



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



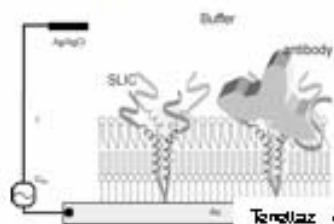
"Nano" medicine

Minaturisation

**Devices
Analytical Techniques
Biomedical Materials**



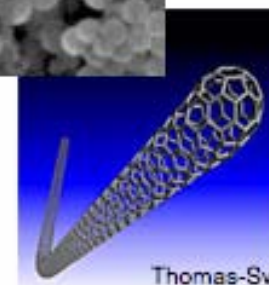
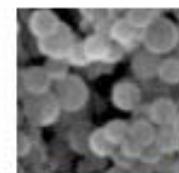
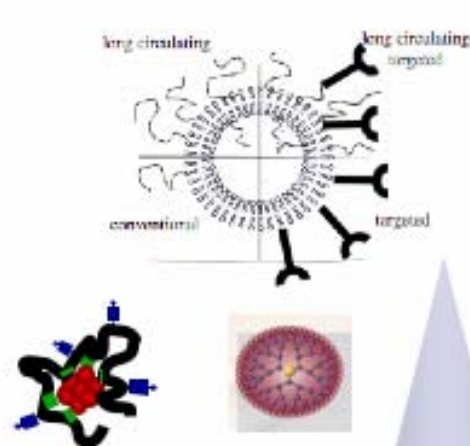
Pierre Puget



Tenellaz et al. *Angew Chem Int Ed* (2001)



Schering

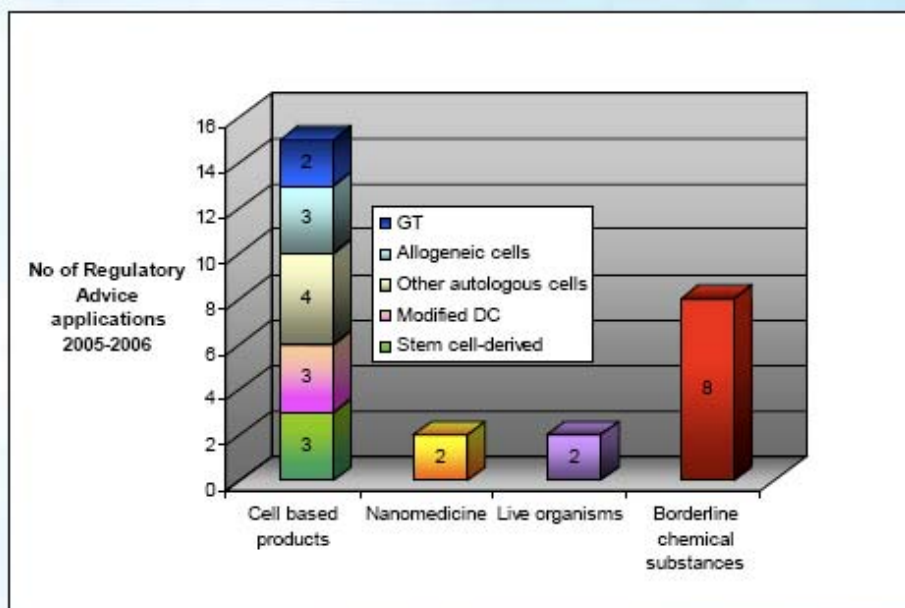


Thomas-Swan

**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



European Medicines Agency
Pre-authorisation Evaluation o

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

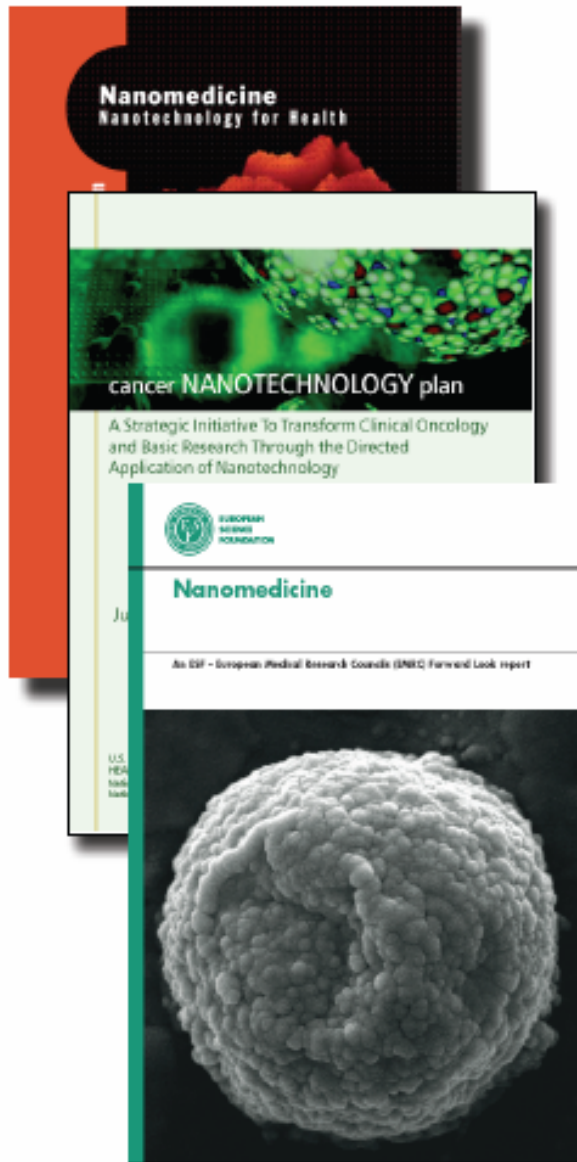
REFLECTION PAPER ON NANOTECHNOLOGY-BASED MEDICINAL PRODUCTS FOR
HUMAN USE

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

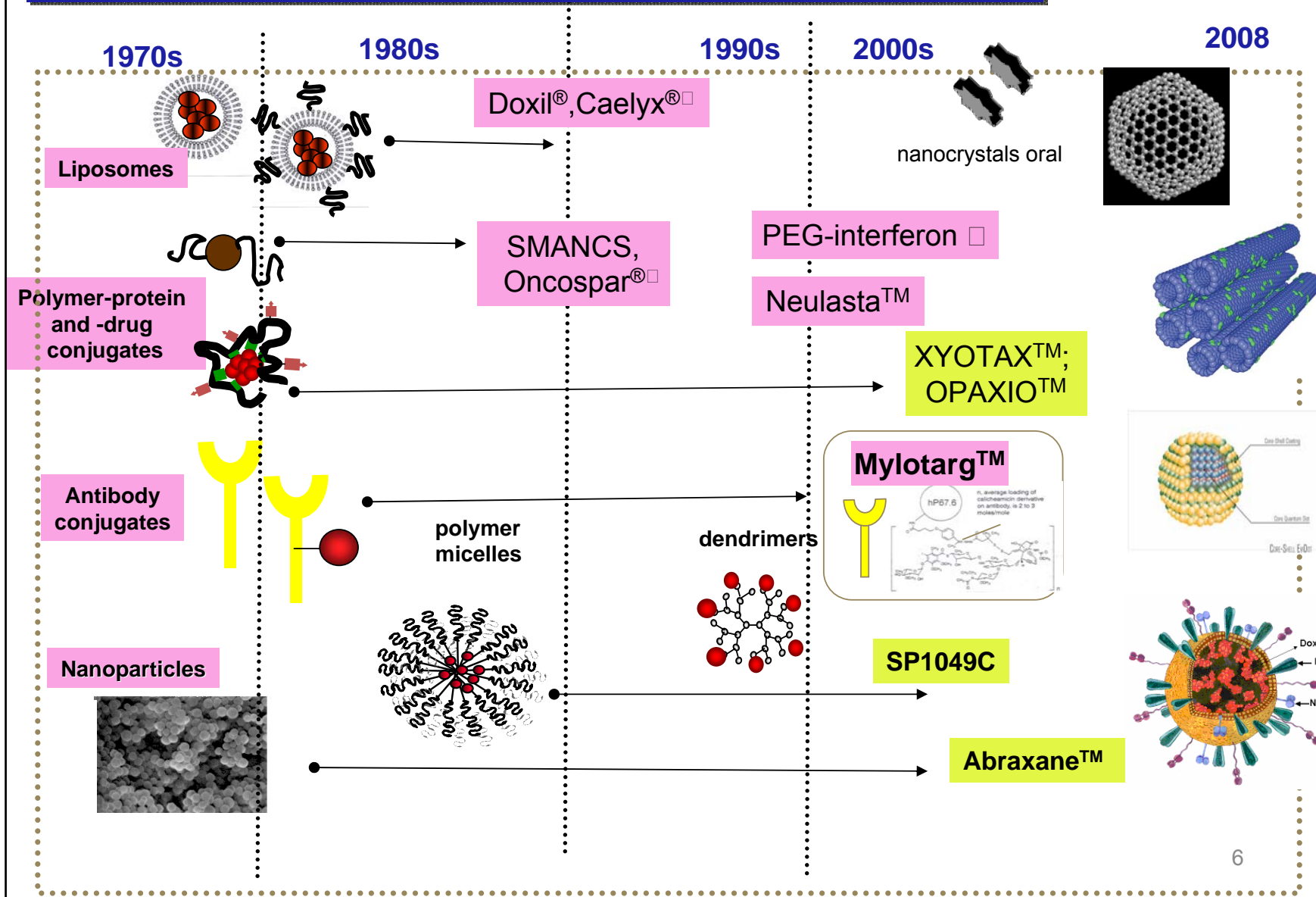


" Nanomedicine(s) or Nanopharmaceuticals"

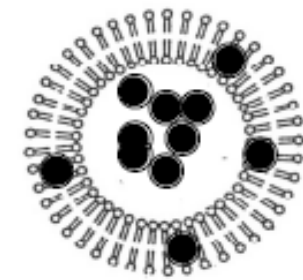
" Nanopharmaceuticals can be developed either as **drug delivery systems** or **biologically active drug products**.

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."

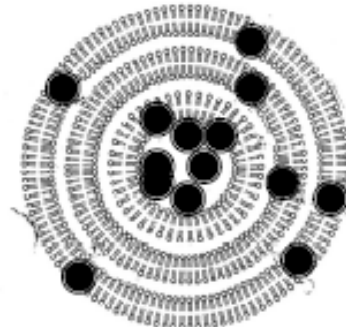
Evolution of Nanomedicines - drug targeting and controlled release



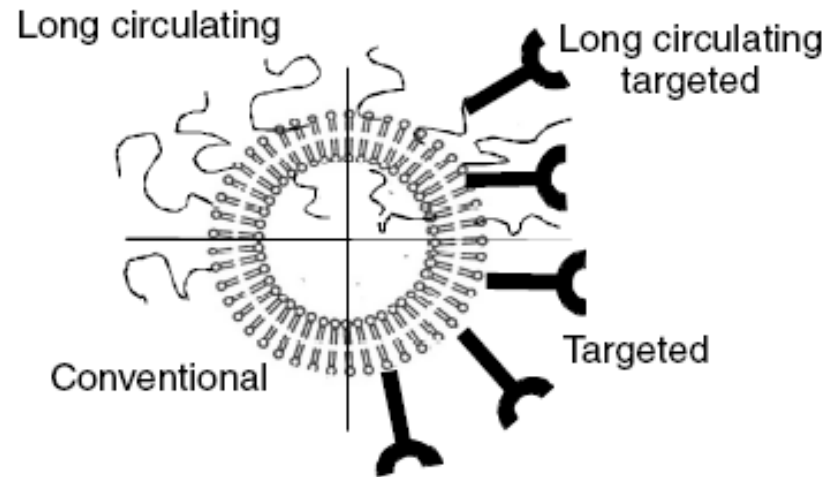
Many multicomponent systems have been described



(a) Unilamellar liposome



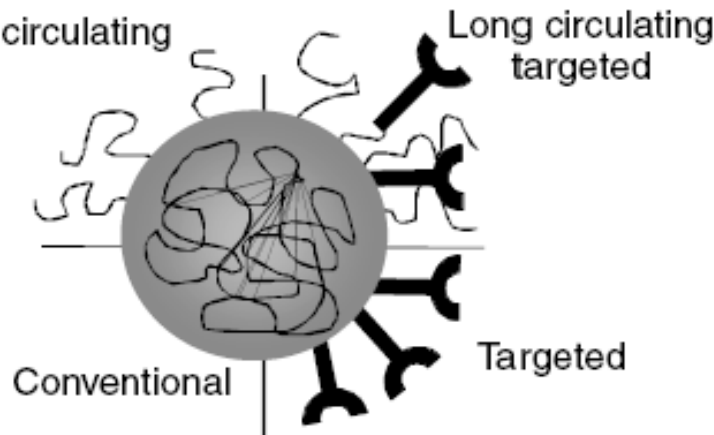
Multilamellar liposome



Nanoparticle



Nanosphere



(b)

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)

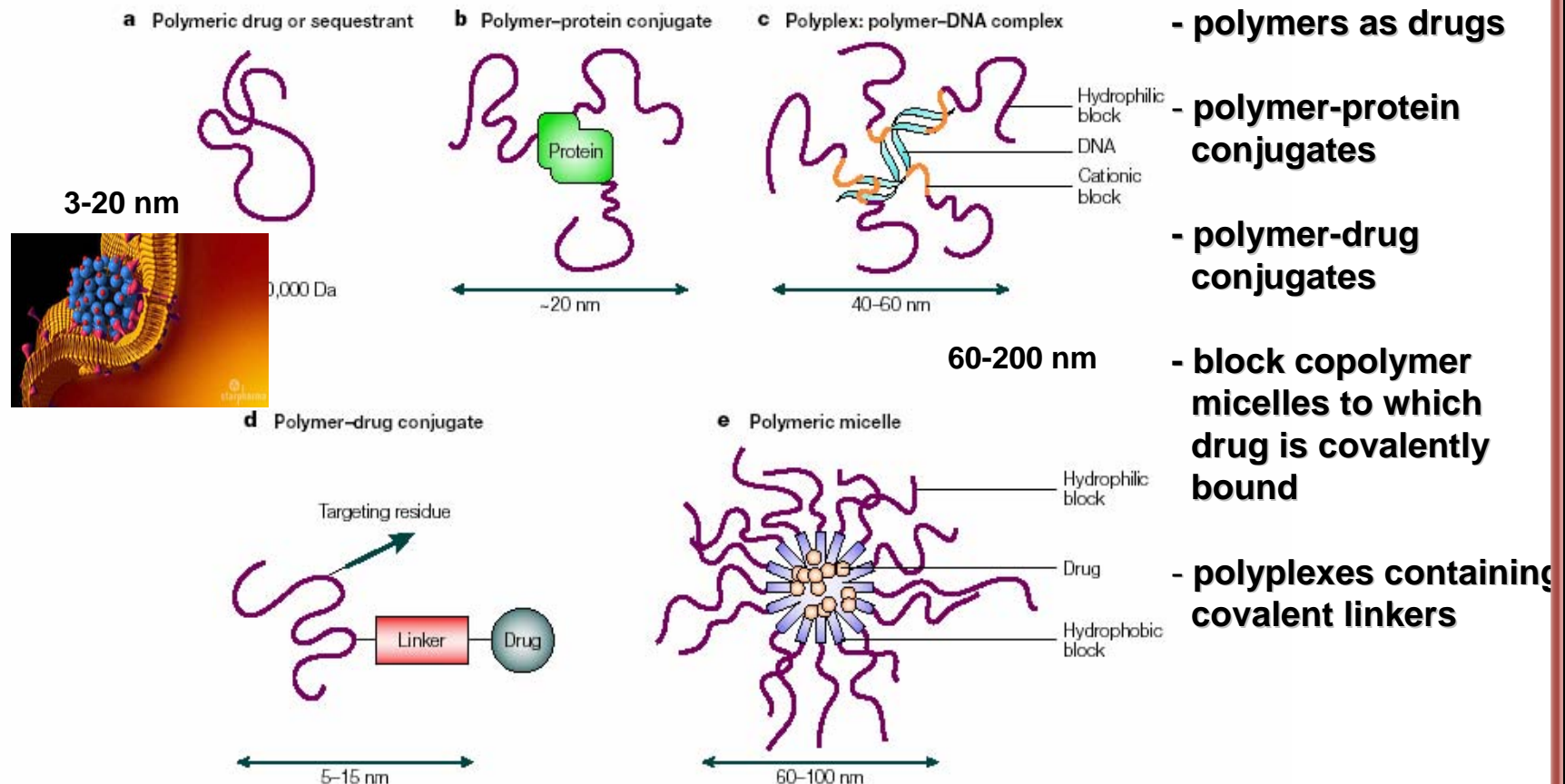


Figure 1 | Schematic representation of polymer therapeutics now in, or progressing towards, clinical development. The nano-sized and frequently multicomponent nature of these structures is visible. *M_w*, molecular weight.

Handbook of Anticancer Drug Development

Daniel R. Budman, M.D.
Alan H. Calvert, M.D.
Eric K. Rowinsky, M.D.

Polymeric Drug Delivery Systems

Ed. G.S. Kwon

1

N-(2-Hydroxypropyl) methacrylamide Copolymer Conjugates

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

17

Polymer-Drug Conjugates

Ruth Duncan

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

ADVANCES IN POLYMER SCIENCE

192

Volume Editors R. Satchi-Fainaro · R. Duncan

Polymer Therapeutics I

Polymers as Drugs, Conjugates and Gene Delivery Systems

Springer

ADVANCES IN POLYMER SCIENCE

Volume Editors R. Satchi-Fainaro · R. Duncan

Polymer Therapeutics II

Polymers as Drugs, Conjugates and Gene Delivery Systems

Springer

Scientific Communication

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 significant addition to the armory currently used for cancer therapy.

Controlled release

Controlled release dosage forms maintain a constant plasma concentration of drug over a prolonged period of time.

Nanomedicine

The newly emerging discipline called 'nanomedicine' describes the application of nanotechnology (usually viewed as 1–1000 nm) to the design of systems and devices that can be used to facilitate a better understanding of disease pathophysiology and therefore enable new target identification for therapeutic intervention; nanomanaging at the cellular and patient level; and the design of nanomedicines and nanodiagnoses. Underpinning fields are nano-related materials, nanomaterial engineering and nano-related toxicology.

Centre for Polymer Therapeutics, Welsh School of Pharmacy, Cardiff University, King Edward VII Avenue, Cardiff CF10 3XF, UK. e-mail: duncanr@cardiff.ac.uk; da1010@cardiff.ac.uk. Published online 10 August 2006

As mortality due to cancer continues to rise, two approaches are bringing hope of improved therapies. On one hand, genomics and proteomics research is identifying new tumour-specific molecular targets; and on the other, innovative drug-delivery systems^{1,2} are being designed to guide drugs more precisely to tumour cells and away from sites of toxicity, and/or to maintain drugs at a therapeutic concentration over long periods of time. The objective of 'perfectly specific' low-molecular-weight drug molecules able to prevent tumour cell growth without causing non-specific side effects has been difficult to realize in practice, particularly for the common solid tumours such as breast, prostate, lung and gastrointestinal cancers. This has been attributed to poorly predictive preclinical models³, a lack of drug specificity in the clinical setting and the problem of acquired drug resistance. Although sometimes overlooked⁴, drug-delivery systems, nano-sized vectors for tumour targeting and synthetic macromolecular therapeutics have begun to make an important contribution to cancer therapy over the last decade.

Biodegradable polymers containing entrapped drug can be placed in the body, and are used for localized drug delivery and/or the controlled release of a drug over a period of months. For example, small polymer rods (Zoladex) and polymer microparticles (Leuprolide (Leupron Depot)) made from polylactide-co-glycolide-entrapping leuprolide hormone releasing hormone (LHRH) analogues are common treatments for prostate cancer. As the polymer slowly degrades, therapeutic levels of the anti-tumour peptide are maintained for up to 3 months, making the therapy very convenient for patient use⁵. Another biodegradable polymeric implant, carmustine (Gliadel), is used to treat brain cancer (glioblastoma multiforme)^{6,7}. In this case, a biodegradable polyanhydride polymer is made

into small polymer discs containing the alkylating agent *h*(2-chloroethyl)nitrosourea (BCNU). These discs are placed into the brain following the surgical removal of the tumour, and thereafter they slowly degrade to deliver the drug locally, therefore preventing tumour re-growth. Although such polymer-based drug-delivery systems have been important advances, the development of nano-sized vectors enables tumours to be targeted more precisely – the vectors can move around in the body and selectively localize a therapeutic drug payload to metastatic tumours.

The medical application of nanotechnology (that is, 'nanomedicine') has enormous potential to improve healthcare, particularly in cancer^{8,9,10}. On one hand, miniaturization is creating devices for use as diagnostics, biosensors and imaging agents, and on the other, ever more sophisticated synthetic chemistry is producing nanovectors for drug delivery. The terminology used is often contentious and can be confusing. Ferrari recently coined a useful definition of cancer nanotechnology¹¹ as 'a vast and diverse array of devices derived from engineering, biology, physics and chemistry, including nanovectors for the targeted delivery of anticancer drugs and imaging contrast agents, and those detection systems such as nanowires and nanocaster arrays under development for the early detection of precancerous and malignant lesions from biological fluids'. Nanovectors have also been called 'nanopartimedicines' or 'nanomedicines'. To distinguish them from biotech products, such as proteins and antibodies (which are also inherently 2–15 nm in size), the European Science Foundation's Forward Look on Nanomedicine defined nanomedicines as 'nanometer size scale complex systems, consisting of at least two components, one of which being the active ingredient'¹².

644 SEPTEMBER 2006 | VOLUME 6

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www.nature.com/reviews/cancer

Anticancer agents



Polymer-drug and Polymer-Protein conjugates

Lab

Clinic

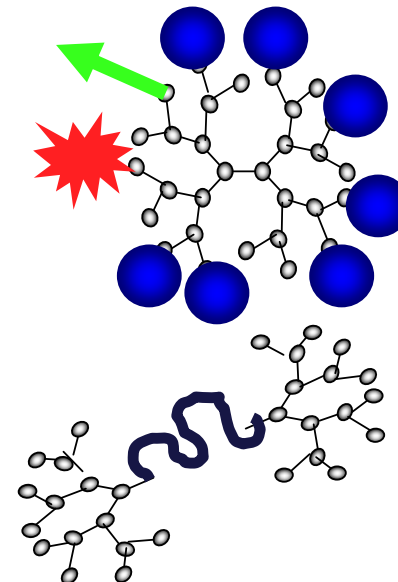


early detection of precancerous and malignant lesions from biological fluids." Nanosensors have also been called "nanomedicines or nanopharmaceuticals." To distinguish them from biotech products, such as proteins and antibodies (which are also technically 2–15 nm in size), the European Science Foundation's Forward Look on Nanomedicine defined nanomedicines as "nanometric size scale complex systems, consisting of

Targeting Residues

Linker

6 - 20 nm





divergent

convergent

polymer

linker

protein

drug

Targeting residue

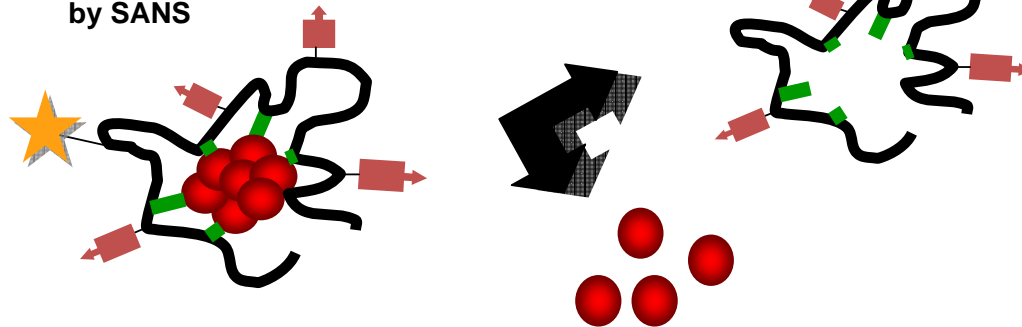
Imaging agent

1. Polymer-Drug Conjugates

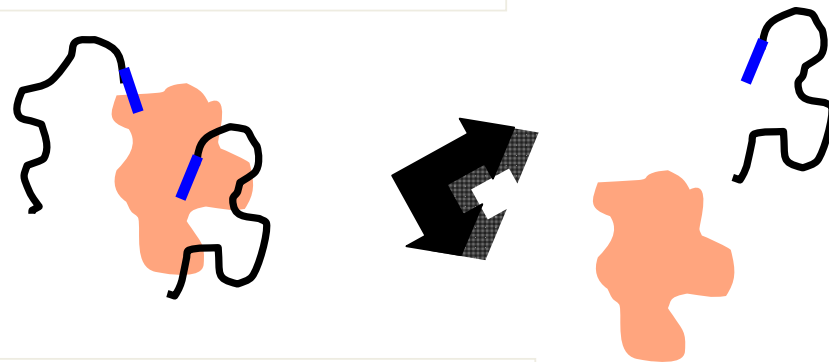
May form a Unimolecular micelle (or other structures) in solution

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

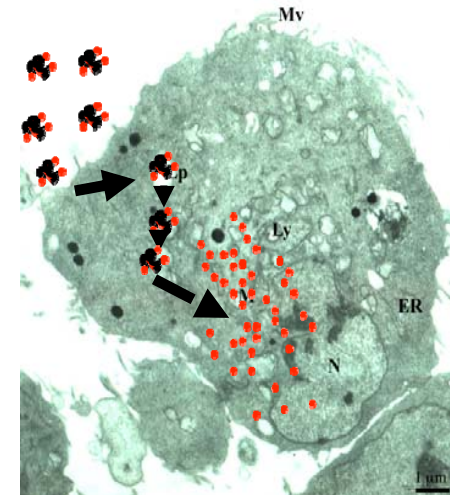
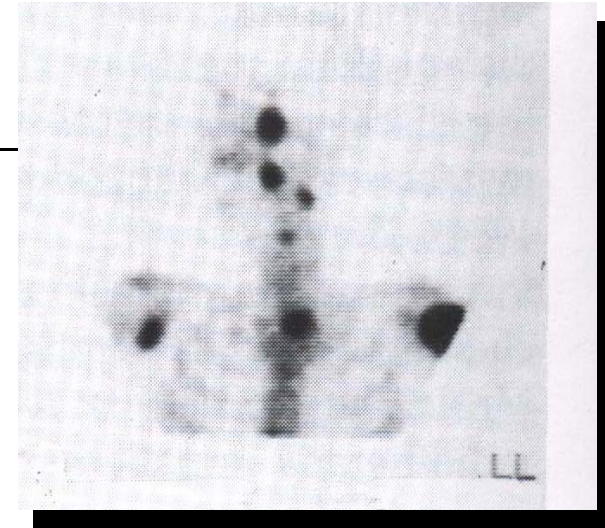
drug/protein

targeting group

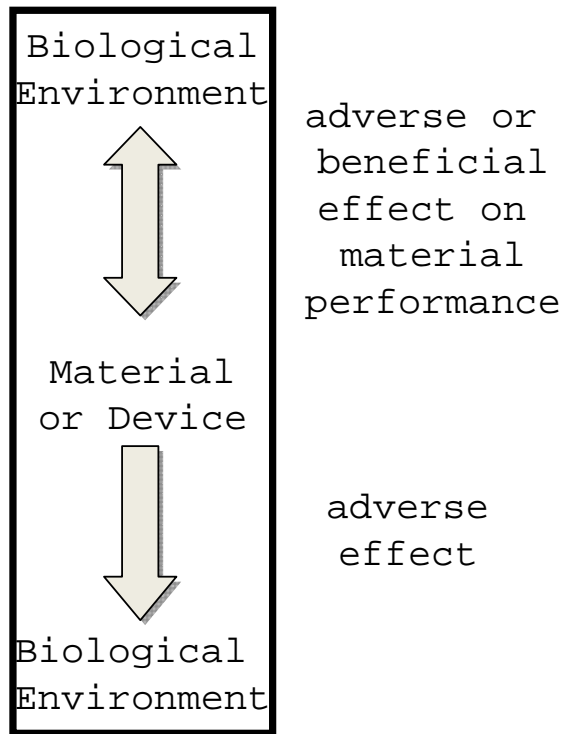
imaging agent

Pharmacokinetics

Methods for physico-chemical characterisation

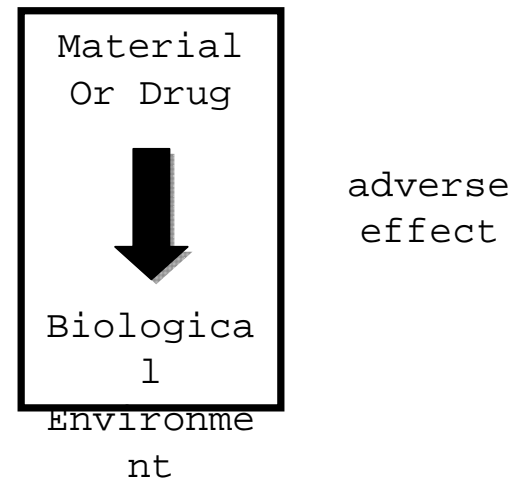


Biocompatibility



OR

Toxicology



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. Vetricka
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. Yeung¹, John W. Hopewell¹, Rosemary H. Simmonds¹, Leonard W. Seymour², Ruth Duncan², Ornella Bellini³, Maria Grandi³, Federico Spreafico³, Jiri Strohalm⁴, and Karel Ulbrich⁴

GLP Preclin Tox

Human & Experimental Toxicology (1998) 17, 93–104
© 1998 Stockton Press. All rights reserved 0144–5952/98 \$12.00

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

R Duncan¹, JK Coatsworth² and S Burtles³

¹Centre for Polymer Therapeutics, The School of Pharmacy, University of London, 29–39 Brunswick Square, London WC1N 1AX, UK; ²BIBRA International Woodmansterne Road, Carshalton, Surrey SM5 4DS, UK; ³Cancer Research Campaign, 10 Cambridge Terrace, London NW1 4JL, 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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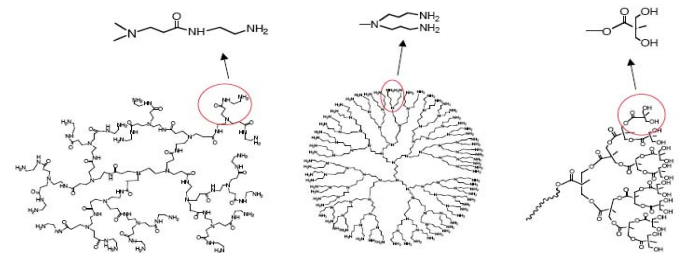
Advanced Drug Delivery Reviews 57 (2005) 2215–2237

Advanced
DRUG DELIVERY
Reviews

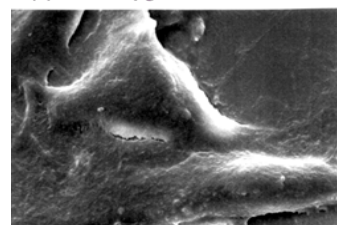
www.elsevier.com/locate/addr

Dendrimer biocompatibility and toxicity ☆

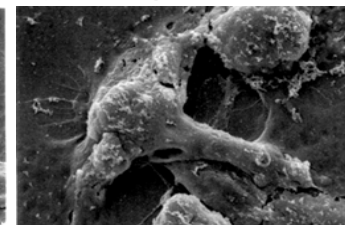
Ruth Duncan ^{a,*}, Lorella Izzo ^{a,b}



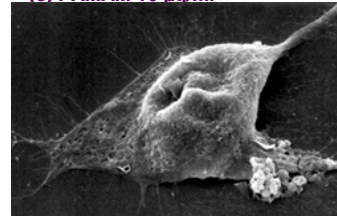
~) DAB 10 µg/ml



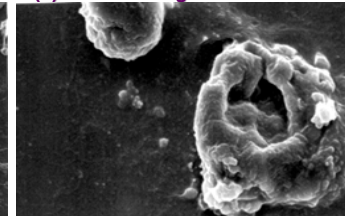
(a) DAB 1 mg/ml



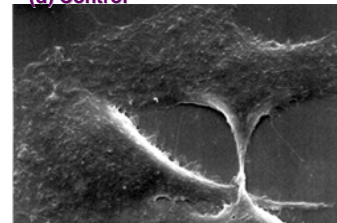
(c) PAMAM 10 µg/ml



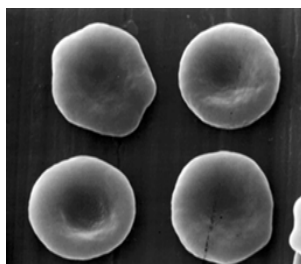
(d) PAMAM 1 mg/ml



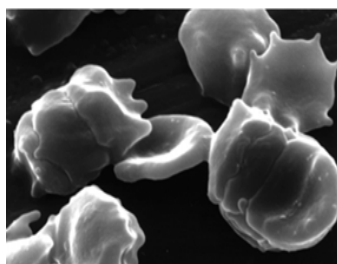
(d) Control



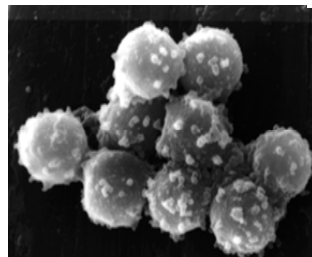
(a) Control



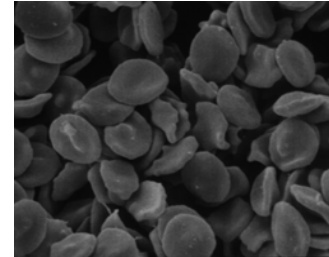
(b) PAMAM gen 4; 10 µg/mL



(c) PAMAM gen 4; 1 mg/mL



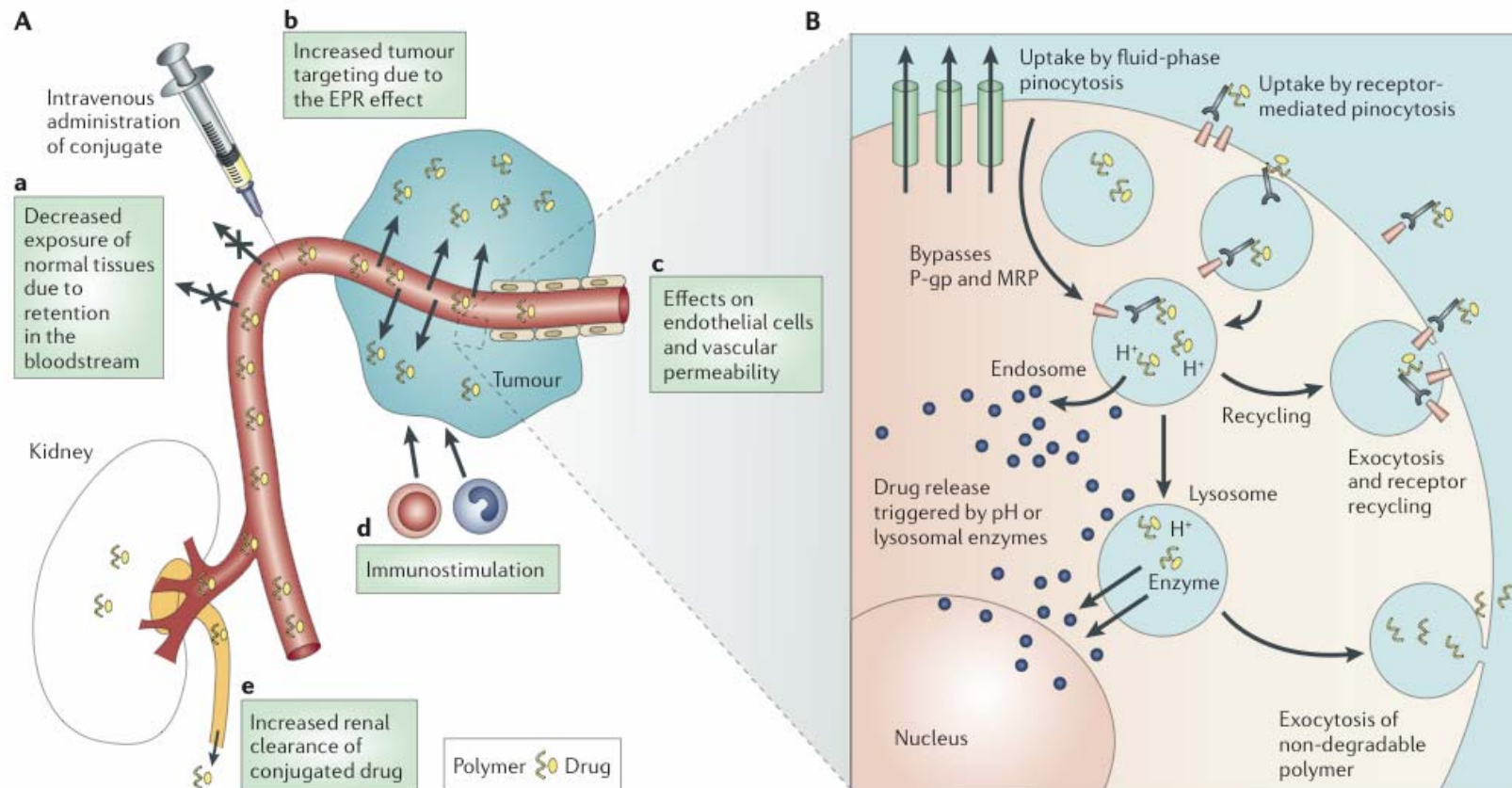
(d) PAMAM gen 3.5; 1 mg/mL



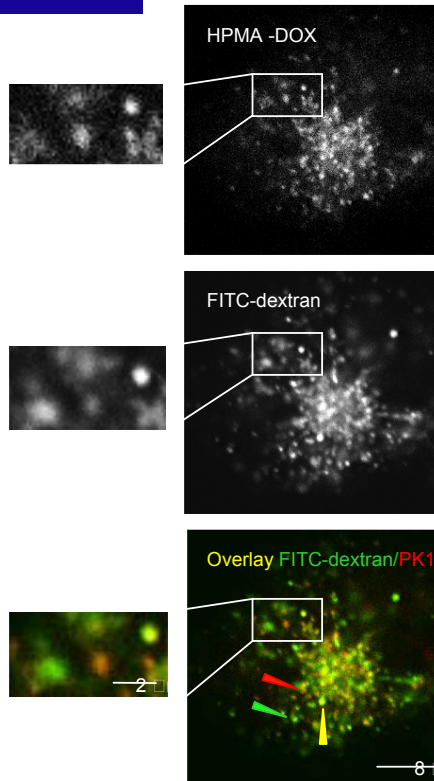
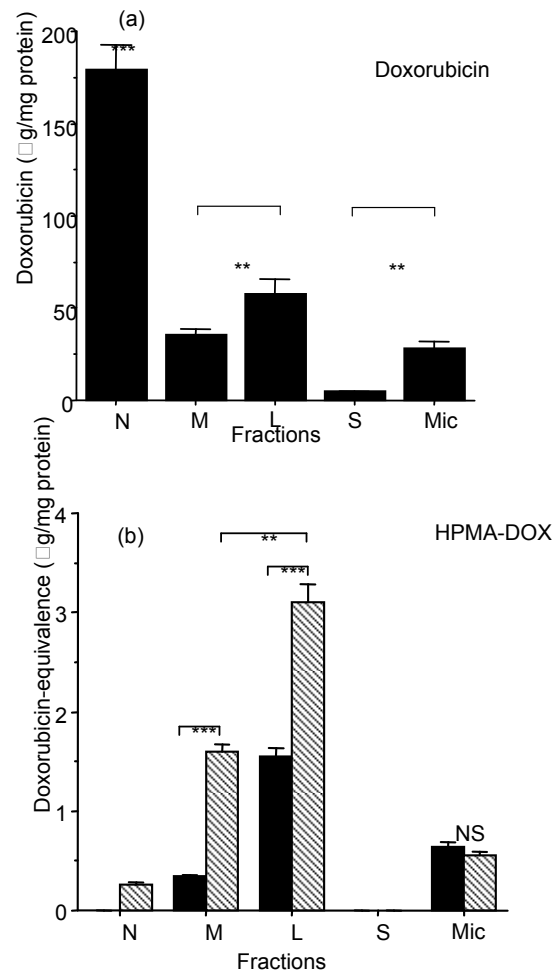
Current Understanding of the Mechanism of Action of Polymer-Anticancer Conjugates

Duncan Nature Reviews Cancer (September 2006)

Importance of Pharmacokinetics



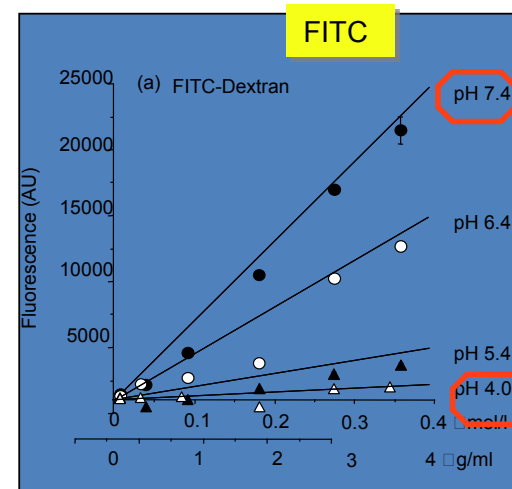
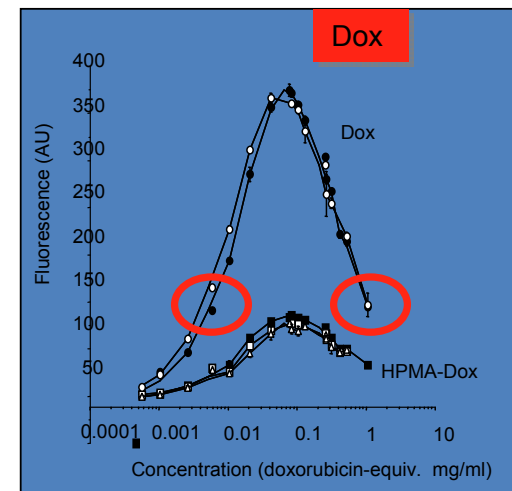
Quantitation of Intracellular Localisation



Nature Reviews 14(7):1-11

The good, the bad and the ugly

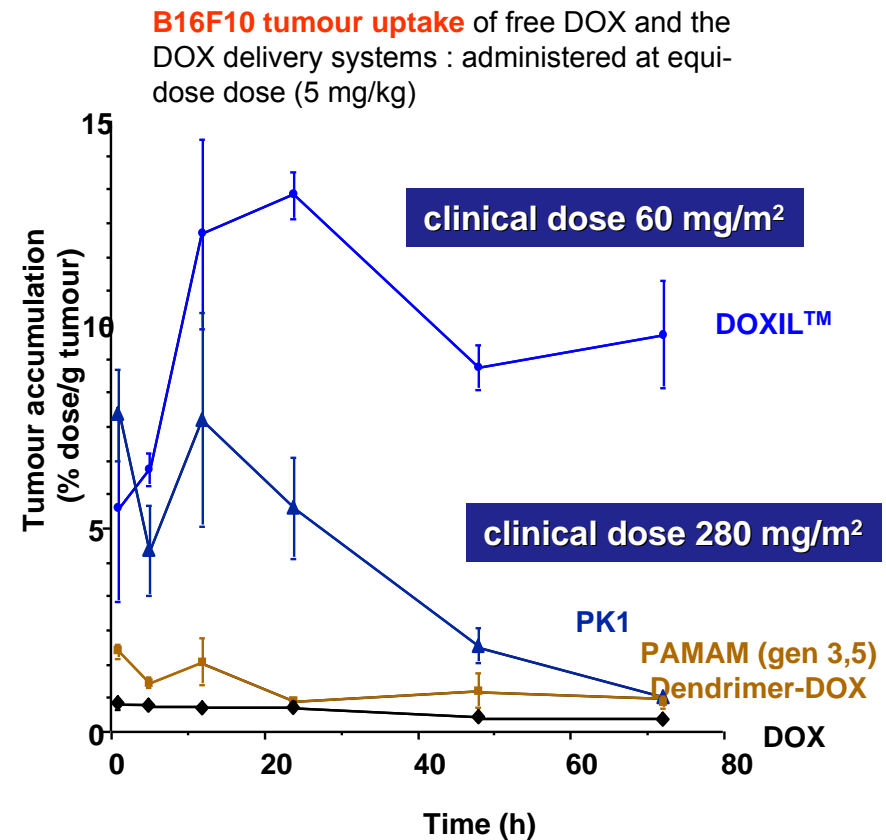
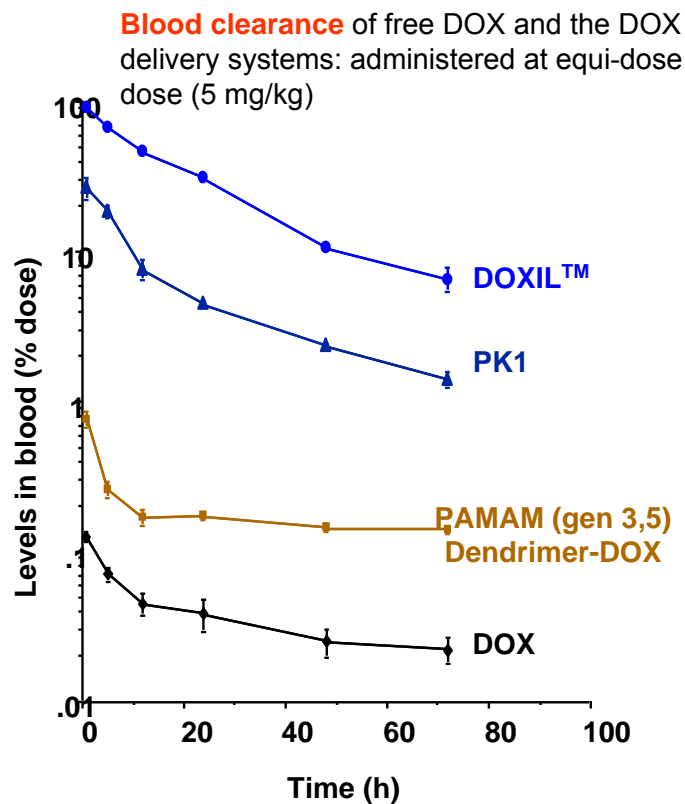
Imaging techniques are revealing biology at a previously unobtainable level and making sense of the data is a challenge for Pearson.



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



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

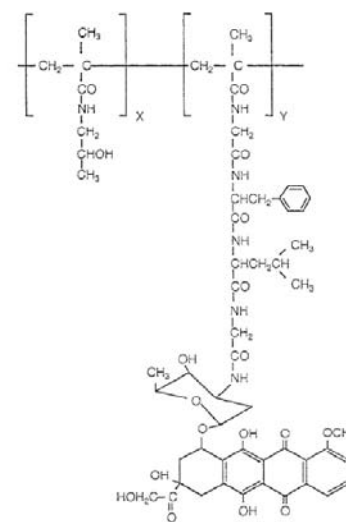


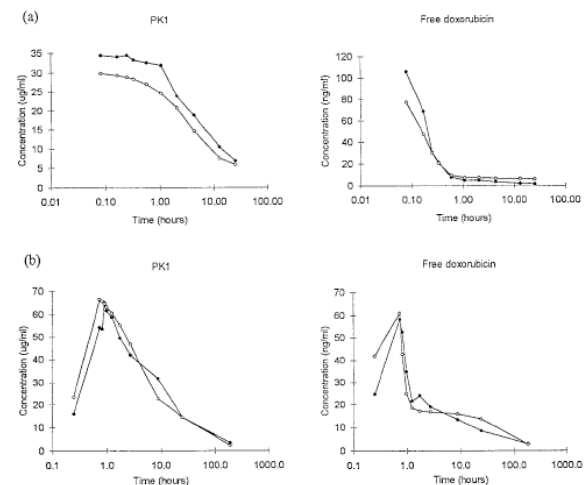
Fig. 1 Structure of PK1 (HPMA copolymer doxorubicin). The molecular weight of the compound is 28,000 (doxorubicin, 8.5% (w/w)).

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/m².

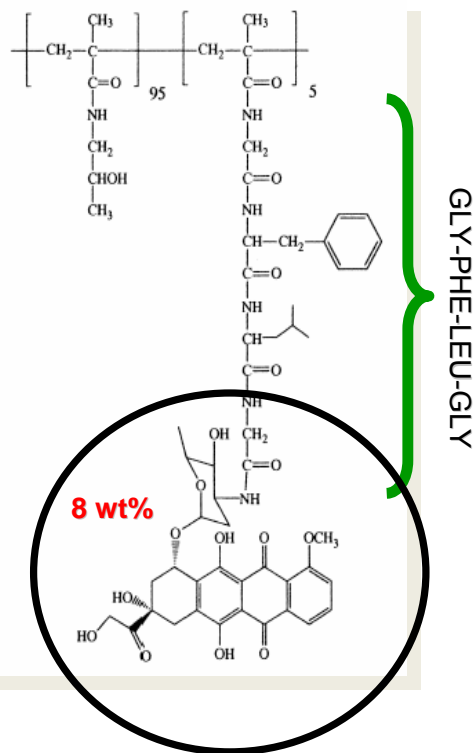
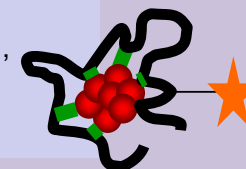
Fig. 4 Measured (●) and population-predicted (○) concentrations of PK1 and free doxorubicin (correlation coefficient, -0.44) for two patients receiving PK1 at 80 mg/m² (a) and 180 mg/m² (b). Time (X axis) is presented on a log scale for clarity.



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.

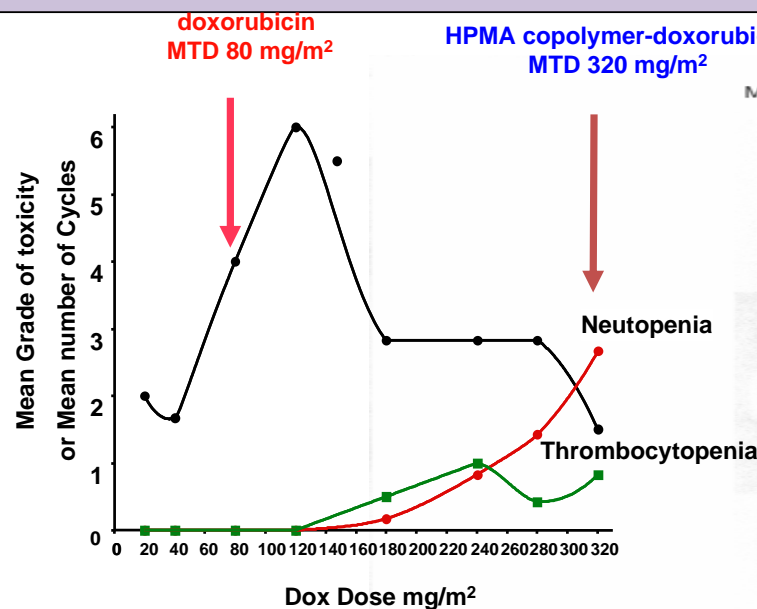
Vasey P., Kaye S.B., Morrison, R., Twelves, C., Wilson, P., Duncan R, Thomson A.H., Murray, L.S., Hilditch, T.E., Murray, T., Burtles, S., Fraier, D., Frigerio, E. and Cassidy, J.

Clinical Cancer Research 5, 83-94 (1999)

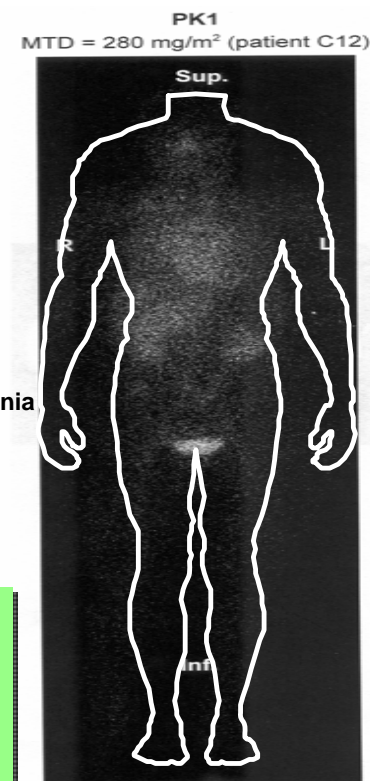


FCE28068

HPMA Copolymer-doxorubicin



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



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

D Bissett^{*,1}, J Cassidy¹, JS de Bono², F Muirhead², M Main¹, L Robson³, D Fraier⁴, ML Magnè⁴, C Pellizzoni⁴, MG Porro⁴, R Spinelli⁴, W Speed⁴ and C Twelves²

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

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 Rosing², S Jansen², M Swart¹, J Lieverst¹, D Fraier³, M Breda³, C Pellizzoni³, R Spinelli³, M Grazia Porro⁴, JH Beijnen^{1,2,5}, JHM Schellens^{1,5} and WW ten Bokkel Huinink¹

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

^an=1. For abbreviations see Patients and methods section.

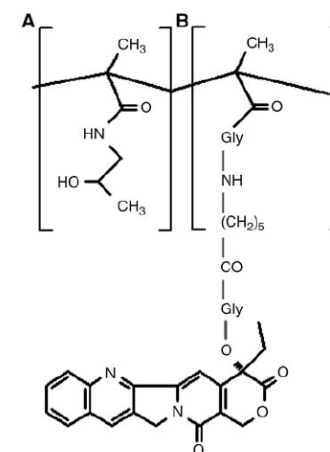


Figure 1 Structure of MAG-CPT. Free camptothecin is released by hydrolysis, which converts (B) to (A).

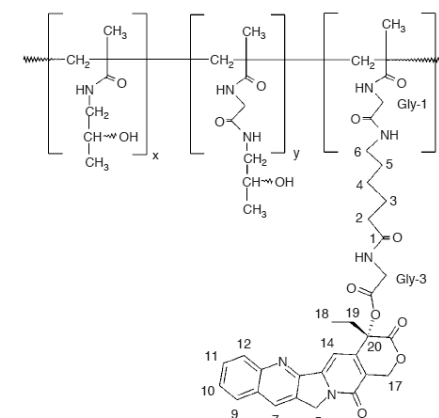
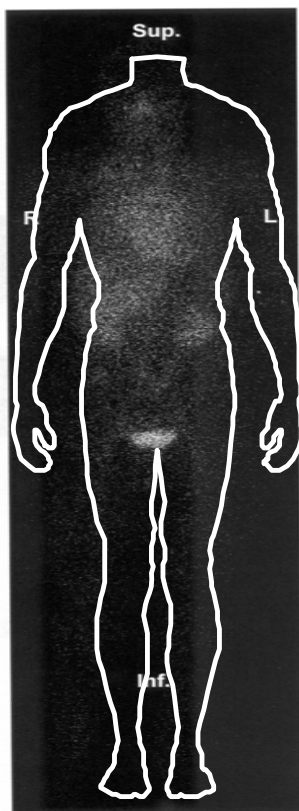


Figure 1 Chemical structure of MAG-CPT.

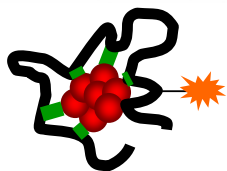
FCE28069 Phase I/II Trials

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

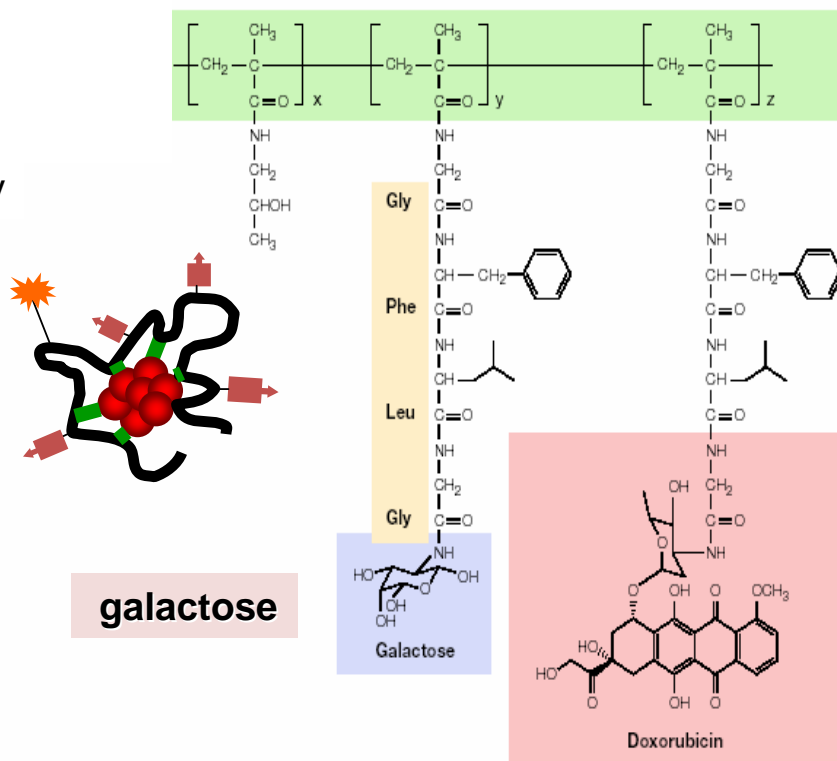
MTD
280 mg/m²



MTD
160 mg/m² Dox-Equiv



Seymour et al. J. Clin. Oncol. 20, 1668 (2002)



- 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**

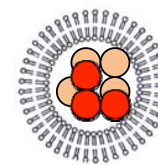
María J. Vicent,* Francesca Greco, Robert I. Nicholson, Alison Paul, Peter C Griffiths, and Ruth Duncan*

Vicent et al. (2005) *Angew. Chem. Int. Ed.* 44, 2 –6.

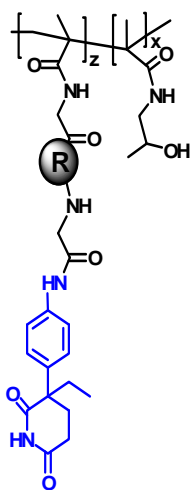
Duncan et al. (2005) *Endocrine-Related Cancer*, 12, S189-S199.

Greco et al. (2005) *J. Drug Targeting* 13, 459-470.

Greco et al. (2007) *J. Controlled Release* 117, 28-39.

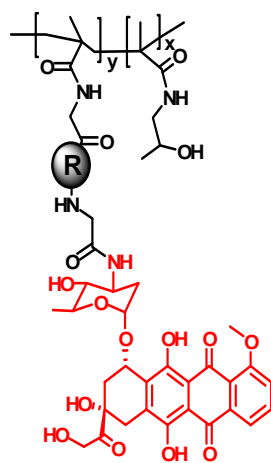


I HPMA-R-AGM



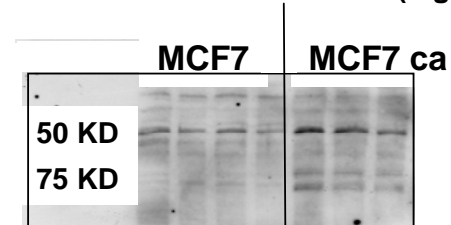
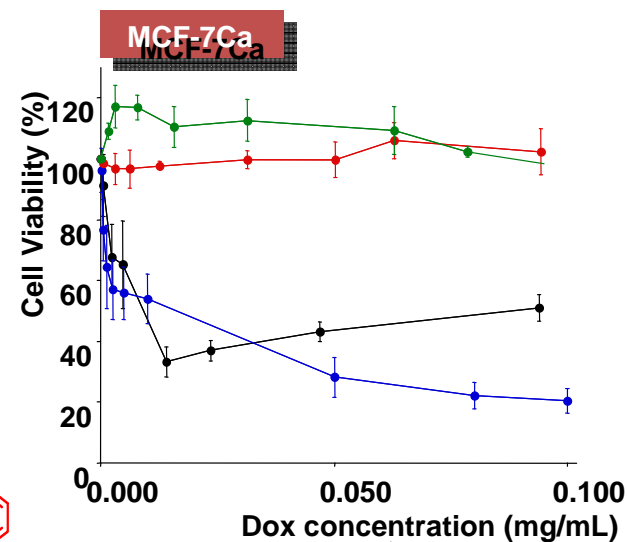
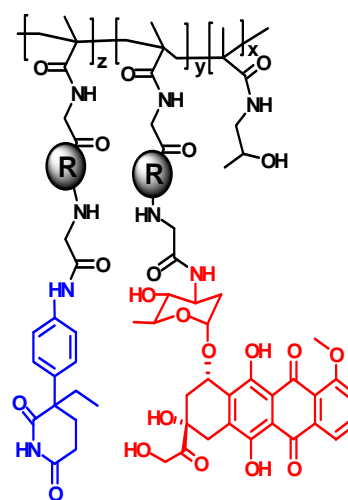
aminoglutethimide

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

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NANOMEDICINE

Dextrin–rhEGF conjugates as bioresponsive nanomedicines for wound repair

Joseph Hardwicke^{a,*,†}, 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 Reporative Dentistry, School of Dentistry, Heath Park Campus, Cardiff CF14 4XN, UK

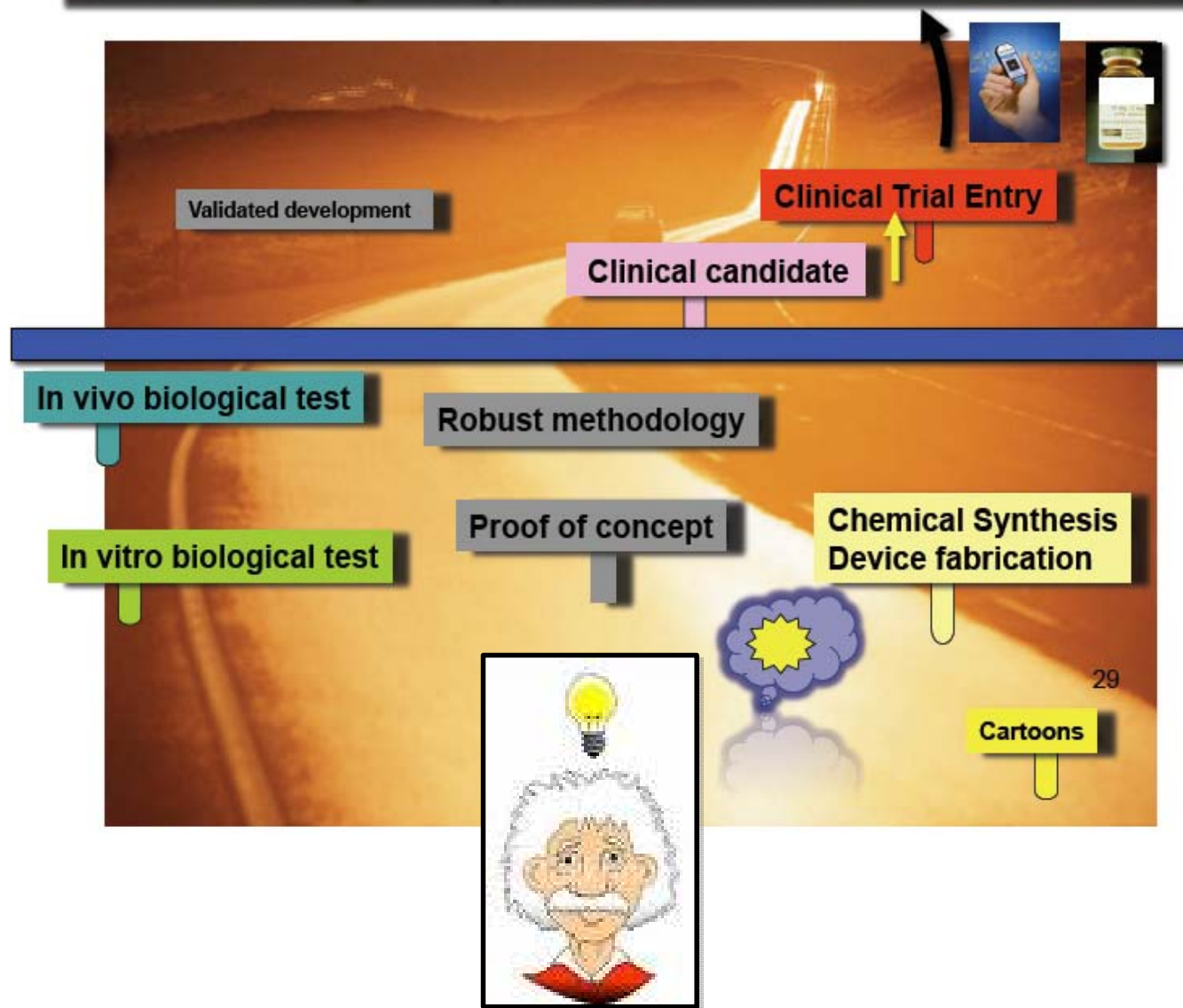
^b Centre for Polymer Therapeutics, Welsh School of Pharmacy, Redwood Building, Ring Adward VII Avenue, Cardiff CF10 1XF, UK

COVER STORY
Dextrin–rhEGF conjugates as bioresponsive nanomedicines for wound repair

College of medicine
GIG CYMRU
Llywodraeth Cynulliad Cymru
Welsh Assembly Government

Understanding where you are on the road Lab to Market



"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