Challenges of innovative oncology drug development: Succeeding slowly is better than failing fast

Hilary Calvert, Emeritus Professor of Cancer Therapeutics, University College London

• Disclosures
  – I will consult for anyone who will listen
  – Inventors rewards on rucaparib
All Innovations have problems that need solving

• My background
  – Practising Academic Medical Oncologist with an interest in drug discovery, particularly
  – Carboplatin – Formula – ovarian cancer
  – Antifolates – pemetrexed – lung cancer, mesothelioma
  – PARP Inhibitors (rucaparib) – BRCA1, BRCA2 and homogenous recombination repair deficient tumours
Platelet Nadirs during the first Phase I Trial of Carboplatin

Adapted from: Calvert et al., Cancer Chemotherapy and Pharmacology, 9:140-147, 1982
Single Agent Phase I Methodology
Mouse / Man Ratios of dose (mg/m²) and AUC at LD10 (Collins *et al*, 1986)

AUC or “systemic exposure” may be a better indicator of drug effect than dose

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Ratio</th>
<th>C × T</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxorubicin</td>
<td>5</td>
<td>0.8</td>
</tr>
<tr>
<td>Diaziquone</td>
<td>1</td>
<td>1.0</td>
</tr>
<tr>
<td>Amsacrine</td>
<td>0.8</td>
<td>1.3</td>
</tr>
<tr>
<td>Pentostatin</td>
<td>0.7</td>
<td>1.1</td>
</tr>
<tr>
<td>Indicine N-oxide</td>
<td>0.9</td>
<td>0.6</td>
</tr>
<tr>
<td>PALA</td>
<td>2.8</td>
<td>3.3</td>
</tr>
<tr>
<td>F-ara-AMP</td>
<td>0.03-0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Dihydroazacytidine</td>
<td>1.2</td>
<td>0.3</td>
</tr>
</tbody>
</table>
Rationale for use of AUC

• Cell kill (normal bone marrow or tumour) should be proportional to number of adducts formed
• Number of adducts formed given by concentration \( \times \) time
• concentration \( \times \) time is Area under the Curve (AUC)

Can we predict AUC for carboplatin?
Levels of:
- Total platinum
- Ultrafilterable platinum
- Intact Carboplatin

After administration of carboplatin to a patient.
Area under the Curve (AUC) Based Dosing of Carboplatin

**Carboplatin infusion**

\[ \text{Dose} = \text{AUC} \times (\text{GFR} + 25) \]


Model solution in the form:

\[ C = Ae^{-\alpha t} \]

1. GFR Method developed by Cyril Chantler at UCL
## Treatment Failure in Testicular Cancer

From Childs et al, Annals of Oncology 3:291, 1992

<table>
<thead>
<tr>
<th>Carboplatin dose parameter</th>
<th>Total Patients</th>
<th>Treatment Failures</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC &gt;= 5</td>
<td>72</td>
<td>2</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>AUC &gt; 5</td>
<td>47</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>AUC &gt;= 4.5</td>
<td>98</td>
<td>3</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>AUC &lt; 4.5</td>
<td>23</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Dose &gt;= 450 mg/m²</td>
<td>28</td>
<td>1</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Dose &lt; 450 mg/m²</td>
<td>93</td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>
Formulae sell drugs

- Three formulae
- “Calvert” formula the most widely used (1408 citations to date)

- Standard of care for ovarian cancer
- Widely used for
  - Lung Cancer
  - Her2 positive breast cancer
  - Paediatric cancers
  - seminoma

*Merrill Egorin 1948-2010
How have things changed for new cancer drug development?

- Regulation – Carboplatin Phase III (carbo vs cis in ovarian cancer)
  - Carboplatin Phase III (1980s) under a Doctors and Dentists Exemption. No regulatory approval required.
  - No toxicology required (although some done)
  - Carboplatin obtained from a research lab and formulated in dextrose, inline filter to remove particles of platinum
  - Ethical approval minimal, informed consent not requested from all patients.
Folate-based Inhibitors of Thymidylate Synthase with Clinical Data


Raltitrexed (Tomudex™)
ICR/Astrazeneca: Follow-up to CB 3717. Licensed for colon cancer in some countries. Less toxicity but still problems.

Response of Pleural Mesothelioma in Pemetrexed + Carboplatin Phase I

CT scan 03/09/99
pre-treatment

CT scan 15/12/99
post 4 cycles

Responses are associated with symptomatic improvement – median duration about 1 year
Responses had previously been seen in a Phase I of pemetrexed + cisplatin (Hanauske, 1999)
In 2010 there were 2543 cases of mesothelioma in the UK

Sporadic Serious Toxicities of Antifolates

- Raltitrexed – reported drug-related deaths
  - 16/699 (2.2%) in three Phase III Trials†
- Pemetrexed
  - 4% in early Phase II trials without vitamin supplementation§
- Not possible to predict these toxicities on the basis of plasma or red-cell folate levels

† Zalcberg et al, JCO 14:716, 1996
† Cunningham et al, Ann Oncol 7:961, 1996
† Maughan et al, Proc ASCO18:Abs 1007, 1999
§ Niyikiza et al, Seminars in Oncology 29:6(Suppl 18):24, 2002
Interaction of folate metabolism and plasma homocysteine

- PAMM Meeting Bordeaux 1990, Organised by Jaques Robert
  - Presentation by Benedict Christensen (Bergen) showing elevation of homocysteine levels following methotrexate treatment.

  - Clinical studies on cancer and psoriasis patients have shown that plasma and urinary homocysteine (Hcy) responds to methotrexate (MTX) therapy, indicating that Hcy in extracellular fluids may be an indicator of the antifolate effect.
Interaction of folate and homocysteine metabolism

Homocysteine

Homocysteine

- Methionine

CELLULAR METHYLATION REACTIONS

Methionine Synthase (B_{12} Dependent)

The plasma homocysteine level is a sensitive marker of functional folate or B_{12} deficiency

Drug targets:
- Methotrexate *
- Raltitrexed †
- Pemetrexed ‡
Baseline homocysteine level predicts for pemetrexed-related haematological toxicity (n=267)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.9735</td>
<td>0.8050</td>
<td>0.6136</td>
<td>0.5120</td>
</tr>
<tr>
<td>Gender</td>
<td>0.2528</td>
<td>0.5208</td>
<td>0.1932</td>
<td>0.8705</td>
</tr>
<tr>
<td>BL ALB</td>
<td>0.6348</td>
<td>0.1934</td>
<td>0.3423</td>
<td>0.5391</td>
</tr>
<tr>
<td>BL ALT</td>
<td>0.6916</td>
<td>0.6050</td>
<td>0.2206</td>
<td>0.7246</td>
</tr>
<tr>
<td>BL ALK Phos</td>
<td>0.3874</td>
<td>0.0573</td>
<td>0.9044</td>
<td>0.0452</td>
</tr>
<tr>
<td>BL HCYS</td>
<td>&lt;0.00001</td>
<td>0.0191</td>
<td>&lt;0.00001</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>BL CYST</td>
<td>0.8030</td>
<td>0.5971</td>
<td>0.3907</td>
<td>0.9454</td>
</tr>
<tr>
<td>BL PLT</td>
<td>0.5250</td>
<td>0.8101</td>
<td>0.4457</td>
<td>0.2066</td>
</tr>
<tr>
<td>BL ANC</td>
<td>0.6029</td>
<td>0.2737</td>
<td>0.0736</td>
<td>0.2345</td>
</tr>
<tr>
<td>AUC</td>
<td>0.7298</td>
<td>0.6081</td>
<td>0.9531</td>
<td>0.3204</td>
</tr>
<tr>
<td>Weight</td>
<td>0.6487</td>
<td>0.3182</td>
<td>0.0633</td>
<td>0.9918</td>
</tr>
<tr>
<td>Prior Treatment</td>
<td>0.5059</td>
<td>0.8122</td>
<td>0.4813</td>
<td>0.4788</td>
</tr>
<tr>
<td>Tumor Type</td>
<td>0.4855</td>
<td><strong>0.0153</strong></td>
<td>0.1315</td>
<td>0.4305</td>
</tr>
</tbody>
</table>

Niyikiza et al.. Mol Cancer Ther 2002 1: 545-552
Toxicities in patients receiving pemetrexed with and without folic acid and B<sub>12</sub> restoration

Adapted from Niyikiza et al.. Mol Cancer Ther 2002 1: 545-552
All Innovations have problems that need solving

- **Pemetrexed problems**
  - Activity shown mainly in mesothelioma – “rare” tumour
  - Market predictions minimal
  - Sporadic toxicity had prevented development of previous antifolates
  - Boring drug not seen as a “targeted” agent

- **Solutions**
  - Mesothelioma is not rare
  - Vitamin supplementation
  - Presented pemetrexed as a “targeted” antifolate
  - Promotional video made for Eli Lilly management
Developments in Cancer Therapeutics

- DNA-reactive drugs
- Antimetabolites
- Natural products
- Targeted agents
  - Making targeted agents cancer selective
  - An increasing array of agents targeting tumour-specific mutations / amplifications
    - Her2
    - EGFR
    - C-Kit
    - BcrAbl
    - BRAF
    - ALK
    - ...........
- Use of the synthetic lethal interaction to achieve selectivity
- Effective immunomodulatory agents
DNA Repair – a process essential to cell survival

<table>
<thead>
<tr>
<th>How long is a piece of DNA?</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>DNA length per cell</td>
<td>2 meters</td>
</tr>
<tr>
<td>Cells per human</td>
<td>$2 \times 10^{13}$</td>
</tr>
<tr>
<td>DNA length per human</td>
<td>$4 \times 10^{13}$ meters</td>
</tr>
<tr>
<td>Distance from the Earth to the Sun</td>
<td>$1.49 \times 10^{11}$ meters</td>
</tr>
<tr>
<td>Number of return trips to the Sun</td>
<td>134</td>
</tr>
</tbody>
</table>

- Each cell sustains 10,000 to 30,000 episodes of DNA damage per day
- 5 Basic types of DNA damage – repair pathways
- Redundancy
  - Different pathways
  - 2 Alleles
MAJOR MECHANISMS OF DNA DAMAGE AND REPAIR

Ionising radiation
Antitumour agents

Interstrand crosslink
Double-strand break

UV light
Polycyclic aromatic hydrocarbons

(6–4)PP
Bulky adduct
CPD

Replication errors

A–G mismatch
T–C mismatch
Insertion
Deletion

Ionising radiation
Oxygen radicals
Spontaneous reactions
Antitumour agents
Alkylating agents

Solvent damage

Uracil
Abasic site
8–Oxoguanine
Single-strand break

DNA alkylation
$O^6$–alkylguanine

Recombinational repair (HR, NHEJ)
DNA PKi
ATMi

Nucleotide excision repair

Mismatch repair

Base excision repair

PARPi

Direct reversal
(AGT, MGMT)

$O^6$BG
PaTrin

We were fortunate in 1990 that we knew only about PARP-1
Mechanism of Action of PARP in Base Excision Repair

- Damage-induced DNA single-strand break
- PARP-1
- Poly(ADP-ribose) synthesis
- NAD$^+$
- PARP-1 and chromatin dissociation
- DNA repair
Development of High-Affinity PARP Inhibitors (Newcastle / Agouron)

3-aminobenzamide

\[ Ki = 4 \mu \text{M} \]

PD128763

\[ Ki = 70 \text{nM} \]

Hypothermia

NU 1085

\[ Ki = 10 \text{nM} \]

Rucaparib

\[ Ki = < 5 \text{ nM} \]

Phase I 2003, In clinical development by Clovis
Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase

Helen E. Bryant\textsuperscript{1}, Niklas Schultz\textsuperscript{2}, Huw D. Thomas\textsuperscript{3}, Kayan M. Parker\textsuperscript{1}, Dan Flower\textsuperscript{1}, Elena Lopez\textsuperscript{1}, Suzanne Kyle\textsuperscript{3}, Mark Meuth\textsuperscript{1}, Nicola J. Curtin\textsuperscript{3} & Thomas Helleday\textsuperscript{1,2}

Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy

Hannah Farmer\textsuperscript{1,2}, Nuala McCabe\textsuperscript{1,2}, Christopher J. Lord\textsuperscript{2}, Andrew N. J. Tutt\textsuperscript{2,3}, Damian A. Johnson\textsuperscript{2}, Tobias B. Richardson\textsuperscript{2}, Manuela Santarosa\textsuperscript{2,†}, Krystyna J. Dillon\textsuperscript{4}, Ian Hickson\textsuperscript{4}, Charlotte Knights\textsuperscript{4}, Niall M. B. Martin\textsuperscript{4}, Stephen P. Jackson\textsuperscript{4,5}, Graeme C. M. Smith\textsuperscript{4} & Alan Ashworth\textsuperscript{1,2}
BRCA2-deficient cell lines are hypersensitive to PARP inhibitors (Newcastle / Agouron Compounds)

"Therapeutic ratio" \( \sim 250 \)

AG014699 (Rucaparib)  
AG014361 (this expt)  

Mutation in BRCA1 or BRCA2 Results in Extreme Sensitivity to PARP Inhibition (Kudos/AZ Compounds)

Active
IC50 3.2 nM

Active
IC50 3.4 nM

Inactive Analogue
IC50 730 nM

BRCA1

Figure removed

Wild-type
Heterozygous
Homozygous

BRCA2

Wild-type
Heterozygous
Homozygous

Adapted from: Farmer et al. Nature 434, 917-921, 2005

(Institute of Cancer Research, London, Kudos Pharmaceuticals, Cambridge)
<table>
<thead>
<tr>
<th>Agent</th>
<th>Company</th>
<th>Route</th>
<th>Clinical Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rucaparib</td>
<td>Clovis</td>
<td>IV / Oral</td>
<td>Phase II/III</td>
</tr>
<tr>
<td>Olaparib</td>
<td>Astrazeneca</td>
<td>Oral</td>
<td>Licensed / Phase III</td>
</tr>
<tr>
<td>Veliparib</td>
<td>Abbvie</td>
<td>Oral</td>
<td>Phase I/II Combo?</td>
</tr>
<tr>
<td>Niraparib</td>
<td>Tesaro</td>
<td>Oral</td>
<td>Phase I/II/III</td>
</tr>
<tr>
<td>BMN-673</td>
<td>Biomarin</td>
<td>Oral</td>
<td>Phase I/II/III</td>
</tr>
</tbody>
</table>
Olaparib – Kudos / AstraZeneca

- Orally available PARP inhibitor generated responses in hereditary cancers in Phase I *
- Phase II results in patients with BRCA1 or 2 related breast and ovarian cancer presented at ASCO 2009
- Now licensed for patients with BRCA1 / BRCA2 related ovarian cancer

Olaparib significantly increases progression-free survival in patients with platinum-sensitive ovarian cancer

Rucaparib early development – the pitfalls of a pharmacodynamics endpoint
TBI-361* Inhibits PARP in LoVo Tumour Xenografts

* TBI 361 is a close analogue of rucaparib

Published data from Herbie Newell and other colleagues at the Northern Institute for Cancer Research, Newcastle, UK
Rucaparib (AG014699 Pharmacodynamics)
PARP Inhibitory Dose established using PD assay

PARP inhibition in PBLs
2 mg/m² AG014699

PARP inhibition in PBLs
12 mg/m² AG014699
Mean tumour PARP activity at 6 hours after a single dose of AG014699

![Graph showing PARP activity as % of pre-treatment for different doses of AG014699. The graph compares 4 mg/m², 12 mg/m², and 18 mg/m² doses, with PARP activity decreasing as the dose increases.]
Rucaparib – CR UK Phase II Study in BRCA Patients

Overall response rate 4%, Clinical Benefit Rate 34%

<table>
<thead>
<tr>
<th>Patient baseline characteristics (n=45)</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong> – no. (%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>45 (100)</td>
</tr>
<tr>
<td>Male</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Age - yr</strong></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>51</td>
</tr>
<tr>
<td>Range</td>
<td>28 - 72</td>
</tr>
<tr>
<td><strong>Tumour type – no. (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>19 (42)</td>
</tr>
<tr>
<td>Ovarian</td>
<td>26 (58)</td>
</tr>
<tr>
<td><strong>BRCA mutation/tumour sub-group –no. (%)</strong></td>
<td></td>
</tr>
<tr>
<td>BRCA1 breast</td>
<td>8 (18)</td>
</tr>
<tr>
<td>BRCA2 breast</td>
<td>11 (24)</td>
</tr>
<tr>
<td>BRCA1 ovary</td>
<td>16 (36)</td>
</tr>
<tr>
<td>BRCA2 ovary</td>
<td>10 (22)</td>
</tr>
<tr>
<td><strong>Mean no. prior chemotherapies (range)</strong></td>
<td>2 (1 – 4)</td>
</tr>
</tbody>
</table>

Dose 18 mg/m2/day for 5 days repeated every 3 weeks

Data taken from Yvette Drew et al, ASCO Poster 2011
Rucaparib: Highly Active in Women with mutant BRCA Ovarian Cancer and Prior Chemotherapy

Best target lesion response to rucaparib 600mg BID – both germline and somatic BRCA mutations included

- 71% ORR (RECIST or CA-125)
- 80% DCR
- Median of two prior therapies

Source: Company data
Comparison of two doses of Rucaparib in BRCA-related Ovarian Cancer (various studies)

18 mg/m$^2$ iv daily x 5 repeated every 3 weeks

650 mg/m$^2$ oral twice daily continuous
Clinical development of PARP Inhibitors

• Events leading to delays
  – Rucaparib ready for Phase I in 1998
  – Delayed until 2000 because Agouron taken over by Warner Lambert
  – Delayed until 2003 because of takeover by Pfizer
  – Shelved by Pfizer after Phase II because BRCA market size judged insufficient “5% of breast cancer”
  – Concerns that they may be genotoxic
  – AstraZeneca also stopped clinical development of olaparib and only resumed after a change of management

• Compensating events
  – They actually work! And have mild clinical toxicities
  – BRCA mutations more common than thought – 30% of ovarian cancers
  – BRCA mutations occur in more cancers than thought
  – HR deficit (BRCA-like phenotype) also common and may be detected by genomic markers
  – Evidence for secondary cancers as a result of genotoxicity minimal
Immunotherapy and cancer

- Immunotherapy has been researched for over 100 years (Coley’s toxin)
- In the last decade major advances have been made transforming the treatment of some common cancers
- Biomarkers are needed to identify patients who will benefit
- Promise for combination with immunological agents with each other and with non-immunological therapies
Drug Development in the future: Challenges and possible solutions (1)

- Finding treatments that work
  - Hopefully we are getting better at this!

- Regulation
  - It won’t go away but we should push for a more flexible approach
    - UK Saatchi bill – Advance or Quack’s Charter?

- Risk averse Pharma
  - Enhance academic facilities
  - Stick with small pharma / biotech as long as possible
  - Charitable / pharma partnerships

- Clinical development problems
  - Think of innovative solutions
Challenges and possible solutions

• Pharmaco-economic evaluations
  – Obtain good source data and keep challenging
  – Use PR methods

• Academic prejudice or fashionable areas
  – There is no-one so prejudiced as an academic with an ax to grind
  – This may make it difficult to obtain funding
  – Keep trying

• Cost of licensing trials and biomarker selection
  – Needs international collaboration and collaboration between health services and Pharma

• Silo mentality – designed to mean that no-one is responsible for failure
  – Get rid of it!
Linear Drug Development Pathways

- Target ID
- Target validation
- Screen development
- Primary screening
- Secondary screening
- Lead optimization
- Preclinical development
- Clinical development Phase I-III
- Regulatory approval/manufacture

De-orphaning receptors together with MS

Functional binding assays

Higher-information-content screening giving affinities and kinetics

Monitoring of drug serum levels etc.

High-throughput screening of arrayed targets and ligands

Nature Reviews | Drug Discovery
Interactive Model for Drug Development

- Preclinical testing
- Preclinical pharmacology, toxicology, biomarker development
- Assay Development and Screening
- Medicinal Chemistry
- Target Discovery
- Basic Biology
- Clinical Trials
Acknowledgements - 1

• Cancer Research UK

• Institute of Cancer Research / Royal Marsden Hospital
  – Ken Harrap
  – Eve Wiltshaw
  – Tim McElwain

• Johnson Matthey – Mike Clear

• Astrazeneca – Tom Boyle

• Eli Lilly – Axel Hanauske, Jackie Walling, Paulo Pauletti

• Agouron – Bob Jackson, Zdenek Hostomsky

• Newcastle University
Acknowledgements - 2

- UCL Cancer Institute
  - Chris Boshoff
  - Tariq Enver
  - Martin Forster, Rebecca Kristeleit, Sandra Strauss

- Teams of research nurses

- Colleagues, collaborators and patients

- The first-in Class PARP Inhibitor – Rucaparib - Newcastle Anticancer Drug Development Initiative, 1990
The Origins of the PARP Programme

• 1989 – initiative to discover new anticancer drugs in Newcastle
• Barbara Durkacz – had cloned PARP1
• Bernard Golding – Professor of Medicinal Chemistry - willing to collaborate
• Roger Griffin (5 April 1955 – 24 September 2014)
  – Medicinal Chemist with a brain the size of a planet
  – The Royal Society of Chemistry 2014 George and Christine Sosnovsky Award in Cancer Therapy