and Kids under the Banyan Tree- north Efate
Adequate resources to fund and deliver vaccine

Nepalese school Computer Lab!
Research as the driver for sustainable health – the Virtuous Cycle

Clinical Problem

Basic Research → Translational Research

Knowledge + ACCESS TO IT!

Observation → Education
A vision for medical librarianship in the 21st Century
Custodians of knowledge with social responsibility

• There will be no magic bullets for controlling chronic disease. However, we know what to do to control much chronic disease
  - Clean water and air, safe food, Vaccinations. Personal decisions on Tobacco, Alcohol, Weight, Sun Exposure
  - Knowing our risk of disease may help us to make the right choices—understanding our genes will help
  - Knowing what treatments will work for us will help minimise cost and side effects

• The challenge is to separate the wheat from the chaff!

• Conveying current knowledge to the next generation is critical
  - It's probably too late for us, but they can use it to protect themselves and move things forward, if and only if....

• “Fossilised knowledge” is well preserved and well presented!