The Pharmaceutical Challenge of Cancer Research

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Formulation Unit

• Remit

To develop novel anti-cancer drugs selected by Cancer Research UK New Agents Committee for Phase I and II Clinical Trial

Pharmaceutical Translation Research

• Established in 1983

Bench to Bedside – Powder to Product – Molecule to Medicine
Formulation

- Multiple factors
- One goal
- Limited
  - Knowledge
  - Resource
  - Time

Formulation

- Drug
- Product
- Biopharmacy
- Quality
- Regulatory
- Excipients
- Manufacture
- Distribution
• Early Projects
• Research Advances
• Recent Projects
• Currents Trends
• Potential Answers
Early Example - 1984

• 1, 2, 4-triglycidyl urazol - Limited solubility & stability

• Reconstitution Fluid
  Switch from dextrose to NaCl

The analysis and animal pharmacokinetics of 1,2,4, triglycidyl urazol using a high-pressure liquid chromatographic technique

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Early Projects

- Many and varied
  Exact number unknown
- Small molecules

Trimesamol

RH1

Limonene

SRI 62 834
Clinical Trials

- 1, 2, 4-triglycidyl urazol
- Starting Dose
  - 30mg/m² escalated to 900mg/m²
- Toxicity
  - Myelosuppression, nausea, vomiting, phlebitis

- RH1
- Eligibility criteria
  - Proven cancer, refractory to treatment, no conventional therapy, >18 yrs, life expectancy >3 months

<table>
<thead>
<tr>
<th>Tumour Type</th>
<th>No</th>
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<tbody>
<tr>
<td>Colorectal</td>
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<tr>
<td>Gastric</td>
<td>3</td>
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<tr>
<td>NSCLC</td>
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<td>Melanoma</td>
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<tr>
<td>Merkel cell carcinoma</td>
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<td>Pancreatic</td>
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<tr>
<td>Renal</td>
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Common Issues

- Pharmacology
  - Cytotoxic chemotherapy
  - Limited administration
- Majority of formulations injections
- Drug solubility
  - Range of formulation techniques applied
- Drug stability
  - Hydrolytic – lyophilisation
  - Non-hydrolytic – physicochemistry
- General trials
Research Advances

• Imatinib – 2001
  “Dawn of targeted treatments”
Very Different Drugs

- **imatinib**
  - Solubility: 200mg/ml
  - Oral Bioavailability: 98%

- **nilotinib**
  - Solubility: sparingly
  - Oral Bioavailability: 31%

- **sorafenib**
  - Solubility: (1:2 DMSO:PBS) 0.3mg/ml
  - Oral Bioavailability: 50%
Intestinal Solubility Variation

- Impact of simulated gastrointestinal fluid composition

Impact on Dissolution

- Low solubility
  Slower dissolution
- Natural GIT variation
- Not applicable
  Amorphous
  Bioenhanced
  But does it stay in solution?
Biopharmaceutics Classification System

- **I**: Good Solubility & Permeability
- **IIa**: Dissolution Rate Limited
- **IIb**: Solubility Limited
- **III**: Good Solubility & Poor Permeability
- **IV**: Poor Solubility & Poor Permeability
Impact on pharmacokinetics

- Phase 1 Dose escalation studies – BCS I to BCS II

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<table>
<thead>
<tr>
<th>AUC0-24h (nmol.h.L⁻¹)</th>
<th>Peak Concentration (nM)</th>
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CRUK07/13

Impacts receptor exposure
Bioenhanced Formulations

- Improve dissolution
  Amorphous
  Solid solutions
- Spring and parachute effect
- Stability
  Chemical & Physical
- Solid solution
  Drug/Excipient
  Intimate contact
- Excipient Quality
Common Issues

- Pharmacology
  - Targeted chemotherapy
    - Single pathway
  - Continuous administration
- Majority of formulations oral
- Drug solubility – impacts on drug absorption
- Bioenhanced formulations
  - Stability problems
- Targeted trials
Current Trends I

- Smaller patient numbers
- Therapy cost increases
- Combination therapies
- Agile therapy
- Rapid changes
Current Trends II

Pharmaceutical Hockey Stick

Guide to Good Pharmaceutical Manufacturing Practice 1983
Mass Customisation

• This is not new!
Future Pharmaceutical Challenge

Solutions – scaleable, quick, agile, low cost, GMP compliant, patient friendly

Does one formulation and manufacturing technology fit all?

Are there other aspects that can change?

Basic and applied research required

3D Printing
Just in time manufacture
Small scale development
Individual patient trials
3D Printing & Injection Moulding

• Hot topic – a la mode
  – Multiple groups UK and world-wide - multiple approaches
• Marketed product
  – New field
• Multiple areas of research
  – Equipment, process, parameters, formulation, product
• Future
  – Wide open
Predictive Pharmaceutics

Predict, Integrate, Design, Test

Discovery

Development

Treatment

µg  mg  g(?)

Nature Reviews Drug Discovery

Continuous Unit Operations which could be Continuous
Acknowledgements

• You for listening

• Collaborators
  Many and varied
  Local, national and international

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Gavin Halbert