European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

29th April 2009

Polymer Therapeutics as Nanomedicines

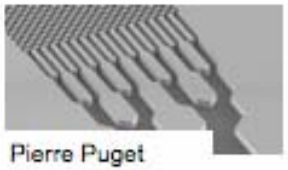
Converging scientific disciplines bringing huge opportunities, but how to ensure healthcare benefits ?

Ruth Duncan
duncanr@cf.ac.uk

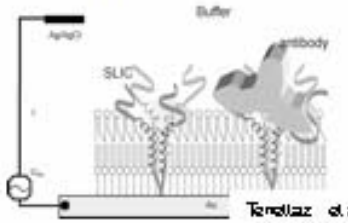
"Nano" medicine

Minaturisation

Devices
Analytical Techniques
Biomedical Materials

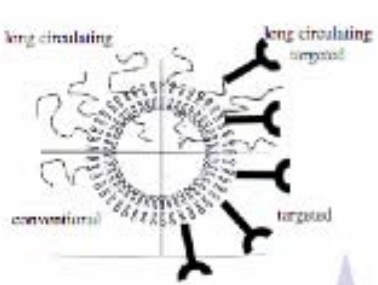


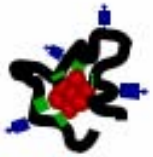
Pierre Puget

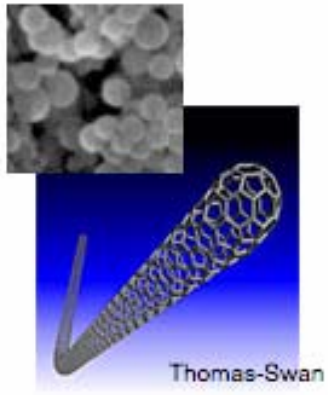


Terstiaz et al. Angew Chem Int Ed (2001)

Schering



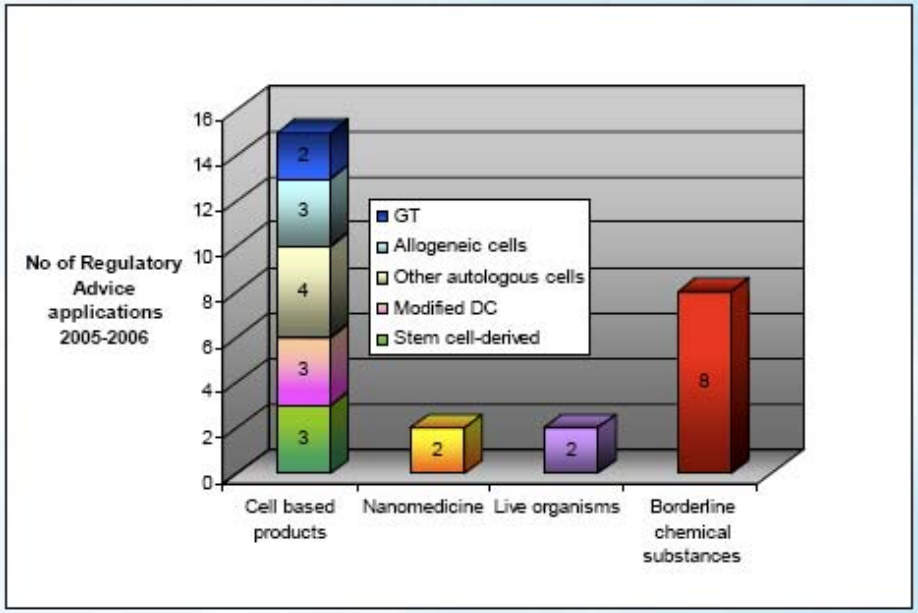




Molecular Engineering and Supramolecular Chemistry

Molecular Assemblies
Drug Delivery Systems
Imaging agents

Product categories under Regulatory Advice



- ✓ Cell-based products represent the majority of products in Regulatory Classification requests
- ✓ Cell-based gene therapy products indicate an emerging trend in new therapies
- ✓ Borderline Chemical substances for innovative diagnostic/therapeutic strategies
- ✓ Nanomedicine, and in particular, therapeutic nanoparticles as one of the newest cancer-specific treatments

How New ??

European Medicines Agency
Pre-authorisation Evaluation o

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

REFLECTION PAPER ON NANOTECHNOLOGY-BASED MEDICINAL PRODUCTS FOR HUMAN USE

ADOPTION BY CHMP FOR RELEASE	June 2006

"Medicinal products containing nanoparticles have already been authorised both in EU and the US under the existing regulatory frameworks"

- **quality**
- **safety**
- **efficacy**
- **risk management**

" Nanomedicine(s) or Nanopharmaceuticals"

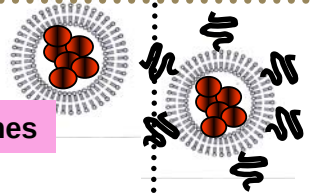
" Nanopharmaceuticals can be developed either as **drug delivery systems** or **biologically active drug products.**

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."

www.esf.org

Evolution of Nanomedicines - drug targeting and controlled release

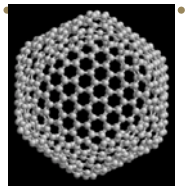
1970s | 1980s | 1990s | 2000s | 2008



Liposomes

Doxil®,Caelyx®

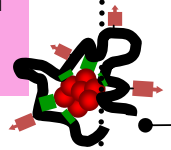
nanocrystals oral



SMANCS, Oncospar®

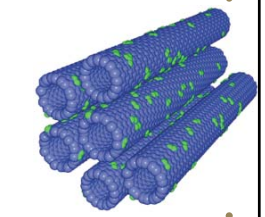
PEG-interferon

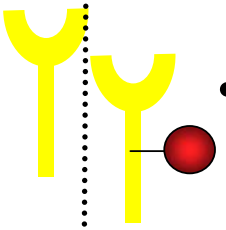
Polymer-protein and -drug conjugates



Neulasta™

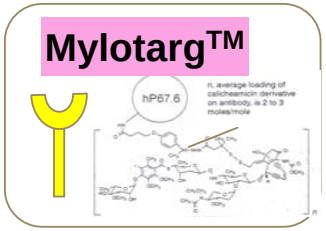
XYOTAX™; OPAXIO™

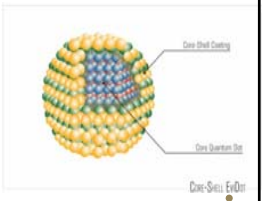




Antibody conjugates

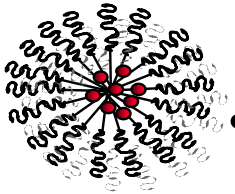
Mylotarg™

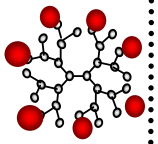




polymer micelles

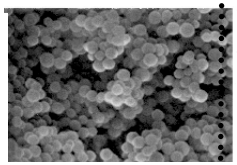
dendrimers

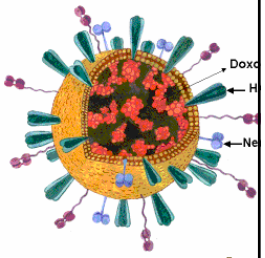




Nanoparticles

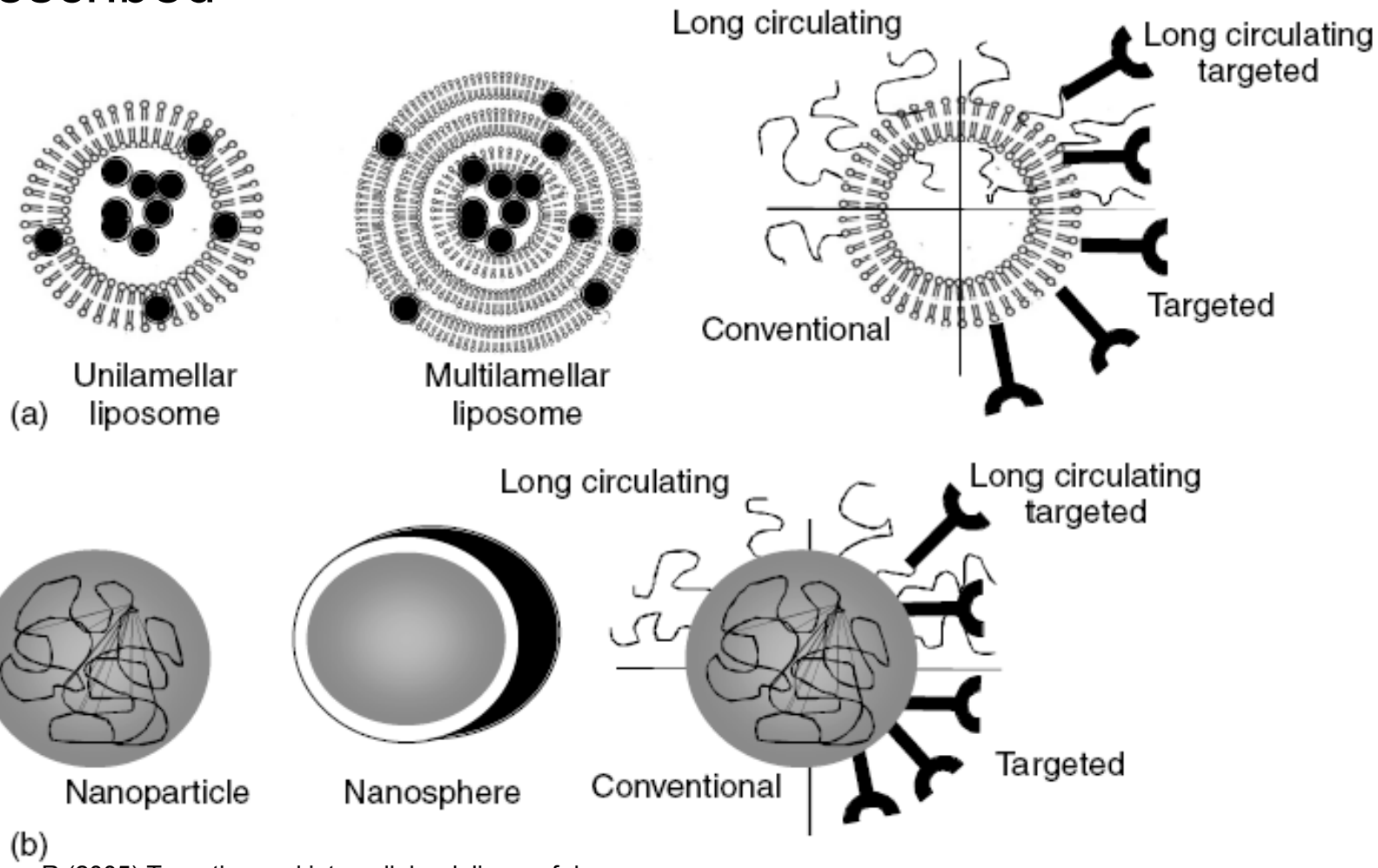
SP1049C





Abraxane™

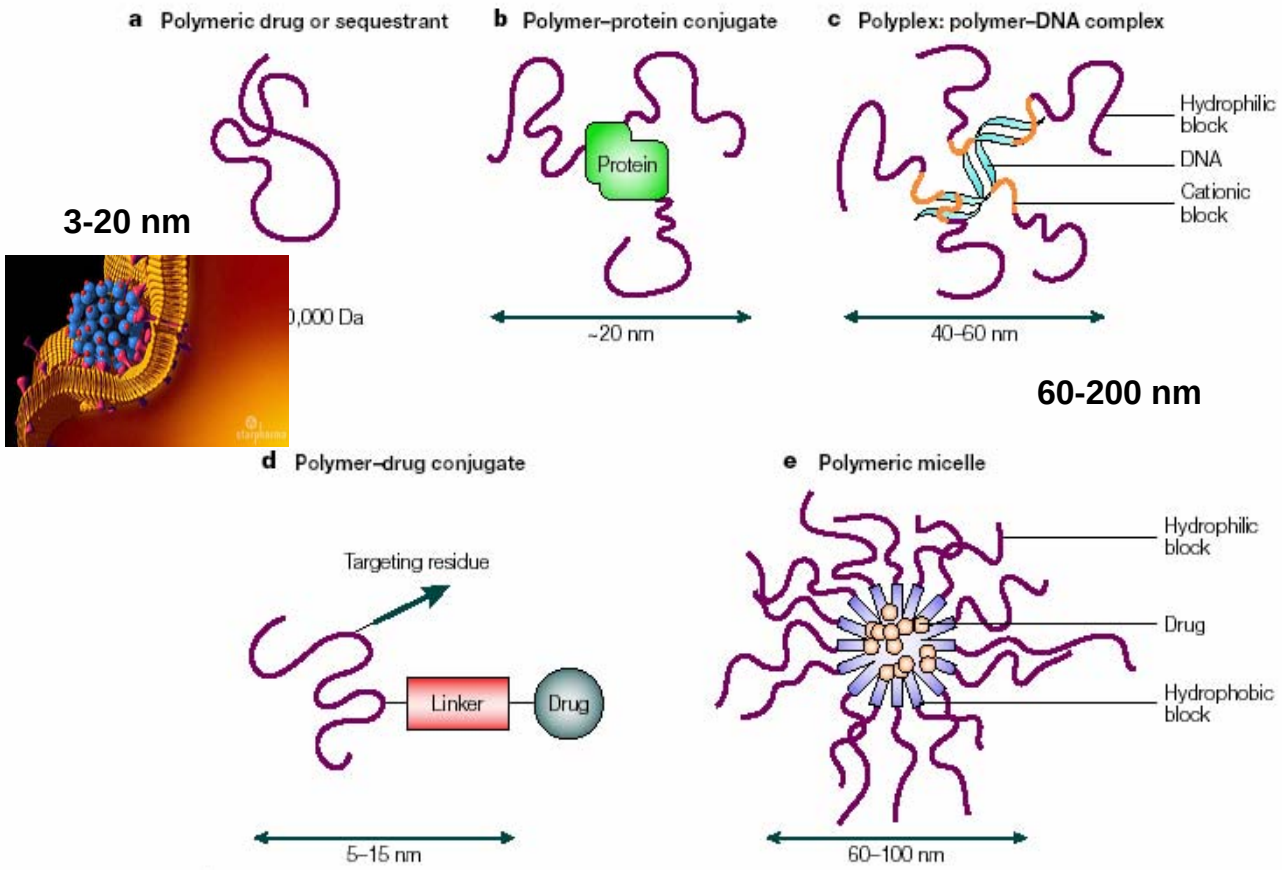
Many muticomponent systems have been described



Duncan R (2005) Targeting and intracellular delivery of drugs.
In: Encyclopedia of Molecular Cell Biology and Molecular Medicine, R. A. Meyers (Ed); WILEY-VCH Verlag, GmbH & Co. KGaA, Weinheim, Germany, pp 163-204

Polymer Therapeutics

Nature Rev. Drug Discov. (2003)
Nature Rev. Cancer (2006)



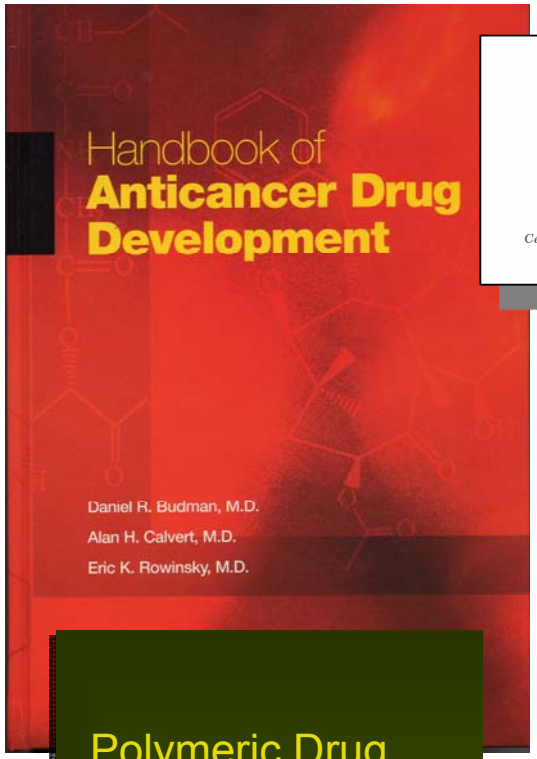
3-20 nm

60-200 nm

Figure 1 | **Schematic representation of polymer therapeutics now in, or progressing towards, clinical development.** The nano-sized and frequently multicomponent nature of these structures is visible. Mw, molecular weight.

- polymers as drugs
- polymer-protein conjugates
- polymer-drug conjugates
- block copolymer micelles to which drug is covalently bound
- polyplexes containing covalent linkers

Scientific Communication

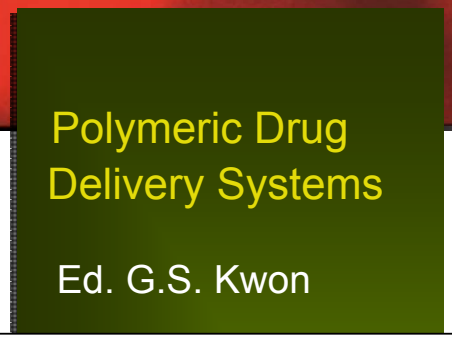


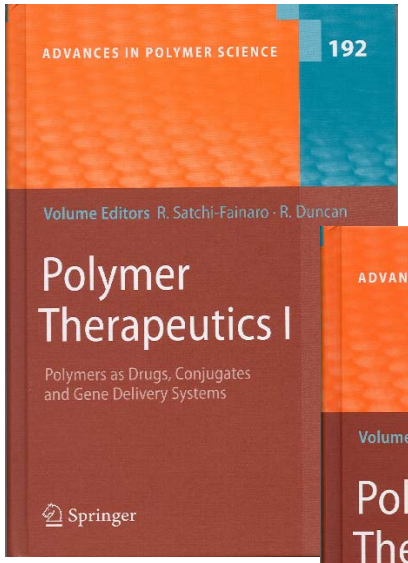
17

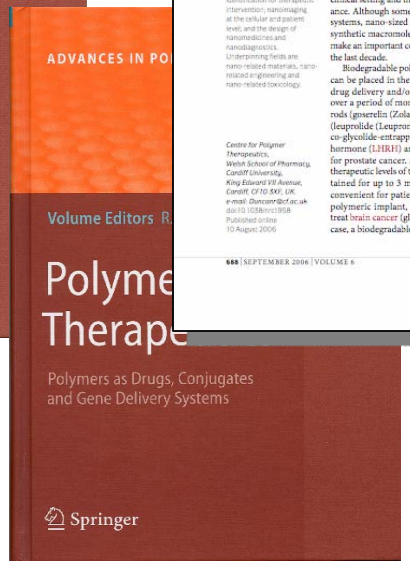
Polymer-Drug Conjugates

Ruth Duncan

Centre for Polymer Therapeutics, Welsh School of Pharmacy, Cardiff University, Cardiff CF10 3XF, United Kingdom





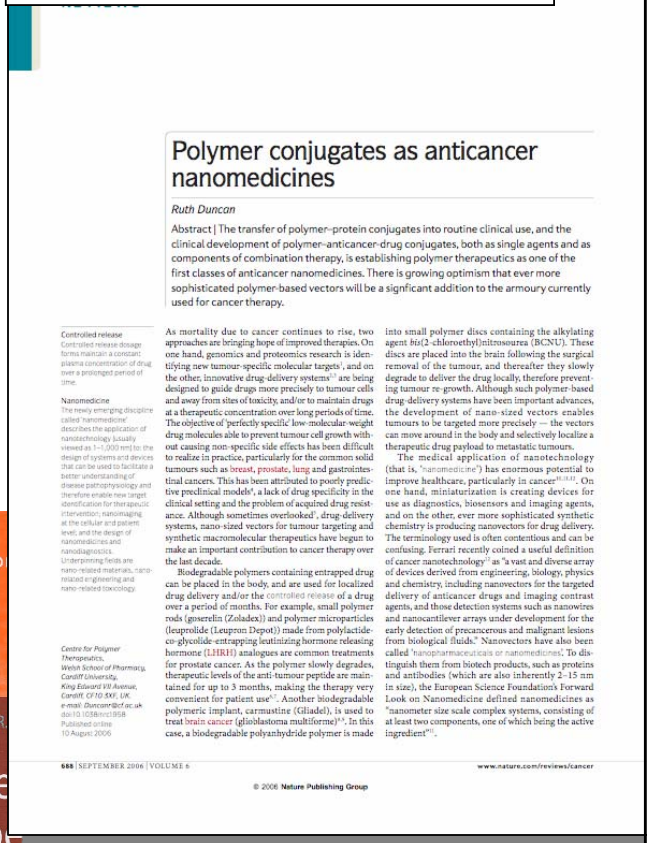


1

N-(2-Hydroxypropyl) methacrylamide Copolymer Conjugates

RUTH DUNCAN

Centre for Polymer Therapeutics, Welsh School of Pharmacy, Cardiff University, Cardiff, U.K.

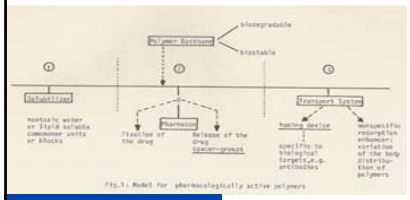


Polymer conjugates as anticancer nanomedicines

Ruth Duncan

Abstract | The transfer of polymer–protein conjugates into routine clinical use, and the clinical development of polymer–anticancer-drug conjugates, both as single agents and as components of combination therapy, is establishing polymer therapeutics as one of the first classes of anticancer nanomedicines. There is growing optimism that ever more sophisticated polymer-based vectors will be a signficant addition to the armoury currently used for cancer therapy.

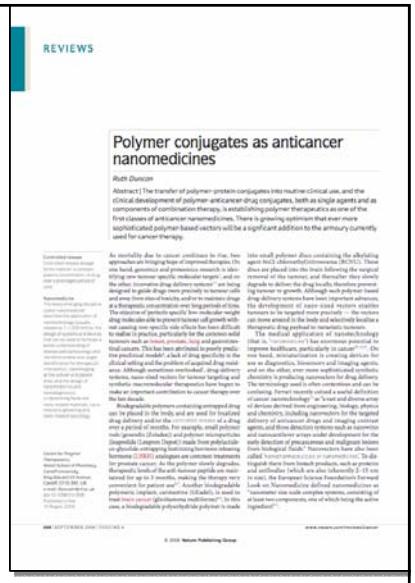
Ringsdorf Model 1975



Anticancer agents

CANCER RESEARCH UK

Lab → **Polymer-drug and Polymer-Protein conjugates** → Clinic

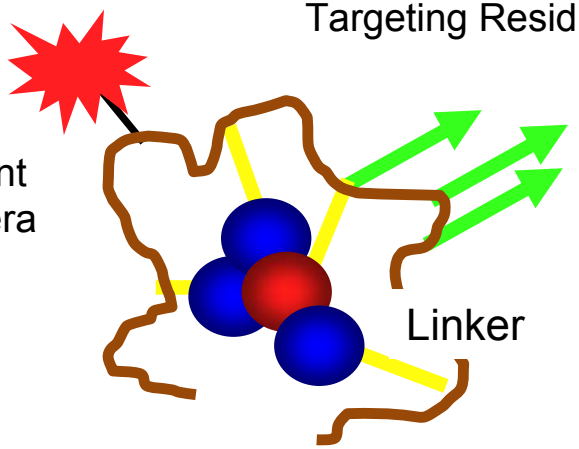

REVIEWS

Polymer conjugates as anticancer nanomedicines

Ruth Duncan

Targeting Residues

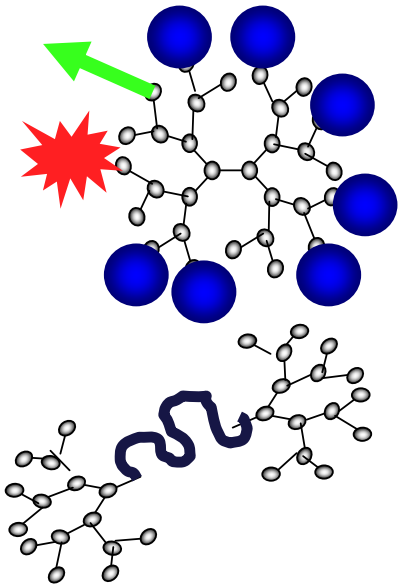
Imaging Agent
gamma camera

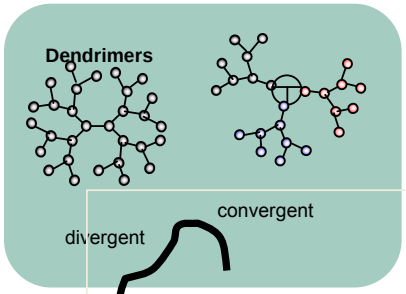


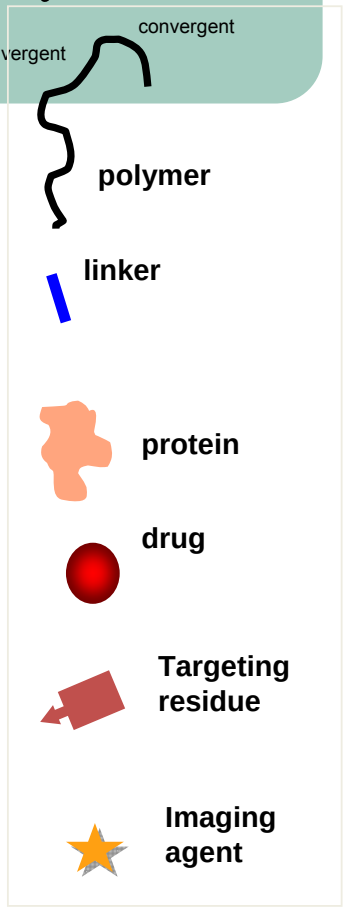
Linker

Drug and Drug Combinations

6 - 20 nm





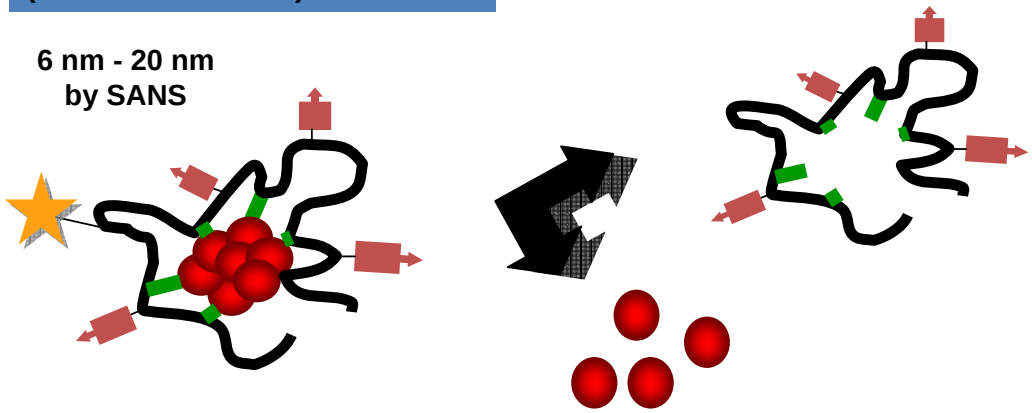


1. Polymer-Drug Conjugates

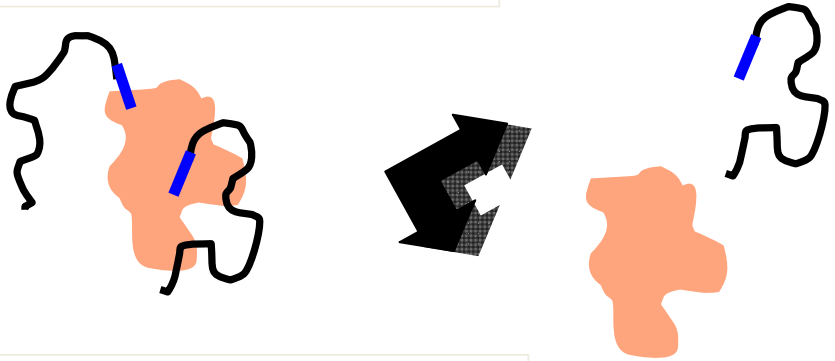
May form a Unimolecular micelle (or other structures) in solution

At least Two Primary Metabolites

6 nm - 20 nm by SANS



2. Polymer-Protein Conjugates

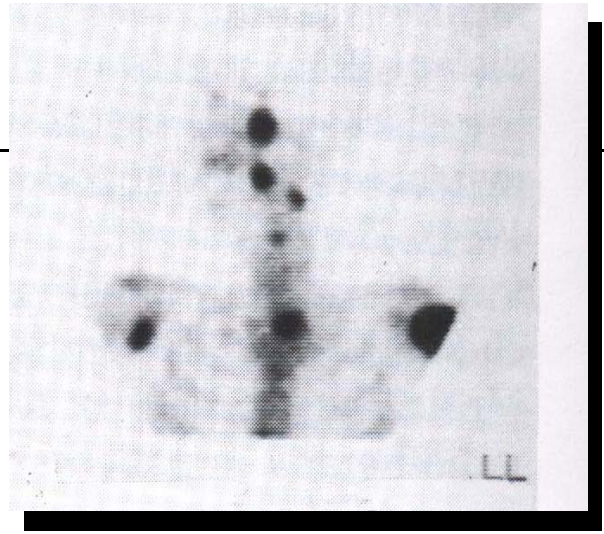


3. Bioresponsive endosomolytic polymers for cytosolic delivery

Preclinical evaluation of polymer-bound doxorubicin

Duncan, R., Seymour, L.W., O'Hare, K.B., Flanagan, P.A., Wedge, S., Hume, I.C., Ulbrich, K., Strohalm, J., Subr, V., Spreafico, F., Grandi, M., Ripamonti, M., Farao, M., Suarato, A

Journal of Controlled Release 19, 331-346 (1992)



Rationale for design

Tools

polymer

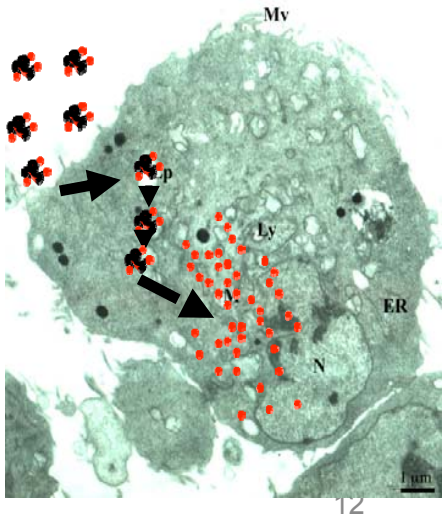
linker

drug/protein

targeting group

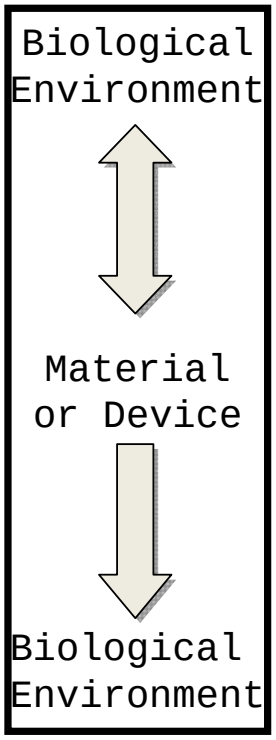
imaging agent

Pharmacokinetics



Methods for physico-chemical characterisation

Biocompatibility

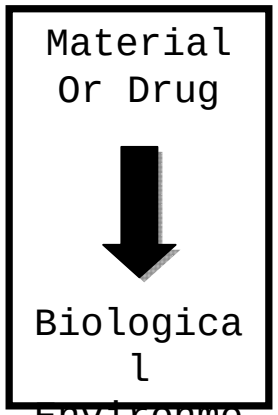


adverse or beneficial effect on material performance

adverse effect

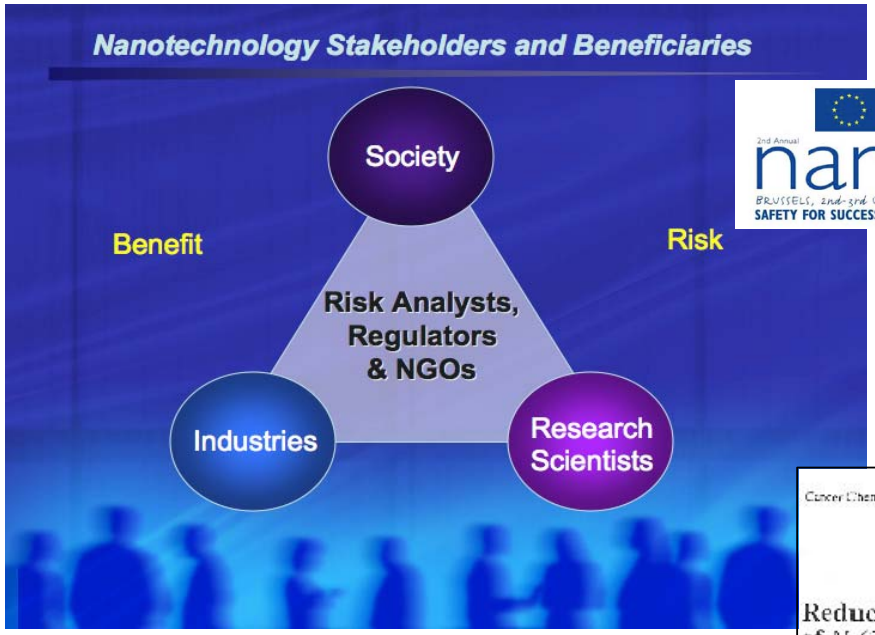
OR

Toxicology



adverse effect

Ensuring sensible choice of materials suitable for human use.....



environment accidental human purposeful human

Biomaterials 1989, Vol 10 July 335

Biocompatibility of *N*-(2-hydroxypropyl) methacrylamide copolymers containing adriamycin

Immunogenicity, and effect on haematopoietic stem cells in bone marrow *in vivo* and mouse splenocytes and human peripheral blood lymphocytes *in vitro*.

B. Rihova, M. Bilej and V. Vetvicka
Institute of Microbiology, Czechoslovak Academy of Sciences, CS-142 20 Prague, Czechoslovakia

K. Ulbrich, J. Strohalm and J. Kopecek
Institute of Macromolecular Chemistry, Czechoslovak Academy of Sciences, CS-16206 Prague, Czechoslovakia

R. Duncan
Cancer Research Campaign Polymeric-Controlled Drug Delivery Group, Department of Biological Sciences, University of Keele, Staffordshire, ST5 5BG, UK
(Received 1 February 1988; accepted 1 May 1988)

Cancer Chemother Pharmacol (1991) 29: 105–111
Cancer Chemotherapy and Pharmacology
© Springer-Verlag 1991

Reduced cardiotoxicity of doxorubicin given in the form of *N*-(2-hydroxypropyl)methacrylamide conjugates: an experimental study in the rat

Tai K. Yeung[1], John W. Hopewell[1], Rosemary H. Simmonds[1], Leonard W. Seymour[2], Ruth Duncan[2], Ornella Bellini[3], Maria Grandi[3], Federico Spreafico[3], Jiri Strohalm[4], and Karel Ulbrich[4]

GLP Preclin Tox

Human & Experimental Toxicology (1998) 17, 93–104

Preclinical toxicology of a novel polymeric antitumour agent: HPMA copolymer-doxorubicin (PK1)

R Duncan[1], JK Coatsworth[2] and S Burtles[3]

[1]Centre for Polymer Therapeutics, The School of Pharmacy, University of London, 29–39 Brunswick Square, London WC1N 1AX, UK; [2]BIBRA International Woodmansterne Road, Carshalton, Surrey SM5 4DS,UK; [3]Cancer Research Campaign, 10 Cambridge Terrace, London NW1 4JI, UK on behalf of the CRC Phase I/II Clinical Trials Committee

About 90 % of materials being proposed are unsuitable for **proposed use**
…….. Reflect on safety and suitability for manufacture early

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Available online at www.sciencedirect.com

SCIENCE DIRECT

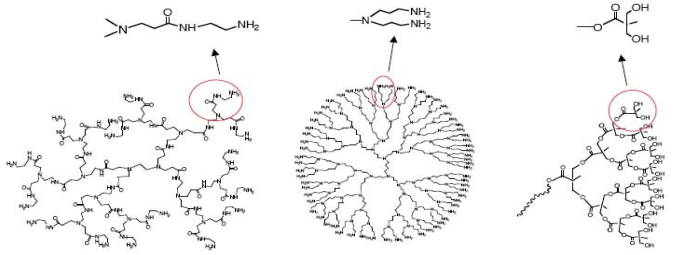
Advanced Drug Delivery Reviews 57 (2005) 2215–2237

Advanced DRUG DELIVERY Reviews

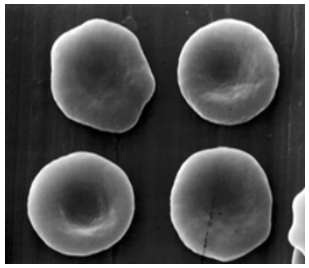
www.elsevier.com/locate/addr

Dendrimer biocompatibility and toxicity ☆

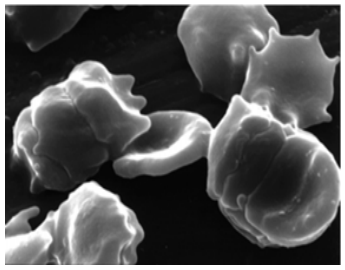
Ruth Duncan [a,*], Lorella Izzo [a,b]



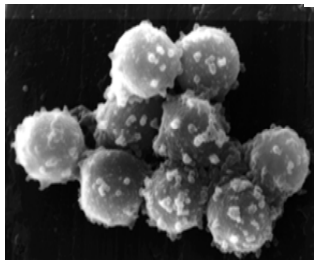
(a) Control



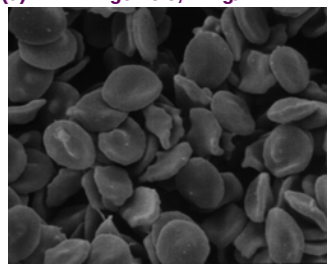
(b) PAMAM gen 4; 10μg/mL



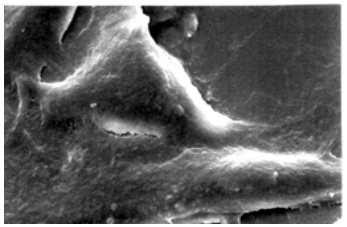
(c) PAMAM gen 4; 1 mg/mL



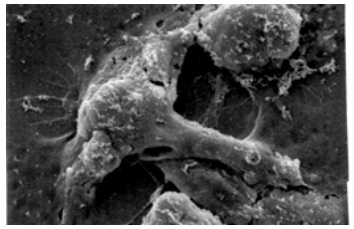
(d) PAMAM gen 3.5; 1 mg/mL



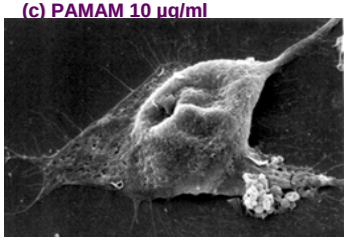
(b) DAB 10 μg/ml



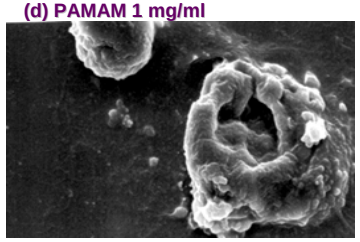
(a) DAB 1 mg/ml



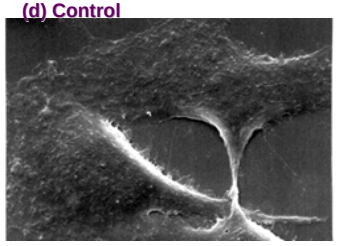
(c) PAMAM 10 μg/ml



(d) PAMAM 1 mg/ml



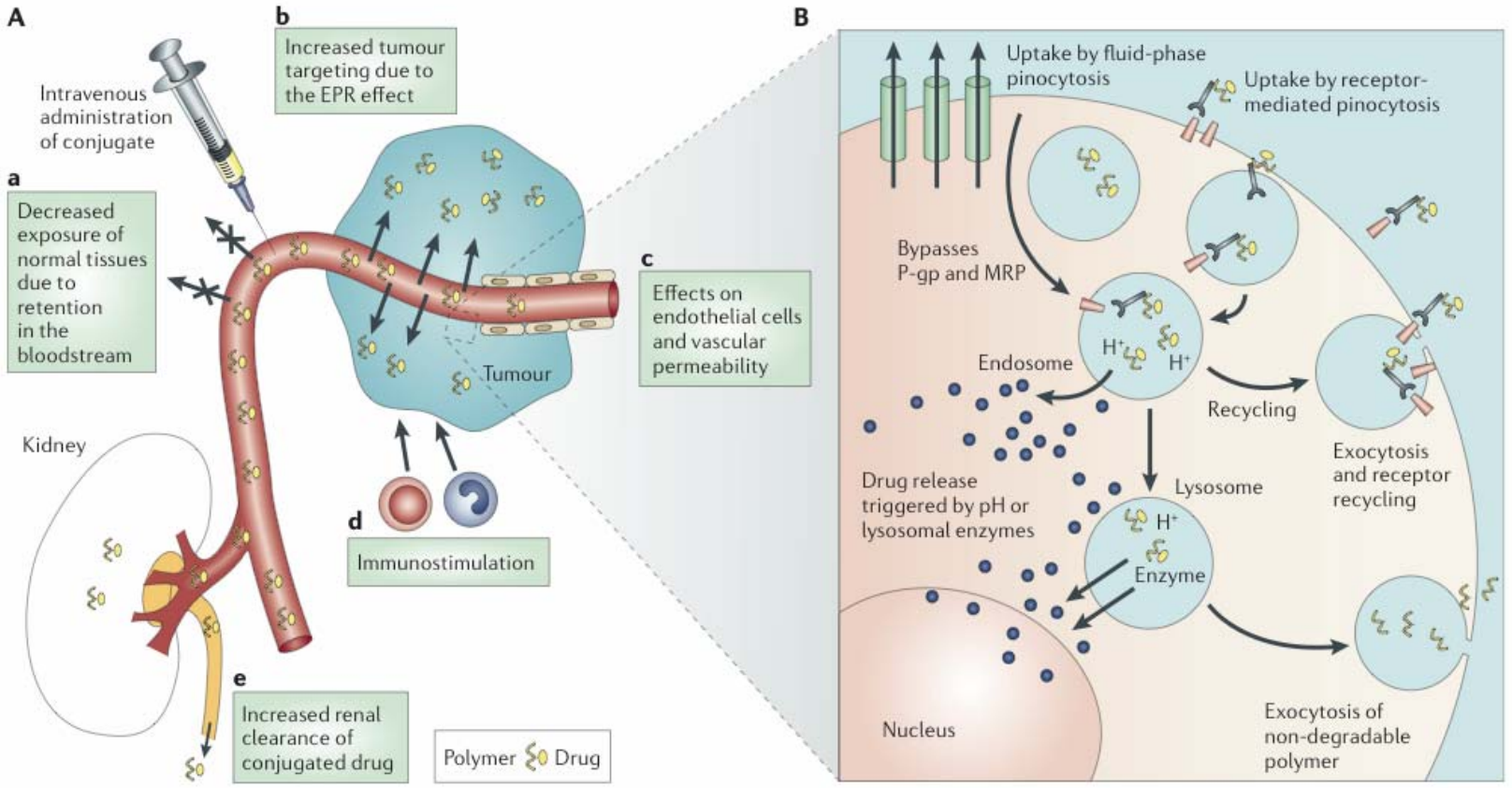
(d) Control



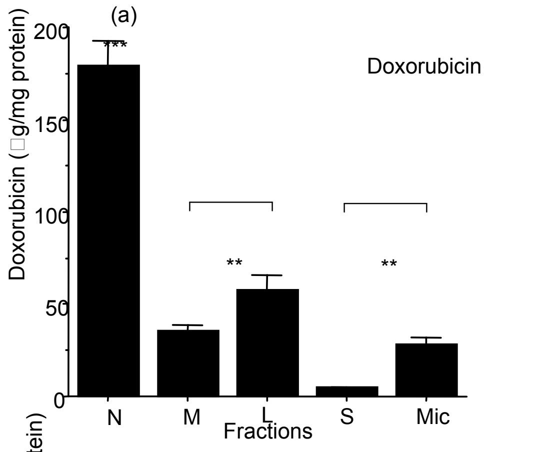
Current Understanding of the Mechanism of Action of Polymer-Anticancer Conjugates

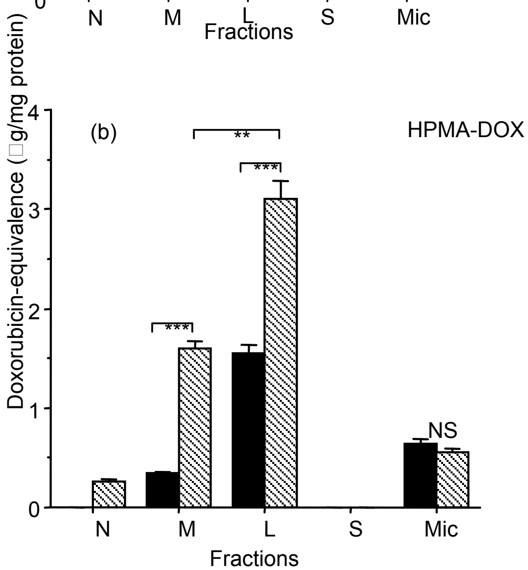
Duncan Nature Reviews Cancer (September 2006)

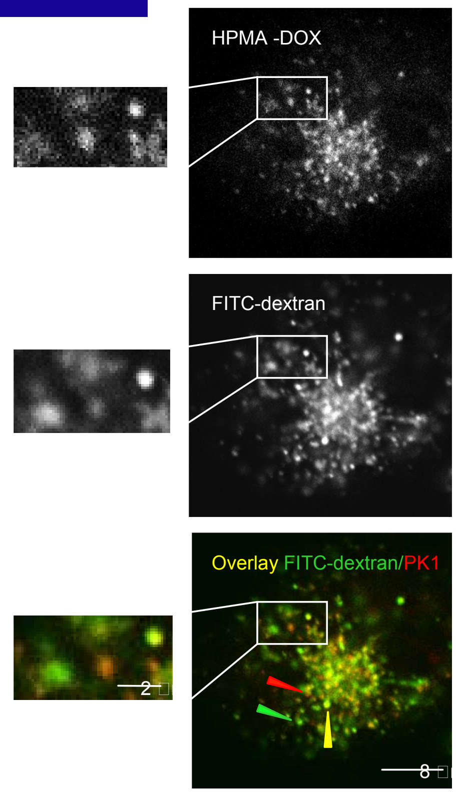
Importance of Pharmacokinetics



Quantitation of Intracellular Localisation







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The good, the bap3and the ugly

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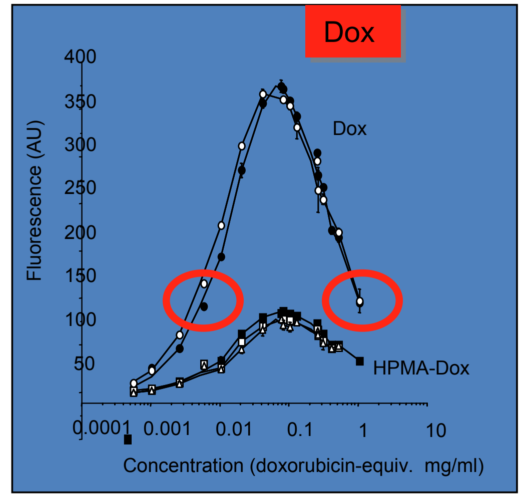
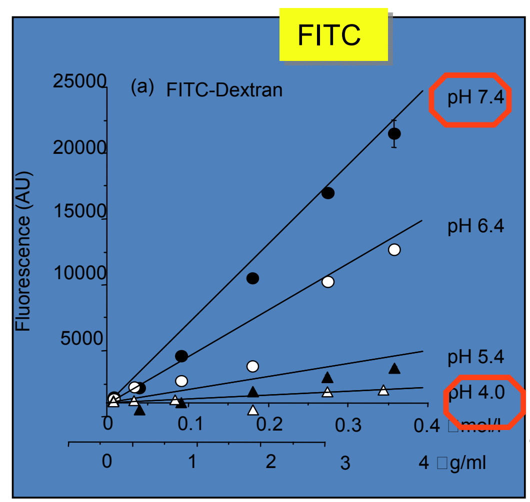


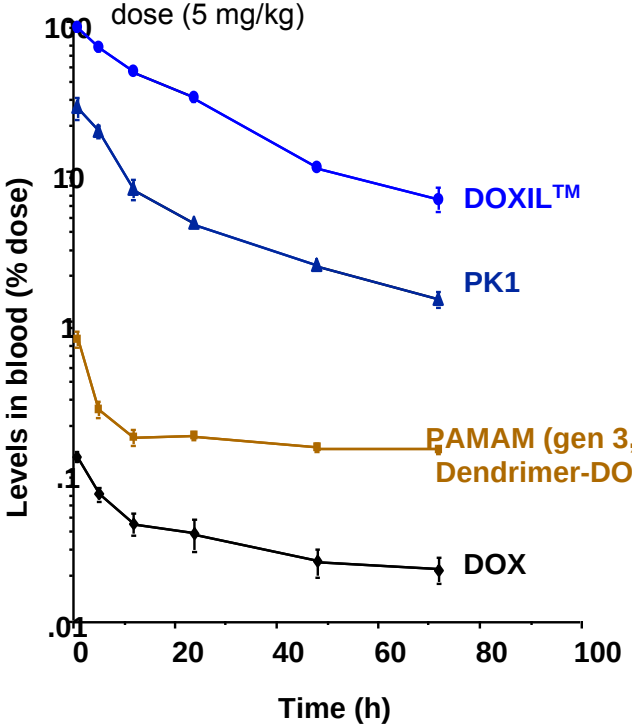


Manunta et al. (2007) J. Drug Targeting, 15(1): 37–50
Seib, et al. (2007) J. Controlled Release, 17, 291-300.
Seib et al. (2006) J. Drug Targeting 14, 375-90.

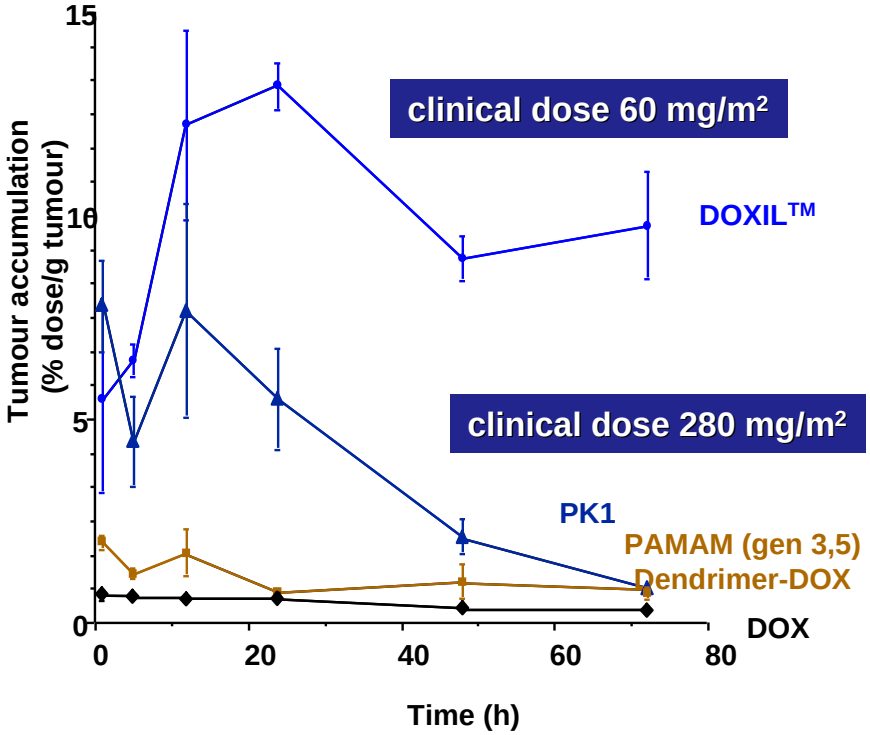
In Vivo Pharmacokinetics

Passive TARGETING RELIES ON PLASMA CONCENTRATION

Blood clearance of free DOX and the DOX delivery systems: administered at equi-dose dose (5 mg/kg)



B16F10 tumour uptake of free DOX and the DOX delivery systems : administered at equi-dose dose (5 mg/kg)



Duncan et al, (1986) BBA, 880,62
Seymour et al (1987) J Biomed Mater Res 21,1341
Seymour et al., (1994) Brit J Cancer; (1995) Eur J Cancer
Noguchi et al (1998) Japanese J Cancer Res

Yee Nee Sat, et al.

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

Phase I Clinical and Pharmacokinetic Study of PK1 [*N*-(2-Hydroxypropyl)methacrylamide Copolymer Doxorubicin]: First Member of a New Class of Chemotherapeutic

Paul A. Vasey,[2] Stan B. Kaye, Rosemary Morrison, Chris Twelves, Peter Wilson, Ruth Duncan, Alison H. Thomson, Lilian S. Murray, Tom E. Hilditch, Tom Murray, Sally Burtles, D. Fraier, E. Frigerio, and Jim Cassidy, on behalf of the Cancer Research Campaign Phase I/II Committee

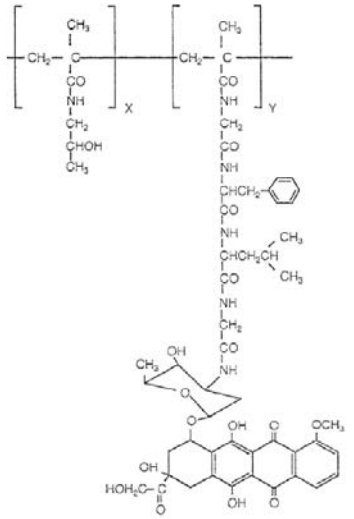


Fig. 1 Structure of PK1 (HPMA copolymer doxorubicin). The molecular weight of the compound is 28,000 [doxorubicin, 8.5% (w/w)].

Table 2 Dose escalation scheme

Dose (mg/m^2 doxorubicin equivalent)	No. of patients	No. of courses/ patient	Median cumulative dose, mg/m^2 (range)
20	3	2, 1, 3	40 (20–60)
40	3	2, 1, 1	40 (40–80)
80	3	6, 2, 4	320 (160–480)
120	3	7, 4, 7	840 (480–840)
180	6	1, 6, 1, 7, 1, 1	180 (180–1260)
240	6	1, 4, 2, 4, 2, 4[a]	480 (240–960)
280	6	2, 3, 6, 1, 2, 3	700 (280–1680)
320	6	2, 2, 1, 1, 1, 2	480 (320–640)

[a] Courses 3 and 4 for this patient were at 280 mg/m^2.

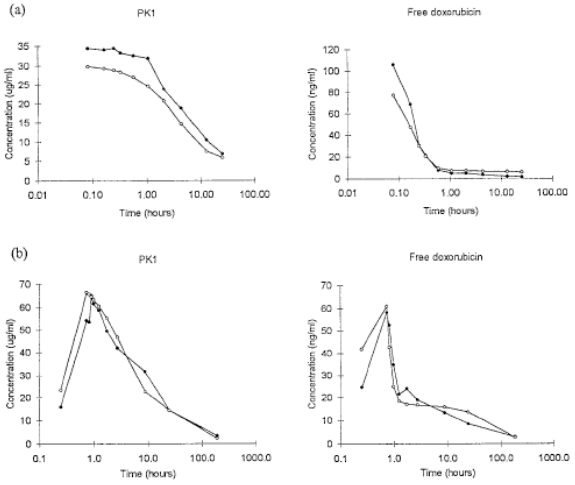
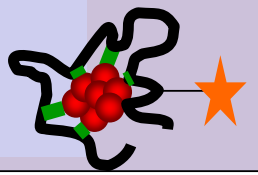
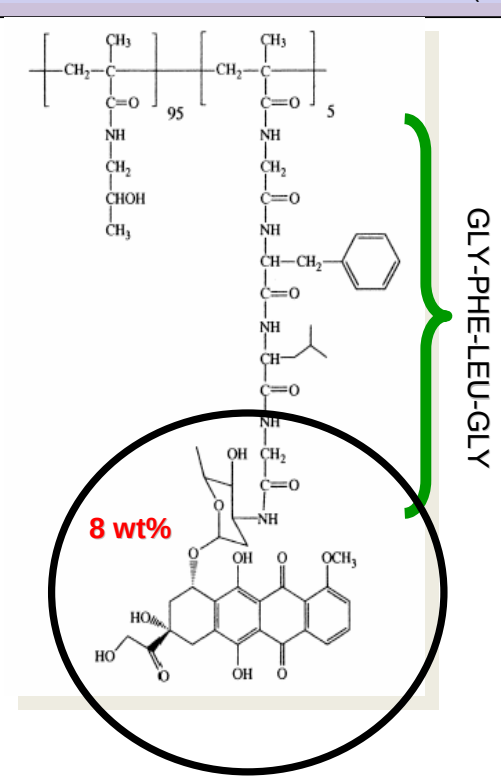


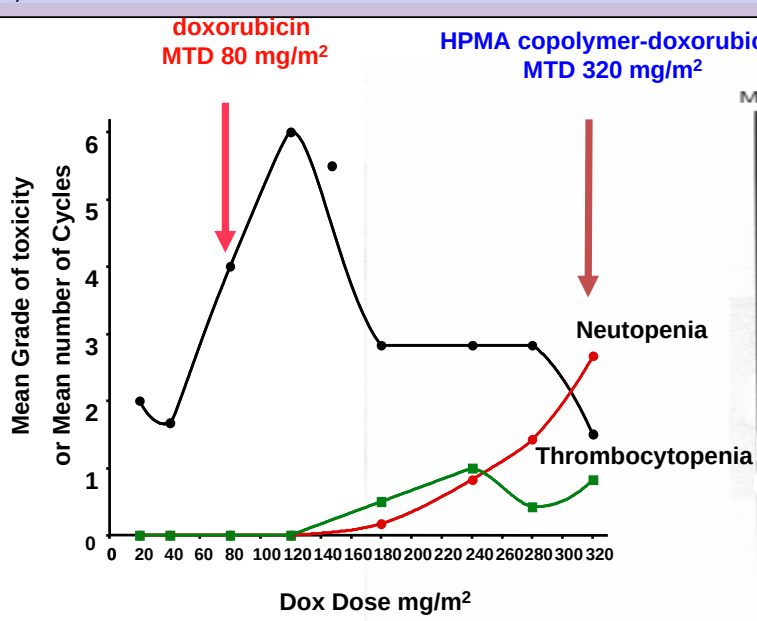
Fig. 4 Measured (●) and population-predicted (○) concentrations of PK1 and free doxorubicin (correlation coefficient, −0.44) for two patients receiving PK1 at 80 mg/m^2 (*a*) and 180 mg/m^2 (*b*). Time (*X axis*) is presented on a log scale for clarity.

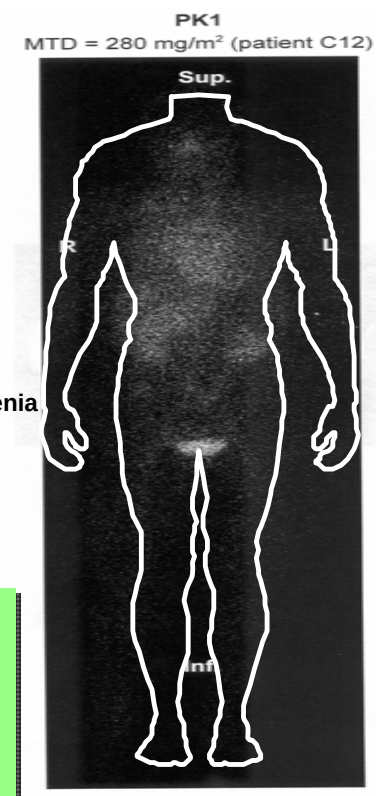
Phase I clinical and pharmacokinetic study of PK1 [N-(2-hydroxypropyl)methacrylamide copolymer doxorubicin]: first member of a new class of chemotherapeutic agents - drug-polymer conjugates. Vasey P., Kaye S.B., Morrison, R., Twelves, C., Wilson, P., Duncan R, Thomson A.H., Murray, L.S., Hilditch, T.E., Murray, T., Burtles, S., Fraier, D., Frigerio, E. and Cassidy, J.

Clinical Cancer Research 5, 83-94 (1999)









FCE28068
HPMA Copolymer-doxorubicin

- **Polymer conjugate was 4-5 fold fold less toxic than doxorubicin**
- **Activity seen in Breast and NSCLC**
- **HPMA was shown 'safe' as a new carrier**

CANCER RESEARCH UK

British Journal of Cancer (2004) 91, 50–55

Phase I and pharmacokinetic (PK) study of MAG-CPT (PNU 166148): a polymeric derivative of camptothecin (CPT)

D Bissett*[,1], J Cassidy[1], JS de Bono[2], F Muirhead[2], M Main[1], L Robson[3], D Fraier[4], ML Magnè[4], C Pellizzoni[4], MG Porro[4], R Spinelli[4], W Speed[4] and C Twelves[2]

[1]Department of Medical Oncology, University of Aberdeen, Aberdeen Royal Infirmary, Foresterhill, Aberdeen AB25 2ZN, UK; [2]Cancer Research UK Department of Medical Oncology, University of Glasgow, Beatson Oncology Centre, Western Infirmary, Glasgow G11 6NT, UK; [3]Cancer Research UK, Drug Development Office, London, UK; [4]Pharmacia and Upjohn, Nerviano, Italy

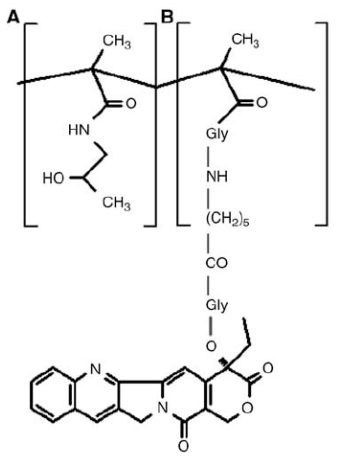


Figure 1 Structure of MAG-CPT. Free camptothecin is released by hydrolysis, which converts (**B**) to (**A**).

British Journal of Cancer (2002) 87, 608–614

A phase I and pharmacokinetic study of MAG-CPT, a water-soluble polymer conjugate of camptothecin

NE Schoemaker*[,1,2], C van Kesteren[1,2], H Rosing[2], S Jansen[2], M Swart[1], J Lieverst[1], D Fraier[3], M Breda[3], C Pellizzoni[3], R Spinelli[3], M Grazia Porro[4], JH Beijnen[1,2,5], JHM Schellens[1,5] and WW ten Bokkel Huinink[1]

[1]Department of Medical Oncology, Antoni van Leeuwenhoek Hospital/The Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX, Amsterdam, The Netherlands; [2]Department of Pharmacy and Pharmacology, The Netherlands Cancer Institute/Slotervaart Hospital, Louwesweg 6, 1066 EC, Amsterdam, The Netherlands; [3]Global Drug Metabolism, Pharmacia, Viale Pasteur 10, 20014 Nerviano, Milan, Italy; [4]Clinical Research Oncology, Pharmacia, Viale Pasteur 10, 20014 Nerviano, Milan, Italy; [5]Division Drug Toxicology, Faculty of Pharmacy, Utrecht University, Sorbonnelaan 16, 3584 CA, Utrecht, The Netherlands

Table 5 Urinary excretion of total camptothecin after intravenous administration of MAG-CPT

Dose mg m^{-2} day^{-1}	*n*	Urinary excretion %	Cl_R ml h^{-1}
17	1	84	157
34	1	57	141
57	1	81	105
68	3	52±6	87±25
85	3	58±5	63±7
100	2	97±19	105±47
130	3	68±9	197[a]
Mean		68±17	105±45

[a]*n*=1. For abbreviations see Patients and methods section.

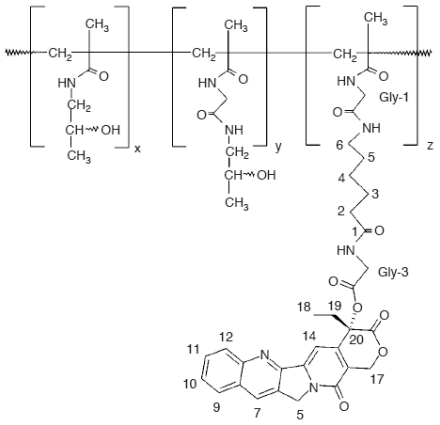


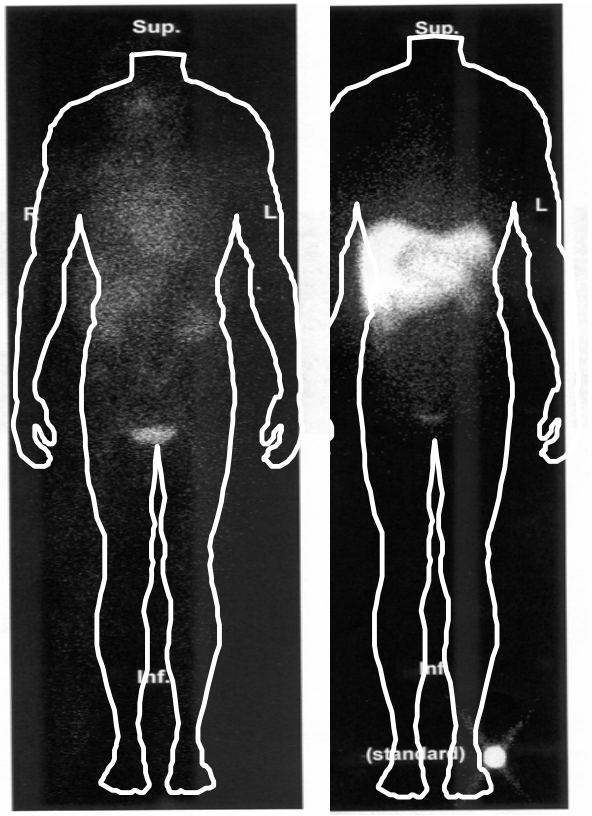
Figure 1 Chemical structure of MAG-CPT.

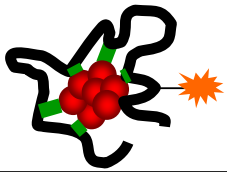
FCE28069 Phase I/II Trials

HPMA copolymer -Gly-Phe-Leu-Gly -doxorubicin-galactose

MTD 280 mg/m^2

MTD 160 mg/m^2 Dox-Equiv





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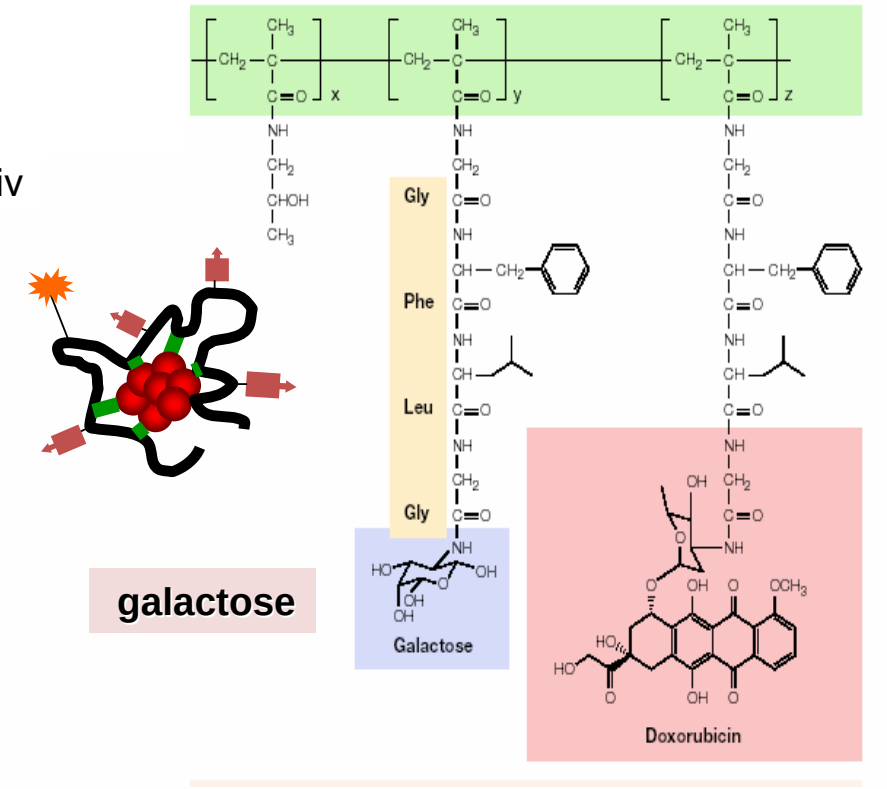


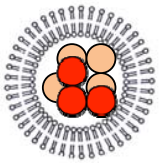
- **Polymer conjugate was 2 fold less toxic than doxorubicin**
- **Liver targeting confirmed – via asialoglycoprotein receptor on hepatocytes**
- **Activity seen in hepatocellular carcinoma**
- **HPMA was shown 'safe' as a new carrier**

STATE OF ART IS (i) drug combinations

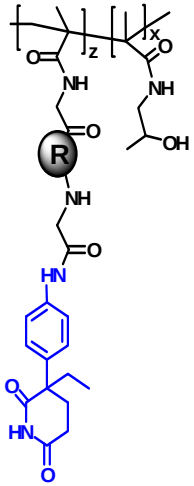
Polymer Therapeutics Designed for a Combination Therapy of Hormone-Dependent Cancer**

María J. Vicent, Francesca Greco, Robert I. Nicholson, Alison Paul, Peter C Griffiths, and Ruth Duncan**

Vicent et al. (2005) Angew. Chem. Int. Ed. 44, 2 –6.
Duncan et al. (2005) Endocrine-Related Cancer, 12, S189-S199.
Greco et al. (2005) J. Drug Targeting 13, 459-470.
Greco et al. (2007) J. Controlled Release 117, 28-39.

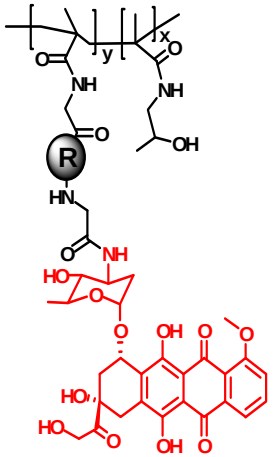


I HPMA-R-AGM



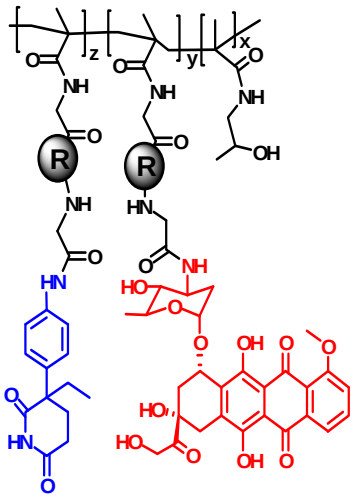
aminoglutethimide

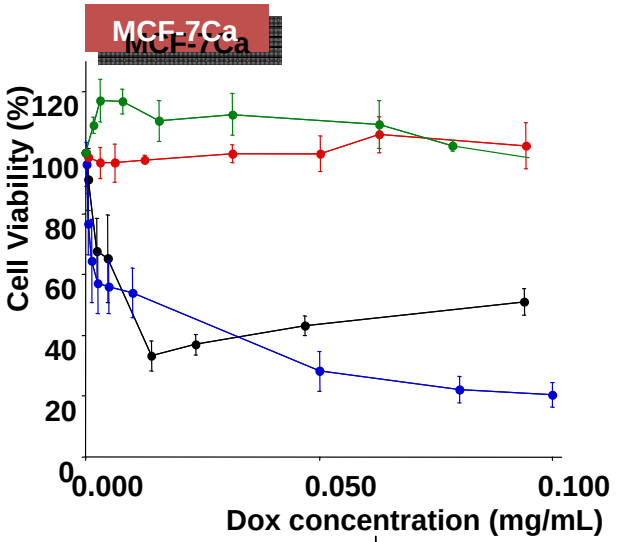
II HPMA-R-DOX

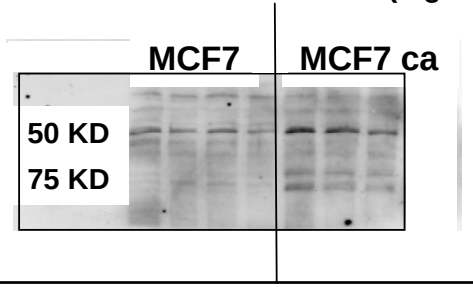


doxorubicin

III HPMA-AGM-DOX







R :Peptidyl linkers (Gly-Gly or Gly-Phe-Leu-Gly)

- Bioresponsive polymer therapeutics for – wound repair
  arthritis, cancer, infectious diseases

  - Need for interdisciplinary teams with early input from medical colleagues

Journal of Controlled Release 130 (2008) 275–283

Contents lists available at ScienceDirect

Journal of Controlled Release

journal homepage: www.elsevier.com/locate/jconrel

NANOMEDICINE

Dextrin–rhEGF conjugates as bioresponsive nanomedicines for wound repair

Joseph Hardwicke [a,b,*], Elaine L. Ferguson [b], Ryan Moseley [a], Phil Stephens [a], David W. Thomas [a,*], Ruth Duncan [b,*]

[a] Wound Biology Group, Cardiff Institute of Tissue Engineering and Repair (CITER), Tissue Engineering and Reparative Dentistry, School of Dentistry, Heath Park Campus, Cardiff, Cardiff CF14 4XY, UK

[b] Centre for Polymer Therapeutics, Welsh School of Pharmacy, Redwood Building, King Edward VII Avenue, Cardiff CF10 3XF, UK

journal of controlled release

OFFICIAL JOURNAL OF THE CONTROLLED RELEASE SOCIETY AND THE JAPANESE SOCIETY OF DRUG DELIVERY SYSTEM

dextrin

rhEGF

TARGET CELL

DAG

PKC

MAPK

STAT1/3

nuclear transcription factors

COVER STORY

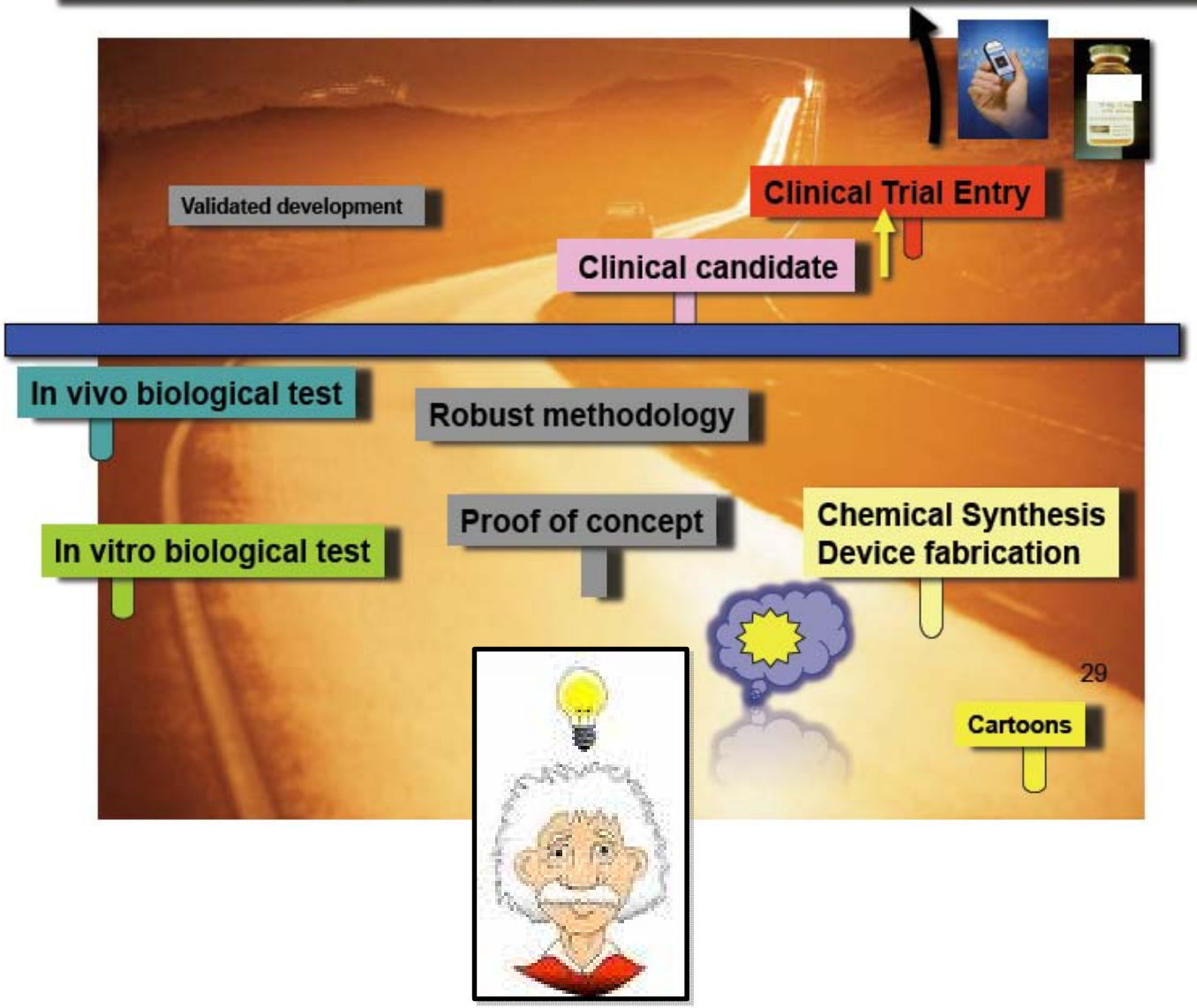
Dextrin–rhEGF conjugates as bioresponsive nanomedicines for wound repair

college of medicine

GIG CYMRU

Llywodraeth Cynulliad Cymru
Welsh Assembly Government

Understanding were you are on the road ..... Lab to Market



European Medicines Agency
Pre-authorisation Evaluation o

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)	
REFLECTION PAPER ON NANOTECHNOLOGY-BASED MEDICINAL PRODUCTS FOR HUMAN USE	
ADOPTION BY CHMP FOR RELEASE	June 2006

"Medicinal products containing nanoparticles have already been authorised both in EU and the US under the existing regulatory frameworks"

- **Although nanosizing does not necessarily imply novelty, it is expected that nanotechnology will yield innovative products.**

- **Such products could span the regulatory boundaries between medicinal products and medical devices, challenging current criteria for classification and evaluation.**

- **Appropriate expertise will need to be mobilised for the evaluation of the**
  quality,
  safety,
  efficacy and risk management

of nanomedicinal products and the need for new or updated guidelines will be reviewed in the light of accumulated experience.

ISSUES

General

- Terminology – what is nano ? – what is a product ?
- Boundaries ….. Drug delivery…device…diagnostic

Specific

-Specification

-justification in respect of toxicity/efficacy

- Reproducible Manufacture of Complex Systems
- Validated techniques – quality of validation

- assessment of key parameters