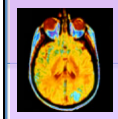




Workshop on Policy Issues in Nanotechnology and Oncology
Washington DC, July 12-13, 2010

Successful Transfer of Innovative Technologies from Lab-Patient-Routine Use

Lessons Learnt and Global Opportunities

Ruth Duncan

Cardiff, UK
profruthduncan@btinternet.com

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?

What policies support product development and regulation internationally?

→

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

Declaration of Interests ..... comments made are personal opinions

supported by Cancer Research Campaign 1975-1992

FARMITALIA CARLO ERBA
Pharmacia
Pfizer

HPMA copolymer anthracyclines

HPMA copolymer camptothecin and paclitaxel

The School of Pharmacy
University of London

Denritech/Dendritic Nanotechnologies

HPMA copolymer platinates

PAMAM Dendrimer platinates

Polymer platinates

Vectura

ML LABORATORIES

Access Pharmaceuticals

PELT

Dextrin-drug conjugates

Member Ad-Hoc Advisory Group Nanomedicine

Member WG SCENHIR Nanomaterials Definition

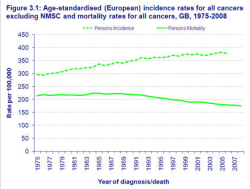
Past member MHRA CPS Sub-committee

For "Effective Policy" there is a need to understand both clinical needs and limitations of technology

Avoidance of 'HYPE'

Even though survival trends in EU are improving the medical needs is evident

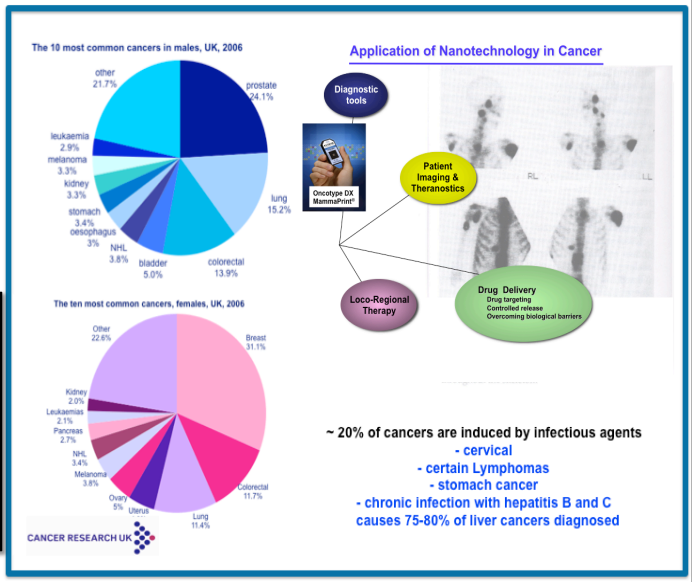
~1 death every 4 min in UK
~ 25 deaths/min Globally



How to harness

i) increased understanding of the molecular basis of cancer(s)

ii) technological opportunities arising from innovation



~ 20% of cancers are induced by infectious agents
- cervical
- certain Lymphomas
- stomach cancer
- chronic infection with hepatitis B and C

causes 75-80% of liver cancers diagnosed

Nanomedicine in Oncology

EACH AREA REQUIRES A DIFFERENT PRODUCT DEVELOPMENT PATHWAY

Diagnostic Tools

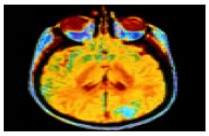
– FOR USE OUTSIDE THE PATIENT

- 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

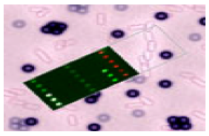
- monitoring of disease/aiding treatment regime/localised treatment
- improved surgical tools
- one shot combinations



Improved Treatments

– FOR PATIENT ADMINISTRATION

- improved tumour drug targeting and delivery
- delivery of drug combinations
- locally activated therapy

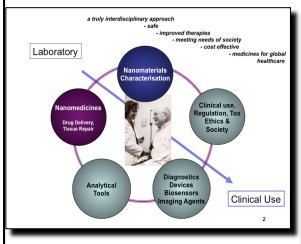


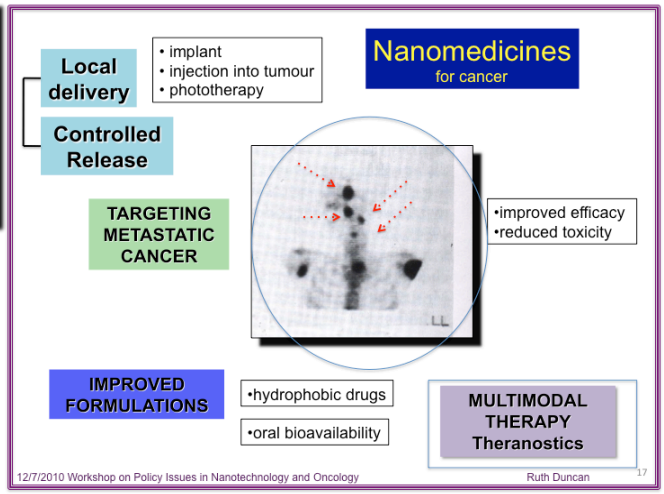
RESEARCH - Build on the Established State of Art for Development of Improved, Innovative Anti-Cancer Therapeutics, Diagnostics and Combinations to Benchmark improvements

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





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')

'quality'

safety

efficacy

There is an awareness of the need to be proactive In identifying any gaps before new, innovative, technologies emerge

Gaspar, R. and Duncan, R. (2009) Polymeric carriers: preclinical safety and the regulatory implications for design and development of polymer therapeutics. In: Vicent, M. J. and Duncan R. (Eds. Theme Issue: Polymer Therapeutics: Clinical Applications and Challenges for Development. Adv. Drug Del. Rev. 61, 1220-1231.

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

Standards

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

Experimental materials and protocols

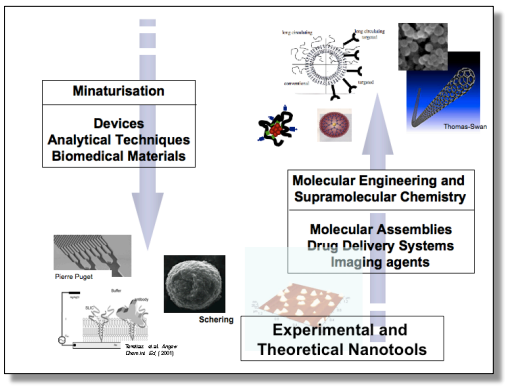
Nanotechnology in Medicine Global Opportunities/Challenge(s)

- **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

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

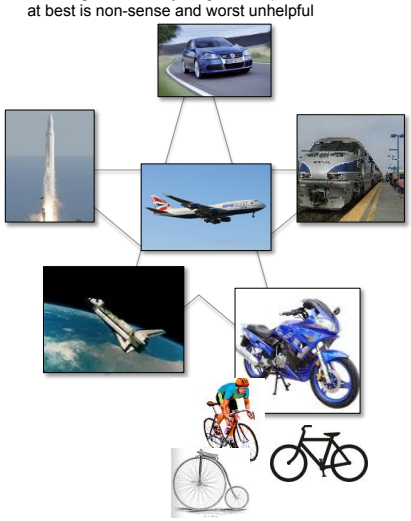
From Metric Units of Measure Nanoscale is 1 - 999 nm
Irrelevant and Unjustified Thresholds a Hindrance not a Help

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



Wise Words – Avoidance of Unsubstantiated Boundaries that create Gaps

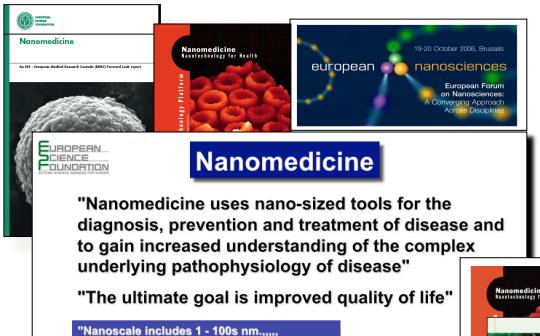
FDA expects many nanotechnology products that we regulate to span the regulatory boundaries between pharmaceuticals, medical devices and biologicals. These will be regulated as **"Combination Products"** for which the regulatory pathway has been established by statute.

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.

www.nanopharmaceuticals.org/**FDA.html**

Terminology: A Strategic Research Agenda Needs to Know What's New and Define the Boundaries – Sound Scientific Basis not just $

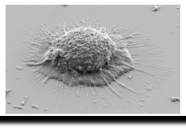


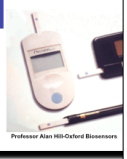
Nanomedicine

"Nanomedicine uses nano-sized tools for the diagnosis, prevention and treatment of disease and to gain increased understanding of the complex underlying pathophysiology of disease"

"The ultimate goal is improved quality of life"

"Nanoscale includes 1 - 100s nm.,,,,,,
Also of relevance are nano-interactions within the framework of a larger device"





1-1000 nm covers many nano-sized products already in the market

each was designed for their unique properties

" Nanomedicine(s) or Nanopharmaceuticals"

" Nanopharmaceuticals can be developed either as drug delivery systems or biologically active drug products.

This sub-discipline was defined as the science and technology of nanometre size scale complex systems, consisting of at ***least two components***, one of which being the active ingredient. In this field the concept of nanoscale was seen to range from 1 to 1000 nm."

Designing Nanopharmaceuticals and Imaging Agents for Oncology Applications

Genomics and proteomics research is identifying
Novel tumor-specific molecular targets

Chabner, B. A. & Roberts (2005)
Nature Rev. Cancer 5 65-72

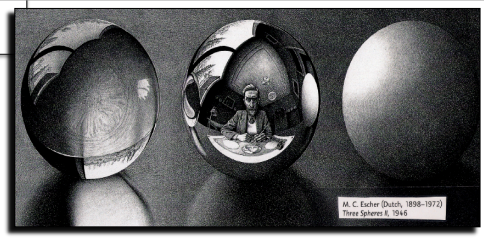
In Cancer > 95 % of drugs entering clinical trial fail in clinical development

Collins and Workman Nature Chemical Biology 2, 689-700 Dec 2006

Innovative Drug Delivery Systems Nanomedicines

Duncan, R. (2006) Nature Reviews Cancer, 6, 688-701

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)

Series of Interdisciplinary Nanomedicine Research Conferences and Summer Schools
– with all stakeholders including ethics, social scientists and patient representatives

- Scientists -Academia -Industry
- Clinicians
- Policy Makers
- Regulators
- Patient Representatives
- Ethics/Social Sciences

The Gordon Research Conference is a very Important Forum

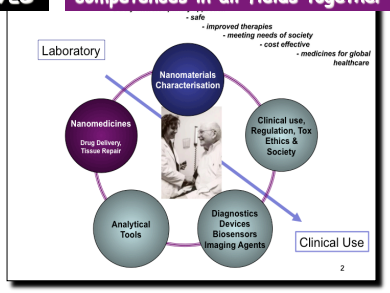
(SINCE 1978)

***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. Desimon
Applications for this meeting must be submitted by **July 25, 2010.**

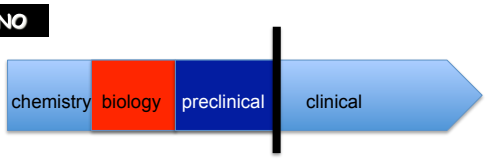
***GRC* Cancer Nanotechnology (Starting 2011)**
July 17-22, 2011 Colby College
Chair: Piotr Grodzinski
Vice Chair: James R. Baker

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

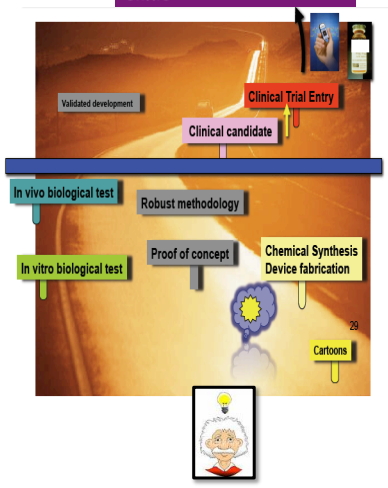
YES — Working in Teams with sound core technical competences in all fields together from day 1



NO



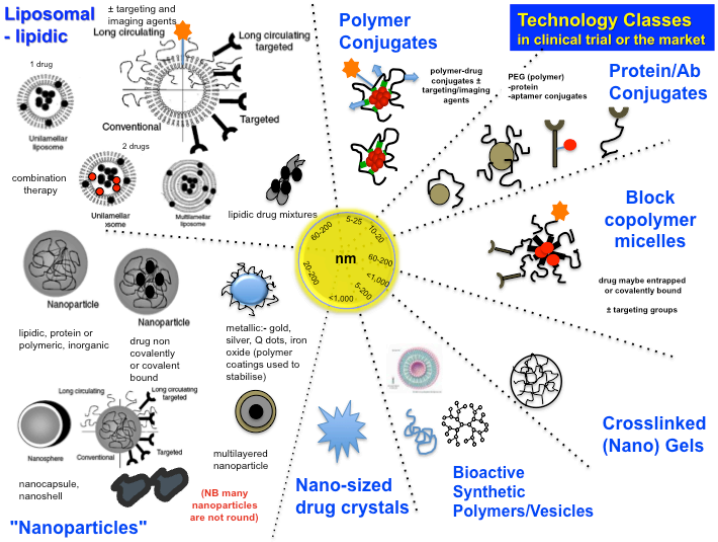
Knowing where you are on the road from lab to clinic



Established Technologies: carefully optimised, complex multicomponent structures

Nanomedicine(s) – Nanopharmaceuticals are not new !!

First products approved ~1990



Theranostics - "Combining Diagnosis and Therapy into a single system that can be localised at the at the Cellular and Molecular level"

The Starting Point: Antibodies Carrying Therapeutic Isotopes

2002 ^{90}Y-ibritumomab tiuxetan **used to treat the indolent form of NHL (based on Rituximab)**

2003 ^{131}I-tositumomab for the treatment of NHL

CURRENT STATUS OF TARGETING

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

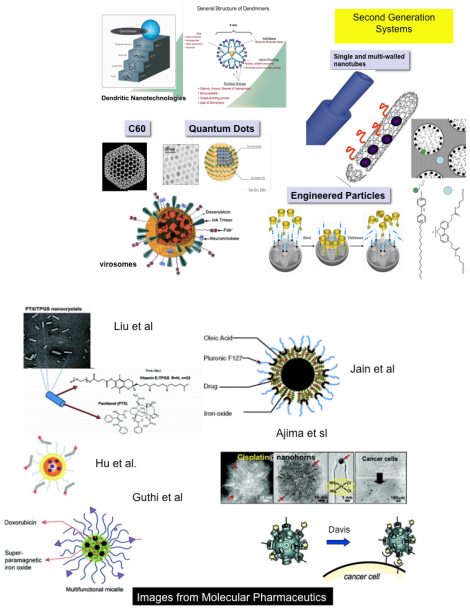
Difficult to treat solid tumours

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**

Optimization of Radioimmunotherapy of Solid Tumors: Biological Impediments and Their Modulation Jain et al. Clin Cancer Res 2007;13(5) 1374

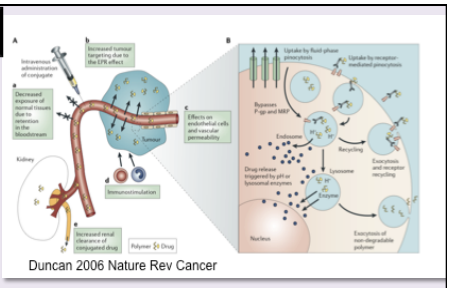
Choosing the right materials for proposed use/route of administration



- 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!!

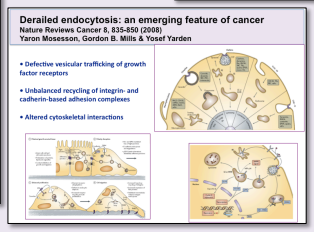
Biological Rationale for Design

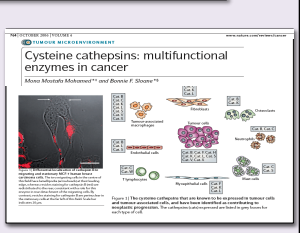
- INTERDISCIPLINARY TEAM FROM DAY ONE
- Agree target disease
- Select most appropriate 'Nanotech'
- Quatitative and **Pharmacokinetically-Guided Design**
  e.g. - stability - drug release rate (and site)
  - intracellular fate
  - biodistribution in vivo
- BENCH MARK OUTCOMES AGAINST EXISTING APPROACHES – pharmacological/imaging

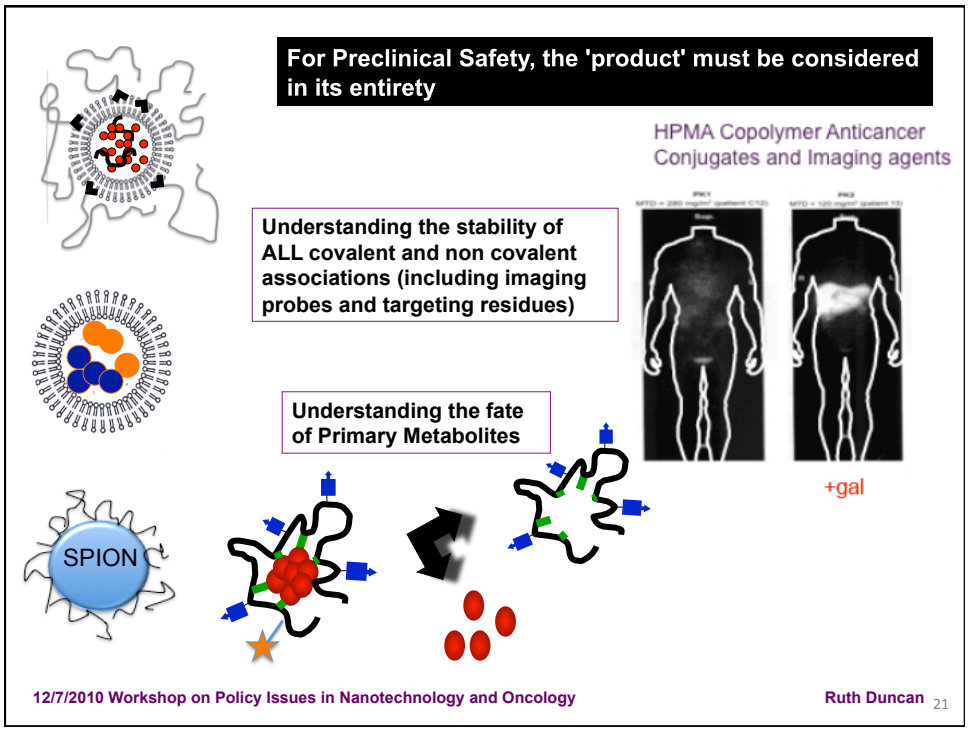

Duncan 2006 Nature Rev Cancer

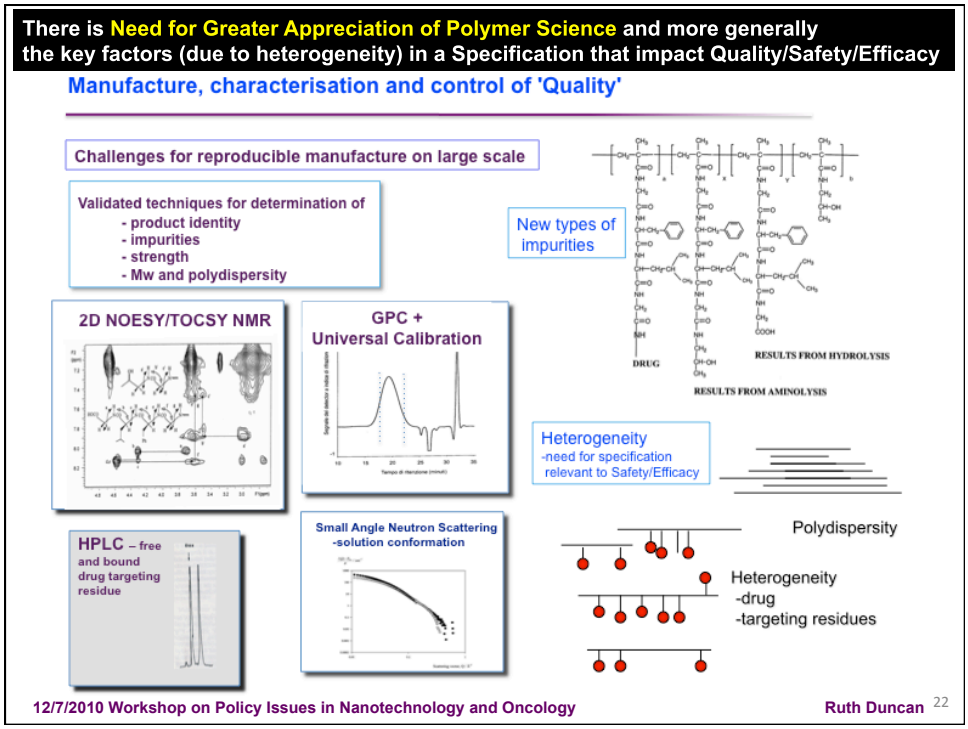
Potential for new mechanisms of resistance
- poor EPR –clinical importance in all tumours ??
- shut down of endocytosis
- wrong intracellular trafficking
- variations in activating enzyme level, pH etc

New PATIENT BIOMARKERS
– PATIENT SELECTION FOR CLINICAL TRIAL






For Preclinical Safety, the 'product' must be considered in its entirety
HPMA Copolymer Anticancer Conjugates and Imaging agents
Understanding the stability of ALL covalent and non covalent associations (including imaging probes and targeting residues)
Understanding the fate of Primary Metabolites
SPION
+gal
12/7/2010 Workshop on Policy Issues in Nanotechnology and Oncology
Ruth Duncan 21


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
DRUG
RESULTS FROM HYDROLYSIS
RESULTS FROM AMINOLYSIS
2D NOESY/TOCSY NMR
GPC + Universal Calibration
Heterogeneity
-need for specification relevant to Safety/Efficacy
HPLC – free and bound drug targeting residue
Small Angle Neutron Scattering -solution conformation
Polydispersity
Heterogeneity
-drug
-targeting residues
12/7/2010 Workshop on Policy Issues in Nanotechnology and Oncology
Ruth Duncan 22

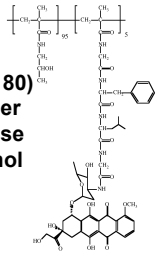
Need for a Greater understanding that Formulations and not the active (nanoparmaceutical) will be given to patients –IMPLICATIONS FORQ/S/E

Challenges for development of polymer conjugates

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

Pharmaceutical Formulation(s)

Formulations containing

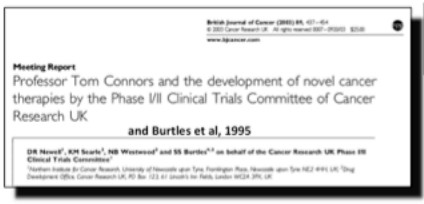


- surfactant (polysorbate 80) as a dissolution enhancer
- a soluble filler like lactose
- a small amount of ethanol

- filter sterilised
- freeze dried

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

Personal CRC Experience - Important Lessons for Translational Research



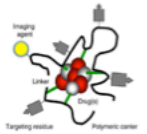
Meeting Report

Professor Tom Connors and the development of novel cancer therapies by the Phase I/II Clinical Trials Committee of Cancer Research UK

and Burtles et al, 1995

1980
The first meeting of the Phase I/II Committee

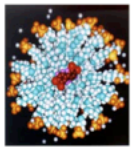
1992
The Drug Development Office (DDO) internationally accepted quality standards to ensure that the data produced be acceptable to the pharmaceutical industry.



. The Committee identified four key needs

- To stimulate the submission of compounds for Phase I testing.
- To simplify and provide access to preclinical toxicology.
- To develop clinically tractable formulations for new drugs that complied with regulatory requirements.
- To open a dialogue with the Committee on Safety of Medicines in order to establish a legal framework within which clinical trials with academic drugs could be undertaken.

- the use of rodent-only toxicology studies for first-in-human trials with direct acting anticancer agents
- compound-orientated protocols -the intended clinical route and schedule of administration is mirrored 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

This approach, coupled with innovative clinical trial designs that promote patient enrolment to doses that are likely to be effective, and the use of clinical centres with proven expertise in early clinical trials, ensures that the need to select a safe starting dose and animal welfare issues are appropriately balanced.

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

From The Times January 14, 2009

TIMESONLINE

2009

UK research trials are on verge of extinction

Clinical research in the UK is a great achievement and it is disturbing that many biotech companies face extinction

"European directives introduced to "harmonise" clinical research have led, in the UK, to an explosion of agencies that add months or even years to the simplest and safest pieces of clinical research, and millions of pounds to the cost — for those few investigators with the patience to persist.

The pharmaceutical industry now recruits only one third the number of patients to clinical trials in the UK compared with the period before the EU clinical trials directive; the number of studies seeking ethical approval has fallen by 30 per cent; and the Government's regulatory agency has logged a 50 per cent reduction in non-commercial trial authorisations."

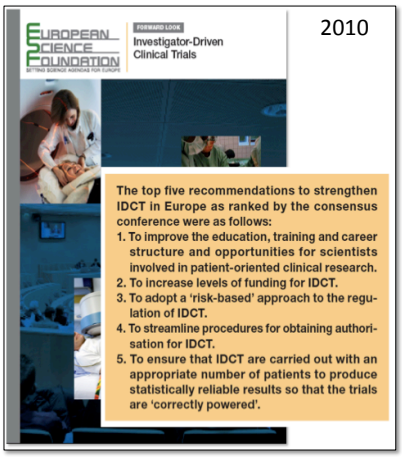
"People of all ages benefit from ethical pharmaceutical and clinical advances used to treat disease. The waste of taxpayers' and charitable money on red tape has managed to reduce productivity but not enhance safety"

Over the same period, since 2004, other European agencies have logged a stable or increased number of trials.

12/7/2010 Workshop on Policy Issues in Nanotechnology and Oncology Ruth Duncan 38

NEXT STEPS ?

2010



The top five recommendations to strengthen IDCT 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 IDCT.
3. To adopt a 'risk-based' approach to the regulation of IDCT.
4. To streamline procedures for obtaining authorisation for IDCT.
5. To ensure that IDCT are carried out with an appropriate number of patients to produce statistically reliable results so that the trials are 'correctly powered'.

12/7/2010 Workshop on Policy Issues in Nanotechnology and Oncology Ruth Duncan 25

Choosing technologies with potential for adequate Quality, Safety and Efficacy

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

Gaspar & Duncan Adv Drud Del Rev 2009

Consideration on a case by case basis

- 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**
- **Pharmacoeconomics**

12/7/2010 Workshop on Policy Issues in Nanotechnology and Oncology Ruth Duncan 31

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

Benchmark against existing technologies Forty Years of Advanced Drug Delivery, Clinical and Regulatory Experience should guide .....what to do .... and even more what not to do

NEED A DISEASE AND PRODUCT FOCUS AS FIRST GOAL

COMMENTARY

Seven challenges for nanomedicine

WENDY R. SANHAI*, JASON H. SAKAMOTO*, RICHARD CANADY* AND MAURO FERRARI*†‡

nature nanotechnology | VOL 3 | MAY 2008 | www.nature.com/naturenanotechnology

~~7.~~ 1. Analytical tool kit for manufacturing, accompanied by specification sheet of toxicological, safety, and biodistribution properties obtained through standardized, validated methods.

1. Determination of the distribution of nanoparticulate carriers in the body
2. Development of imaging modalities for visualizing the biodistribution - with quantitative mass-balance information
3. Quantitation of compartmental transport across boundaries in the body.

4./5. Need for new mathematical and computer models

6. Establishment of reference materials and consensus testing

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 generations 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