Successful Transfer of Innovative Technologies from Lab-Patient-Routine Use
Lessons Learnt and Global Opportunities

Ruth Duncan
Cardiff, UK
profruthduncan@btinternet.com

International Standards: Cooperative Research and Regulation: Lessons and Challenges

Nanotechnology and Oncology

What policies support cooperative research internationally?

RESEARCH
- how to increase the probability of viable candidates for clinical evaluation

What lessons can US regulators learn from regulation of nanotechnology in other countries?

DEVELOPMENT
- how to increase the probability of successful and timely product development

What policies support product development and regulation internationally?
Even though survival trends in EU are improving the medical needs is evident:

- 1 death every 4 mins in UK
- 25 deaths/min globally

How to harness:

i) increased understanding of the molecular basis of cancer(s)
ii) technological opportunities arising from innovation

For “Effective Policy” there is a need to understand both clinical needs and limitations of technology: Avoidance of ‘HYPE’

20% of cancers are induced by infectious agents:
Nanomedicine in Oncology

EACH AREA REQUIRES A DIFFERENT PRODUCT DEVELOPMENT PATHWAY

Diagnostic Tools
- FOR USE OUTSIDE THE PATIENT
- identification of new targets for therapeutic intervention
- improved detection of predisposition
- characterisation of disease (choice of therapy)
- monitoring disease progression (response to treatment)

Diagnostic, Surgical and Theranostic Tools
- FOR PATIENT ADMINISTRATION
- monitoring of disease/aiding treatment regime/localised treatment
- improved surgical tools
- one shot combinations

Improved Treatments
- FOR PATIENT ADMINISTRATION
- improved tumour drug targeting and delivery
- delivery of drug combinations
- locally activated therapy

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RESEARCH - Build on the Established State of Art for Development of Improved, Innovative Anti-Cancer Therapeutics, Diagnostics and Combinations to Benchmark improvements

Lessons that can be learnt from the last three decades
- Lead Candidate Optimisation
  - robust methodology
  - an early understanding of Regulatory needs

DISEASE FOCUS - THEN DESIGN
not random screening

Local delivery
Controlled Release
Nanomedicines for cancer
TARGETING METASTATIC CANCER

Improved Formulations
- hydrophobic drugs
- oral bioavailability

MULTIMODAL THERAPY Theranostics

Improved efficacy reduced toxicity

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Understanding the Industrial and Regulatory Development Requirements

The Regulatory Process

Agencies make an integrated assessment

The risk-benefit balance

Carry out rigorous post-market surveillance ('pharmacovigilance')

'safety'  'efficacy'

There is an awareness of the need to be proactive in identifying any gaps before innovative technologies emerge.


The Presentation will Include Specific Examples to Guide the Discussion

How to Evolve Best Practice (Globally) to Incorporate Advances in Nanoscience and Nanotechnologies?

'The Case by Case Needs

How to avoid Gaps

Written - For Communication? the public; scientists - For Legislation?

Standards

Experimental materials and protocols

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Nanotechnology in Medicine
Global Opportunities/Challenge(s)

• Terminology
  definitions and effective communication

• Good Science
  robust methods and avoiding hype

• Translation
  from lab to patient

• Fragmentation
  • avoid regional/discipline ambition
  • focus on technical competence and past experience
  • bring all stakeholders together from the start

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Nano – Clear Terminology- Avoiding Hype; CASE BY CASE BASIS IS IMPORTANT

From Metric Units of Measure Nanoscale is 1 - 999 nm
Irrelevant and Unjustified Thresholds a Hindrance not a Help

Top Down and Bottom-Up Technologies have equal Importance

Don't Call everything a Plane
Deciding to call everything a ‘nanoparticle’ at best is non-sense and worst unhelpful

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Wise Words – Avoidance of Unsubstantiated Boundaries that create Gaps

FDA expects many nanotechnology products that we regulate to span the regulatory boundaries between pharmaceuticals, medical devices and biologicals. These will be regulated as "Combination Products" for which the regulatory pathway has been established by statute.

It is valuable to repeat here that FDA has traditionally regulated many products with particulate materials in this size range. FDA believes that the existing battery of pharmacotoxicity tests is probably adequate for most nanotechnology products that we will regulate. Particle size is not the issue. As new toxicological risks that derive from the new materials and/or new conformations of existing materials are identified, new tests will be required.

It is quite likely that new therapeutic benefits are being derived from products that are smaller than their traditional form but fall above the 100 nm size-range limit of nanotechnology.

Terminology: A Strategic Research Agenda Needs to Know What's New and Define the Boundaries – Sound Scientific Basis not just $
Genomics and proteomics research is identifying novel tumor-specific molecular targets.


In Cancer > 95% of drugs entering clinical trial fail in clinical development.

Innovative Drug Delivery Systems Nanomedicines


Harnessing the state of the art in all scientific disciplines and stakeholders from the start.

For Translation the importance of an integrated approach to research and development.

Importance of Research Conferences, Workshops and Training incl. World Leading Experts in all fields and with equal participation of ALL stakeholders.

Willingness to listen to others - must avoid the "in and out" syndrome.
- Education early for clinical fellows (scientific basis)
- For scientists (medical reality)

- Scientists -Academia -Industry
- Clinicians
- Policy Makers
- Regulators
- Patient Representatives
- Ethics/Social Sciences
**The Gordon Research Conference is a very Important Forum**

**GRC Drug Carriers in Medicine & Biology (SINCE 1978)**
August 15–20, 2010 Waterville Valley Resort Waterville Valley, NH
Chairs: Patrick S. Stayton & Philip S. Low
Vice Chairs: Vladimir R. Muzykantov & Joseph M. Desimone
Applications for this meeting must be submitted by July 25, 2010.

**GRC Cancer Nanotechnology (Starting 2011)**
July 17–22, 2011 Colby College
Chair: Piotr Grodzinski
Vice Chair: James R. Baker

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**In The Research Phase There are Specific challenges for the Converging Disciplines**

**YES**
- Working in Teams with sound core technical competences in all fields together from day 1

**NO**
- Chemistry
- Biology
- Preclinical
- Clinical

**Knowing where you are on the road from lab to clinic**

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Nanomedicine(s) – Nanopharmaceuticals are not new!!

First products approved ~1990

Established Technologies: carefully optimised, complex multicomponent structures

PROBLEMS
- Only 0.001-0.01% dose localises to tumour
- Labelled antibodies show a significant improvement in shrinking tumors but significantly increased survival is lacking
- Difficult to treat solid tumours

CURRENT STATUS OF TARGETING

Issues
- undesirable pharmacokinetics,
- poor tumor uptake,
- long circulation times delivering radiotoxicity to non-target tissues
- high immunogenicity
- heterogeneous vascularisation of tumours
- heterogeneous receptor distribution and/or saturation

Theranostics - “Combining Diagnosis and Therapy into a single system that can be localised at the cellular and molecular level”

The Starting Point: Antibodies Carrying Therapeutic Isotopes

2002 90Y-Ibritumomab tiuxetan used to treat the indolent form of NHL (based on Rituximab)
2003 131I-Tositumomab for the treatment of NHL
Choosing the right materials for proposed use/route of administration

- Reproducible Preparation
- Sufficient therapeutic carrying capacity
- For meaningful bioassay, need a well characterised material - with well defined impurities
- Need Relevant and Quantitative Assays
- For further development, need early safety information relevant to proposed use
- Keep it simple!!

Potential for new mechanisms of resistance
- poor EPR - clinical importance in all tumours ??
- shut down of endocytosis
- wrong intracellular trafficking
- variations in activating enzyme level, pH etc

New PATIENT BIOMARKERS
- PATIENT SELECTION FOR CLINICAL TRIAL
For Preclinical Safety, the 'product' must be considered in its entirety.

Understanding the stability of ALL covalent and non covalent associations (including imaging probes and targeting residues).

Understanding the fate of Primary Metabolites.

There is Need for Greater Appreciation of Polymer Science and more generally the key factors (due to heterogeneity) in a Specification that impact Quality/Safety/Efficacy.

Manufacture, characterisation and control of 'Quality'

Challenges for reproducible manufacture on large scale.

- Validated techniques for determination of:
  - product identity
  - impurities
  - strength
  - MW and polydispersity
  - New types of impurities

2D NOESY/TOSY NMR

GPC + Universal Calibration

HPLC – free and bound drug targeting residues

Small-Angle Neutron Scattering – solution conformation

Polydispersity

Heterogeneity – drug – targeting residues

Heterogeneity – need for specification relevant to Safety/Efficacy.
Formulations containing:
- surfactant (polysorbate 80) as a dissolution enhancer
- a soluble filler like lactose
- a small amount of ethanol
- filter sterilised
- freeze dried

Lyophilised cake reconstituted with water for injection or NaCl dissolution (~2 min).

Need for a Greater understanding that Formulations and not the active (nanopar pharmaceutical) will be given to patients - IMPLICATIONS FOR QC/SE

Challenges for development of polymer conjugates:
- Terminology for description of polymer conjugates
- Manufacture of reproducible chemistry on large scale
- Validated techniques for determination of conjugate identity
- Strengths - Mw and polydispersity
- Setting an appropriate specification - safety, efficacy
- Formulation development
- Preclinical toxicology - safety studies
- Clinical protocol design

Personal CRC Experience - Important Lessons for Translational Research

1987 The first meeting of the Phase I/II Committee

1992 The Drug Development Office (DDO) internationally accepted quality standards to ensure that the data produced be acceptable to the pharmaceutical industry.

- the use of rodent-only toxicology studies for first-in-human trials with direct acting anticancer agents
- compound-oriented protocols - the intended clinical route and schedule of administration is managed as closely as possible in the preclinical safety studies

- best endeavours GMP Manufacturing (Min. 2 batches)
- GLP Validation of Characterisation Techniques
- Formulation Development
- Accelerated Stability

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Regulation: Not too loose ..... but not too tight
- getting the right balance; a global discussion; must ensure advances reach patients quickly with careful reflection on risk:benefit

Choice of technologies with potential for adequate Quality, Safety and Efficacy

Regulatory Considerations: GLP-GMP-GCP
From active substance and to the finished product

- Non-clinical pharmacology and pharmacokinetics ** Non GLP
- Manufacture, characterisation and control of the 'Drug Substance'
  - active substance
  - impurities
  - specifications
  - analytical procedures
  - analytical validation
- Pharmaceutical Development
  - excipients
  - sterilisation
  - stability
  - radiopharmaceuticals
- Packaging
  - Fixed Combination Medicinal products

Non-clinical safety
- toxicokinetics
- pharmacokinetics
- toxicology - single dose - repeated dose
- genotoxicity
- carcinogenicity
- reproductive and developmental toxicity
- local tolerance
- immunotoxicity

Clinical pharmacology
- clinical trial design (small patient populations)
- specific considerations for target disease/patient population
- drug interactions

Environmental Risk Assessment
- Pharmacovigilance
- Pharmacoconomics

People of all ages benefit from ethical pharmaceutical and clinical advances used to treat disease. The waste of taxpayers' and charitable money on red tape has managed to reduce productivity but not enhance safety.

Over the same period, since 2014, other European agencies have logged a stable or increased number of trials.

The top five recommendations to strengthen IDC in Europe as ranked by the consensus conference were as follows:
1. To improve the education, training and career structure and opportunities for scientists involved in patient-oriented clinical research.
2. To increase levels of funding for IDC.
3. To adopt a 'risk-based' approach to the regulation of IDC.
4. To streamline procedures for obtaining authorisation for IDC.
5. To ensure that IDC are carried out with an appropriate number of patients to produce statistically reliable results so that the trials are 'necessarily powered.'
Some General Conclusions

- Pharmacokinetically-Guided Design
- Using Materials that are fit for "purpose"
- Greater Quantitation and comparison with existing technologies (PK/PD)
- Careful design of appropriate models bearing in mind PK
- Keep it simple
- Choose technologies with greatest possibility to translate to clinical trial

Some Specific Questions

- What is Nanomedicine? **HOW TO AVOID HYPE?**

  - Is it possible to deliver the promise of “Nanotechnology” in Oncology?
    - Can inter-disciplinarity triumph?
    - The role of the coach

  - Will we ever have a terminology that suits all?
    - That avoids hype?
    - That is embraced by all scientific disciplines?
    - Top down and bottom up?
    - That can meet legislative regulatory needs
      - For first generation technologies/ for first generation similars
      - For new technologies; materials and formulations
      - That public and politicians understand

  - We must promote robust methodologies
    - For choice of lead candidates; in vitro in vivo PK/PD
    - For GMP manufacturing validated characterisation, formulation and GLP toxicology
    - For clinical trial design-appropriate biomarkers

  - How to continue evolution of the Regulatory System?
    - Avoid gaps arising from new materials; new technologies; combinations