EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1st International Workshop on Nanomedicines
2nd-3rd September 2010

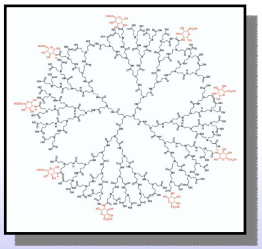
NANOMEDICINES ON THE MARKET AND IN CLINICAL DEVELOPMENT

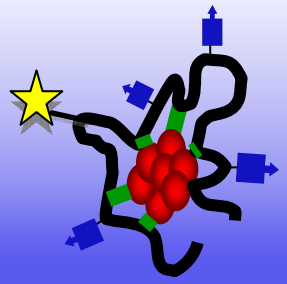
Polymer Conjugates

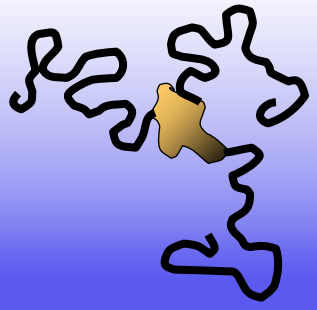
Ruth Duncan

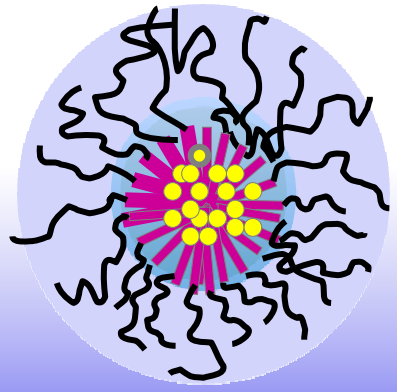
Professor Emerita, Cardiff University

profruthduncan@btinternet.com

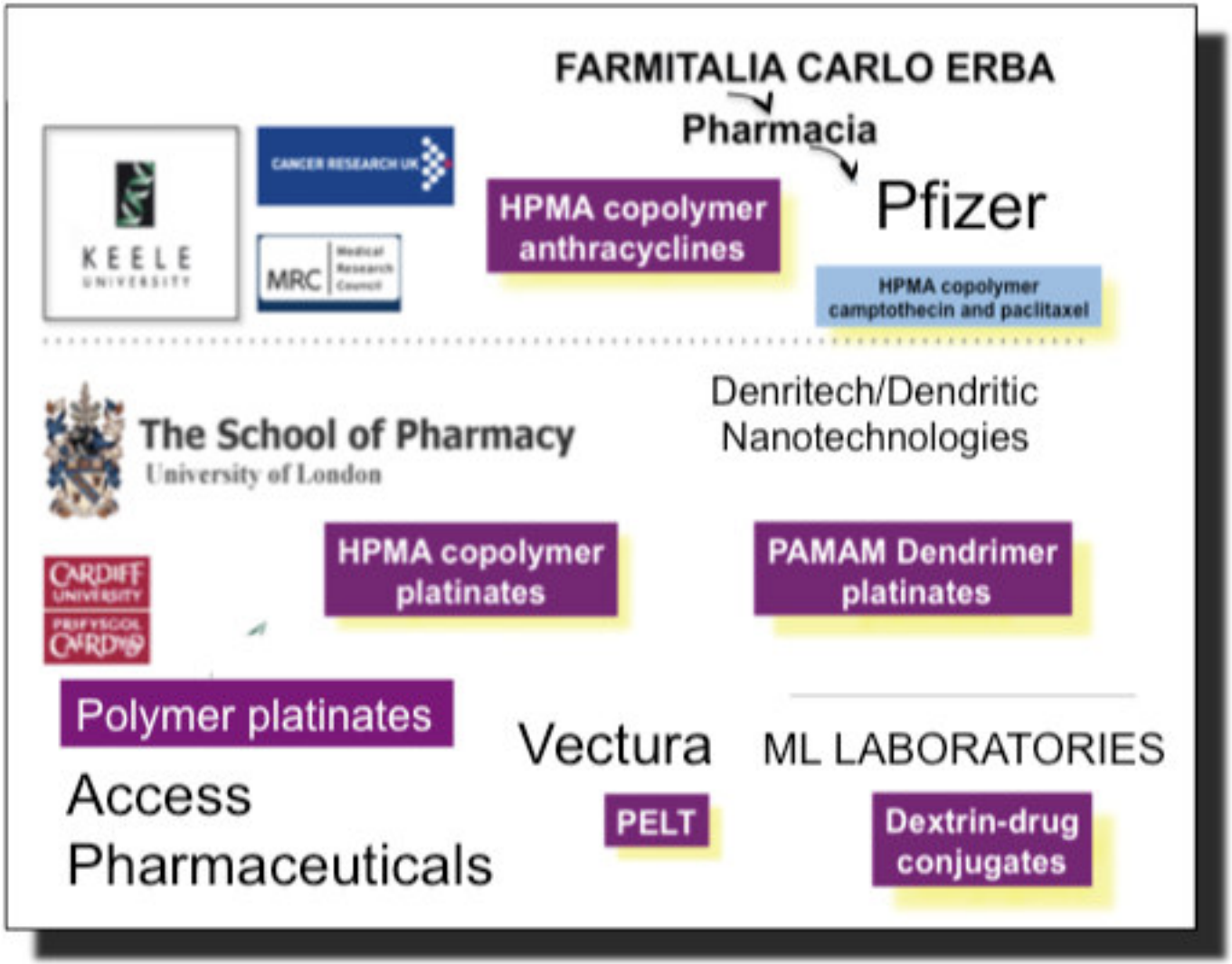








Declaration of Interests ..... comments made are personal opinions



Member Ad-Hoc Advisory Group Nanomedicine

Member WG SCENHIR Nanomaterials Definition

Past member MHRA CPS Sub-committee

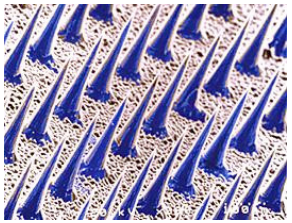
Evolution of Natural and Synthetic Polymers in Healthcare Applications

– a pivotal role in nanomedicines

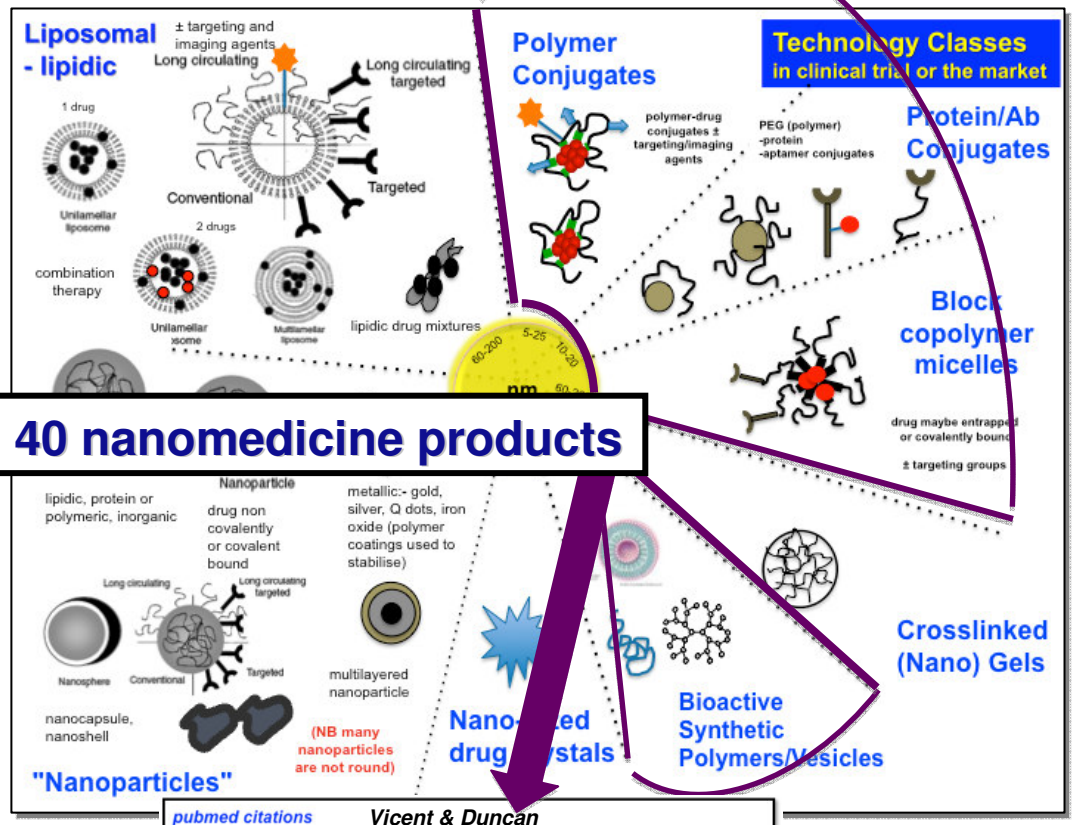
Excipients

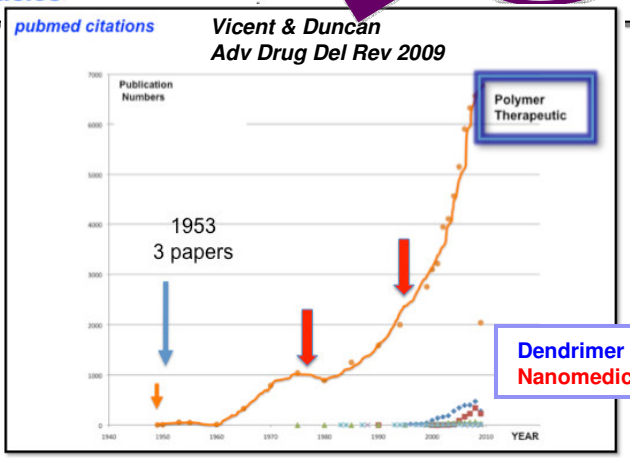
Biomedical Materials and Devices

Local delivery using devices

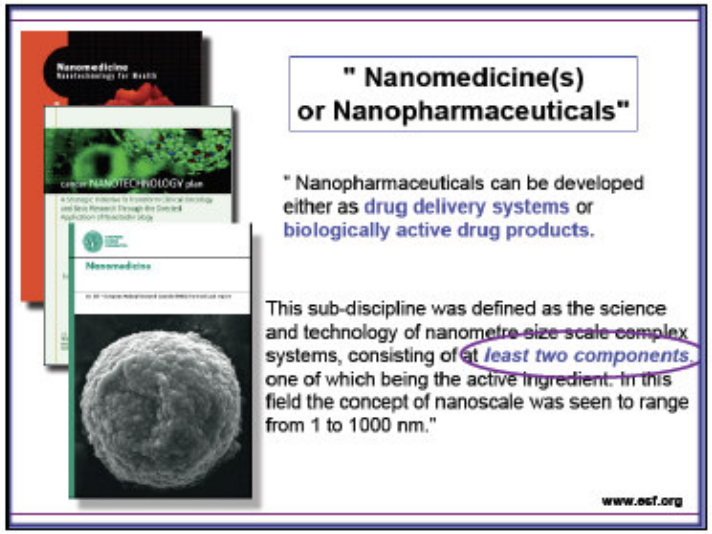


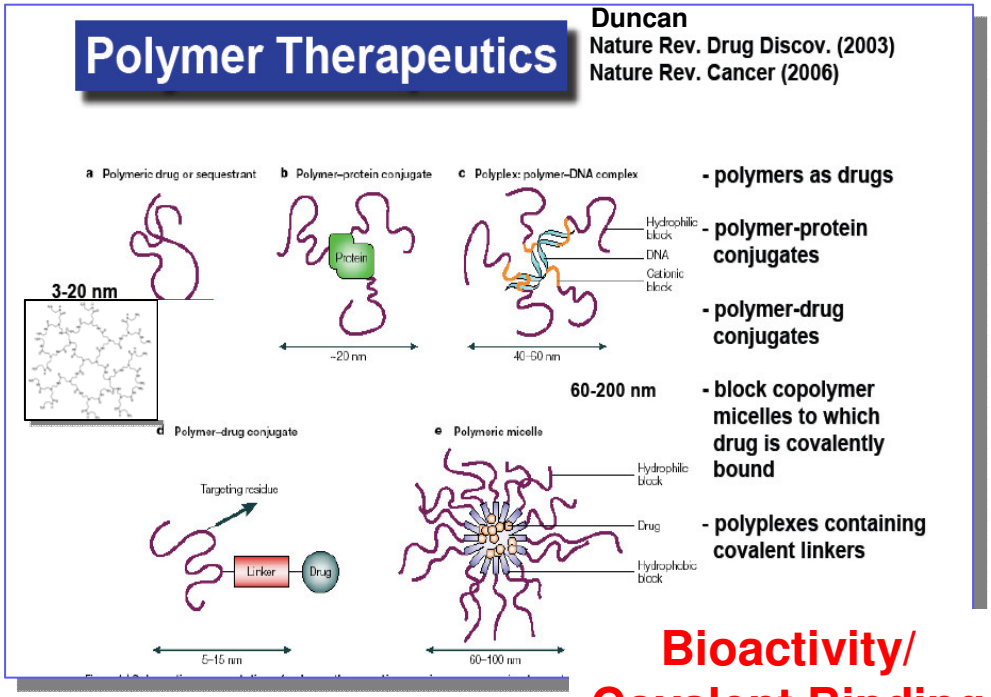
Tissue Engineering Scaffolds





Terminology – Challenges, and the Need for Standardisation



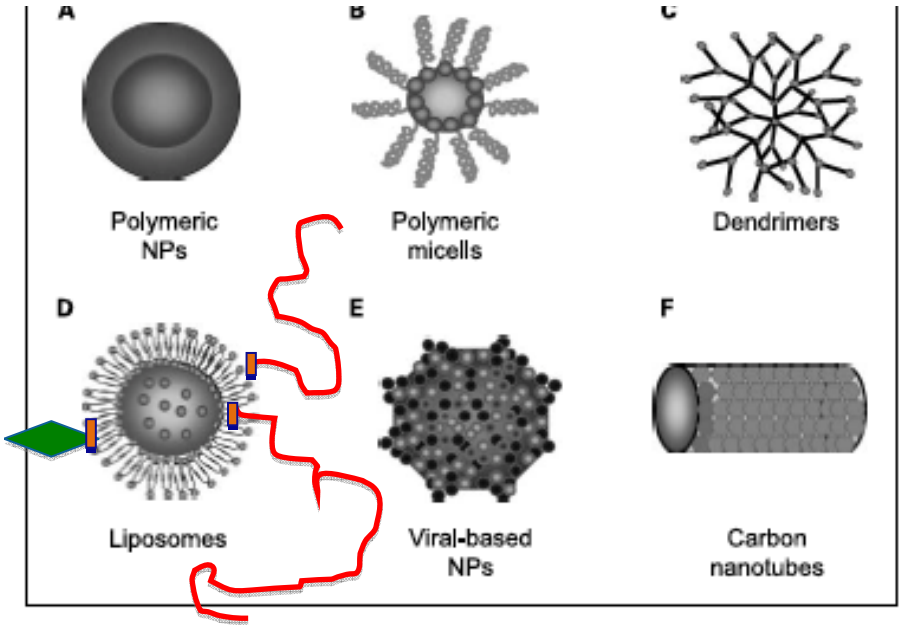


Bioactivity/ Covalent Binding

Therapeutic Nanoparticles for Drug Delivery in Cancer

Kwangjae Cho,[1] Xu Wang,[1] Shuming Nie,[2] Zhuo (Georgia) Chen,[1] and Dong M. Shin[1]

Clin Cancer Res 2008;14(5) March 1, 2008



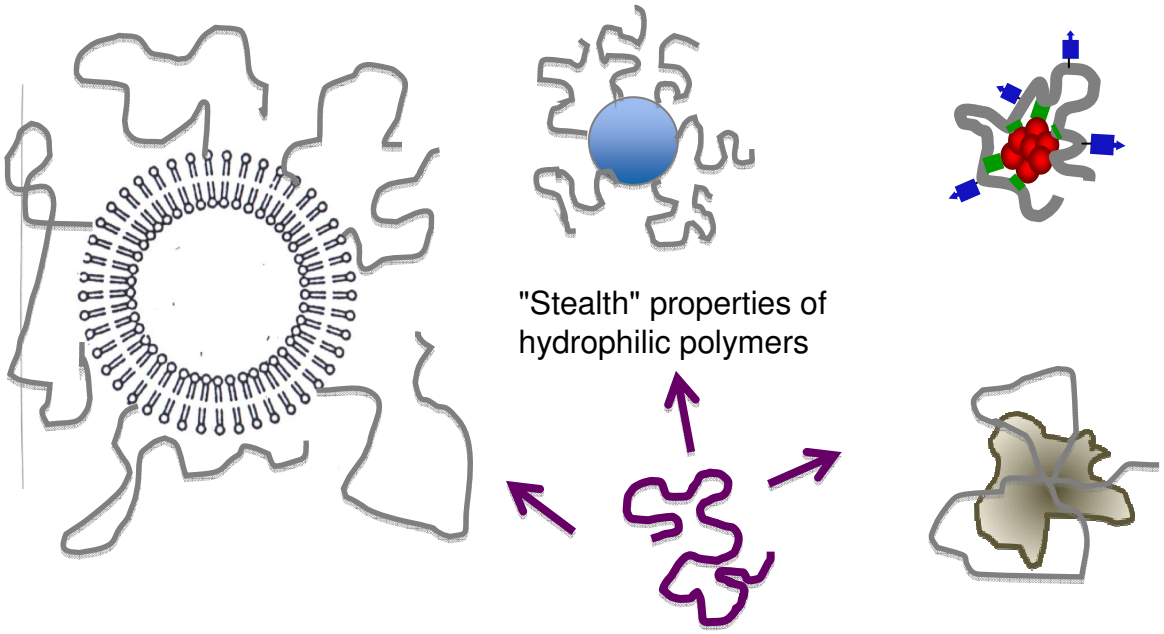

REVIEWS

Strategies in the design of nanoparticles for therapeutic applications

Robby A. Petros* and Joseph M. DeSimone‡§

Abstract | Engineered nanoparticles have the potential to revolutionize the diagnosis and treatment of many diseases; for example, by allowing the targeted delivery of a drug to particular subsets of cells. However, so far, such nanoparticles have not proved capable of surmounting all of the biological barriers required to achieve this goal. Nevertheless, advances in nanoparticle engineering, as well as advances in understanding the importance of nanoparticle characteristics such as size, shape and surface properties for biological interactions, are creating new opportunities for the development of nanoparticles for therapeutic applications. This Review focuses on recent progress important for the rational design of such nanoparticles and discusses the challenges to realizing the potential of nanoparticles.

Beneficial properties of polymer therapeutics



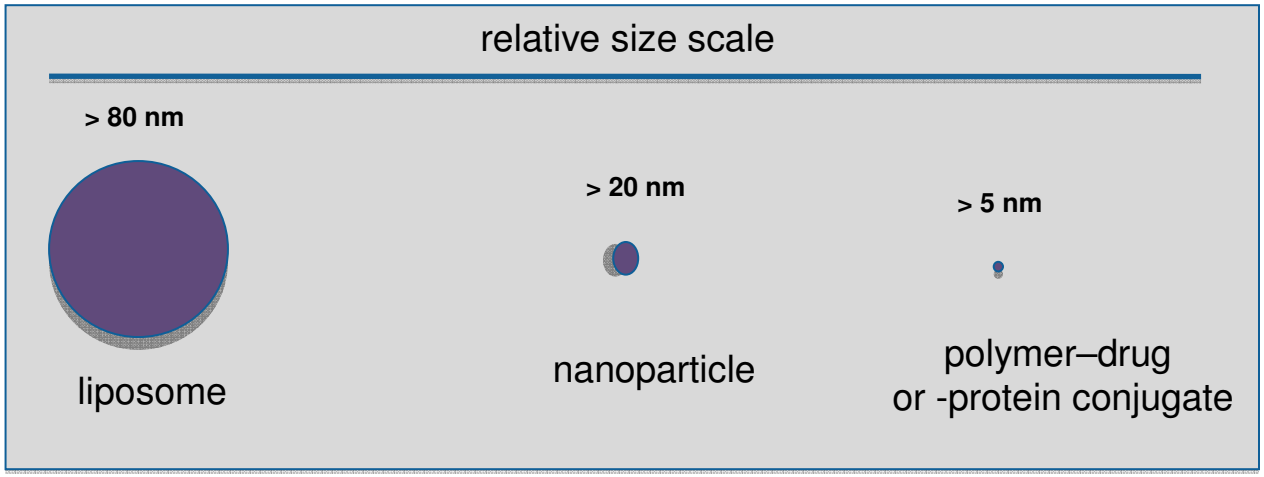
- relatively small
to allow easier access
to some therapeutic targets

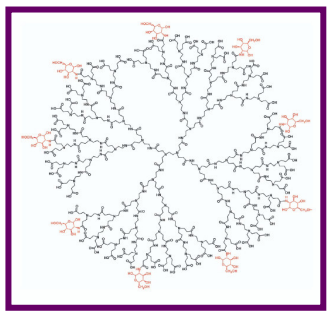
- can evade RES clearance

- linkers allow tuning of rate
(and location) of drug release

- easier to develop validated
assays to determine free and
bound drug

- potential to control
3D architecture



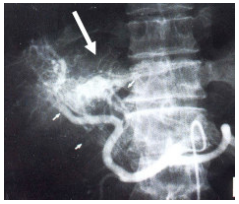


Polymer Therapeutics in the market *(Vicent, Ringsdorf, Duncan Adv. Drug Del. Rev. 2009)*

Product	Company	Trade Name	Indication	~Revenue US$ (bn)	Approval Year
Polymeric Drugs					
Copolymer of Glu Ala/Tyr (subcutaneous injection)	Teva	Copaxone®	Multiple Sclerosis	1.0	2000
Phosphate binding polymer (oral)	Genzyme	Renagel®	End Stage Renal Failure	0.68	1999
Cholesterol binding polymer (oral)	Genzyme	Welchol®	Reduction of elevated LDL-C Reduce glucose Type 2 diabetes	0.22	2000 2008
Polymer-Protein Conjugates					
Styrene Maleic Anhydride-Neocarzinostatin (SMANCS) (intrahepatic artery)	Yamanouchi	Zinostatin Stimaler®	Hepatocellular carcinoma		1990 (Japan)
PEG-adenosine deaminase (intramuscular)	Enzon	Adagen®	Severe Combined Immune Deficiency Syndrome	0.02	1990
PEG-asparaginase (intravenous or intramuscular)	Enzon	Oncospar®	Acute Lymphocytic Leukaemia	0.02	1990
PEG-interferon alfa-2b (subcutaneous)	Schering Plough	PEGINTRON®	Chronic hepatitis C	0.75	2001
PEG-interferon alfa-2a (subcutaneous)	Roche	PEGASYS®	Chronic hepatitis C	1.2	2002
PEG-human G-CSF (subcutaneous)	Amgen	Neulasta®	Febrile neutropenia	1.1	2002
PEG-HGH antagonist (subcutaneous)	Pfizer	Somavert®	Acromegaly	0.01	2003
Peg-antiTNF Fab (subcutaneous)	UCB Pharma	Cimzia®	Crohn's Disease Arthritis		2008 2009
Polymer-aptamer					
PEG-aptamer (aptanib) (intravitreous)	OSI-Eyetech	Macugen®	AMD	0.19	2004

Local administration

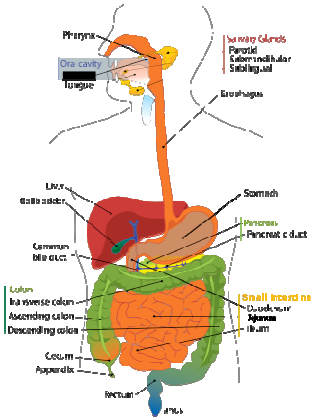
via the hepatic artery



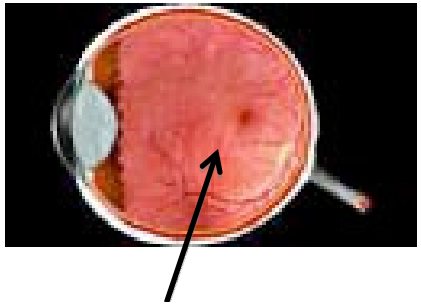
Parenteral administration

- intravenous
- subcutaneous
- intramuscular

Oral administration



Macugen®



intravitreal

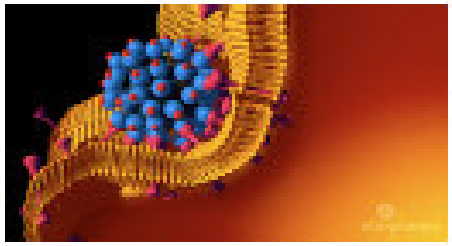
Table 2 Polymer therapeutics that have entered clinical trial (Vincent, Ringsdorf, Duncan ADDR 2009)

Product	Company	Trade Name	Indication	Clinical Phase
Polymeric Drugs				
Lysine-based dendrimer (topical microbiocide)	Starpharma	VivaGel®	prevention of transmission of genital herpes and HIV	Phase II
Polymeric sequestrant for phosphate (oral)	Ilypsa/Amgen	ILY101/ AMG 223	hyperphosphatemia in chronic kidney disease patients on heamodialysis.	Phase I
Polymer-Protein Conjugates				
PEGylated -anti VEGFR2 Fab fragments as an angiogenesis inhibitor	UCB Pharma	CDP 791	non small cell lung cancer	Phase II
PEG-haemoglobin	Sangart	Hemospan®	delivery of CO and O_2 in trauma patients	Phase II
Polymer-drug conjugates				
polymer-cyclodextrin nanoparticle-siRNA (intravenous)	Calando Pharmaceutical	CALAA-01	solid tumours	Phase I
PEG-docetaxel (intravenous)	Nektar	NKTR-105	solid tumours including hormone-refractory prostate cancer	Phase I
biodegradable polymer-camptotehcin (intravenous)	Mersana	XMT-1001	solid tumours	Phase I
polymer-cyclodextrin nanoparticle-camptothecin (intravenous)	Calando Pharmaceuticals	IT-101	solid tumours	Phase I/II
PEG-irinotecan (intravenous)	Nektar	NKTR-102	colorectal, breast, ovarian and cervical cancers	Phase II
HPMA copolymer platinate (intravenous)	Access Pharmaceuticals	ProLindac®	ovarian cancer	Phase II
PEG-naloxone (oral)	Nektar	NKTR-118	opioid-induced constipation	Phase II
Polyglutamic acid-paclitaxel (intravenous)	Cell Therapeutics	XYOTAX™, OPAXIO™	NSCLC	Phase III

TOPICAL ADMINISTRATION

Vivagel®

StarPharma



Design For Specific Function

first product approval

1970-1990 → 2010

Similars/Generics

→ 2020

New polymers

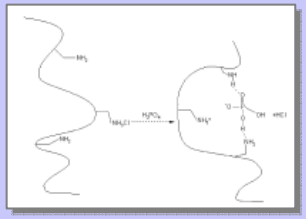
New multi-component nano-sized systems

Combination Therapy

Polymeric Drugs

Copaxone® leading therapy for multiple sclerosis in USA http://www.tevapharm.com

Oral Polymeric Sequestrants



Renagel®
(sevelamer hydrochloride)

phosphate binder
in renal failure

http://www.genzyme.com

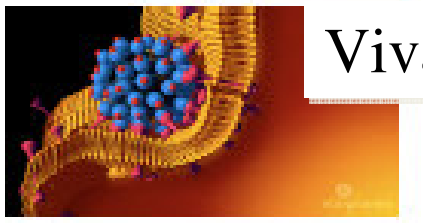
Welchol®
(colesevelam HCl)

lowers LDL

http://www.daiichisankyo.com

Functional polymers as therapeutic agents: Concept to market place
Adv. Drug Del. Rev, 61, 1121-1130
P. K. Dhal, S. C. Polomoscanik, L.Z. Avila, S. R. Holmes-Farley, R. J. Miller

Clinical Development



Vivagel®

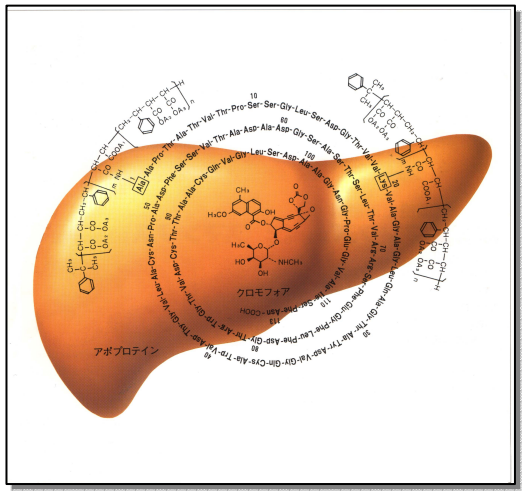
http://www.starpharma.com

prevention of sexually
transmitted infections
e.g. genital herpes, HIV infection and HPV

Safety, tolerability, and pharmacokinetics of SPL7013 gel (VivaGel): a dose ranging, phase I study
Sex Transm Dis. 2010 37, 100-104 **O'Loughlin et al.**

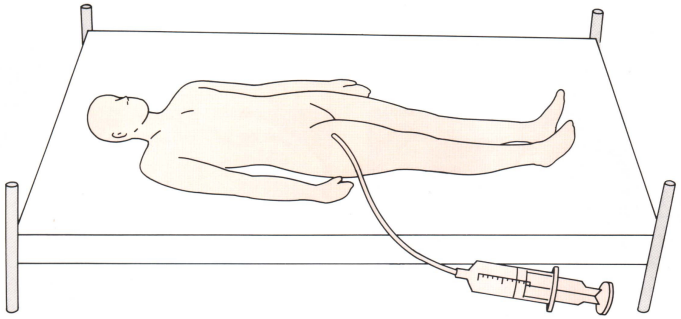
Polymer-Protein Conjugate for Local Administration

Maeda H et al. Polymeric drugs for efficient tumor-targeted drug delivery based on EPR-effect. Eur J Pharm Biopharm. 2009; 71(3):409-19.

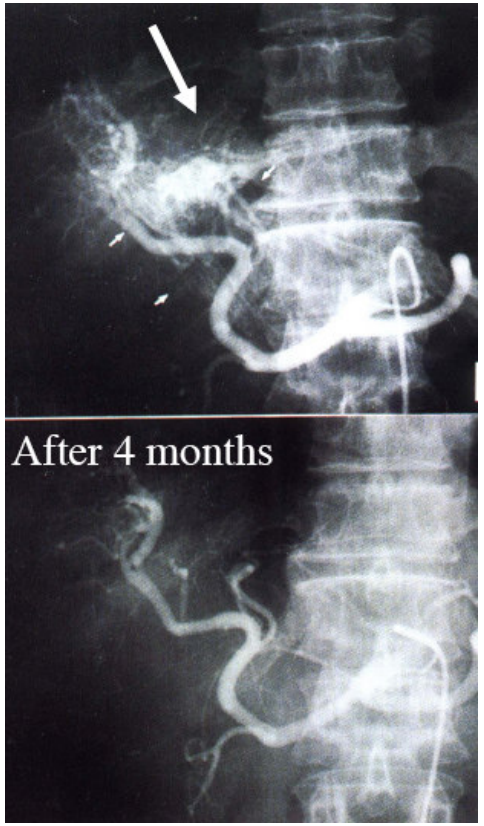


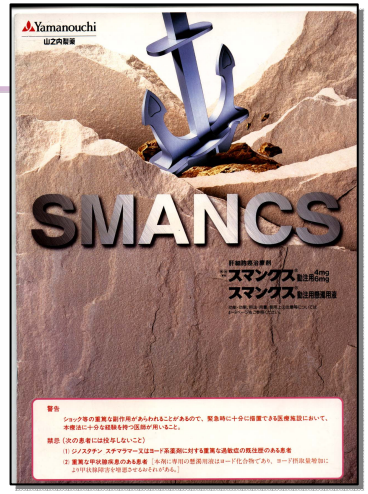
Styrene co-maleic acid-neocarzinostatin

YM881 (Zinostatin Stimalamer)



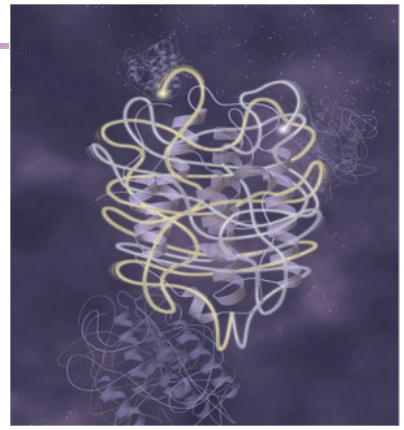
administered via the hepatic artery in Lipiodol (femoral artery access)





PEG-Protein Conjugates - Sustained Activity

J M Harris and R B Chess Nature Reviews in Drug Discovery March (2003)
Veronese Adv Drug Delivery Reviews (2008)



Neulasta™
PEG-asys®
PEG-Intron™

- **Improved stability**
- **Reduced immunogenicity**
- **Prolonged Plasma half-life**
- **Less frequent dosing due to greatly increased circulation time and slow absorption from subcutaneous injection site**

CLINICAL DEVELOPMENT INCL. COMBINATIONS

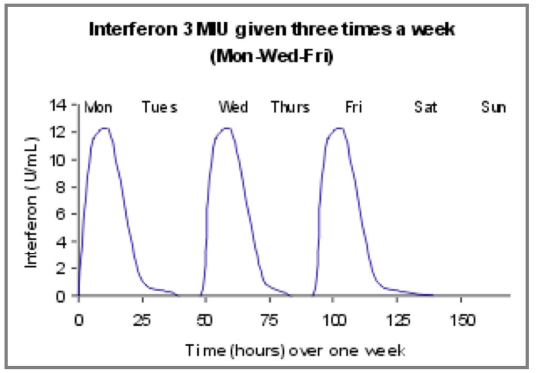
PEG-arginine deiminase

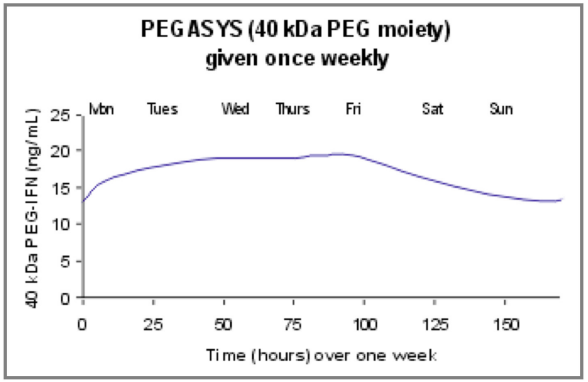
PEG-uricase

PEG-glutaminase combined with a glutamine antimetabolite 6-diazo-5-oxo-L-norleucine (DON)

PEG-D-amino acid oxidase (DAO) combined with the substrate DAO, D-proline

PEG-anti-VEGFR antibody fragment





PEG-Protein Conjugate Cimzia® - as innovative therapeutics

- 2007 Switzerland approved Cimzia® for the treatment of active Crohn's disease
- 2008 Cimzia® approved by FDA for the treatment of patients with Crohn's Disease
- 2009 Cimzia® approved by FDA/EMEA/Canada for the treatment of rheumatoid arthritis

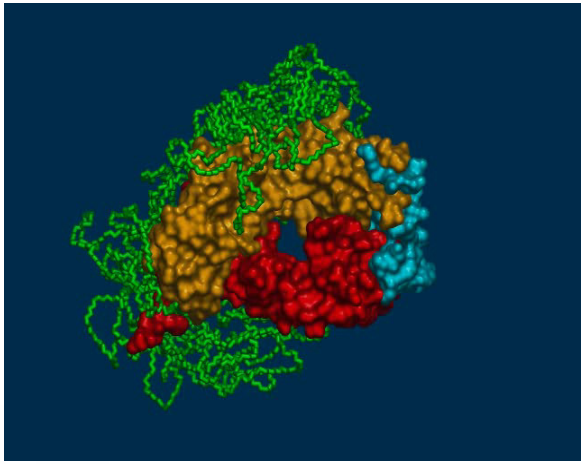
- NICE Recommends Approval in UK

a PEGylated
Fc-free TNF-alpha inhibitor

s.c injection

used in combination
with methotrexate

prefilled syringe

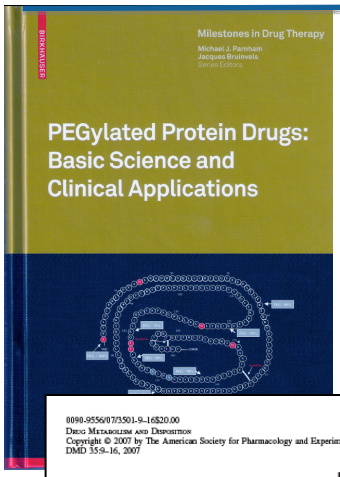


Mike Eaton UCB Pharma

neutralises membrane-associated and soluble human TNFα in a dose-dependent manner

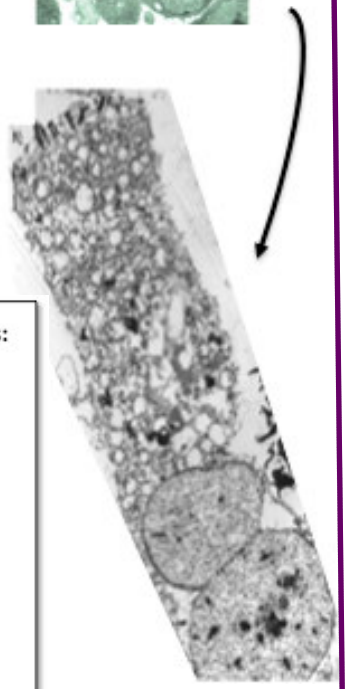
http://www.ucb.com

Safety of PEG ? Use, dose, route, frequency



There is more than one "PEG"

- *Mw*
- *Architecture*
- *linking chemistry*
- *impurities*



0090-9556/07/3501-9–16$20.00
DRUG METABOLISM AND DISPOSITION
Copyright © 2007 by The American Society for Pharmacology and Experimental Therapeutics
DMD 35:9–16, 2007
Vol. 35, No. 1
12419/3160041
Printed in U.S.A.

Minireview

PEGylated Proteins: Evaluation of Their Safety in the Absence of Definitive Metabolism Studies

Rob Webster, Eric Didier, Philip Harris, Ned Siegel, Jeanne Stadler, Lorraine Tilbury, and Dennis Smith

Pharmacokinetics, Dynamics and Metabolism (R.W., D.S.) and Clinical Research and Development (E.D., P.H.), Pfizer Global Research and Development Sandwich, Kent, United Kingdom; Pfizer Global Research and Development, Amboise Cedex, France (J.S., L.T.); and Pfizer Global Research and Development, Chesterfield, Missouri (N.S.)

F.M. Veronese (Ed) 'Series-**Milestones in Drug Therapy: PEGylated Protein Drugs: Basic Science and Clinical Applications,** Birkhauser Verlag (2009)

R Webster, V elliott, B K Park D Walker
PEG and PEG conjugate toxicity:towards an understanding of toxicity of PEG and its relevance to Pegylated biologicals *... discussion on human studies and methods for measuring pk/ metabolism*

JK Amstrong
The occurrence, induction, specificity and potential effect of antibodies against PEG
..... discussion of human studies ..... anti-PEG IgM and IgG induction and pre-existing anti-PEG antibodies

T X Viegas and FM Veronese
Regulatory strategy and approval processes considered for PEG-drug Conjugates and other nanomedicines *..... discussion on current status and emerging similars*

Biodegradable polymers preferable especially for chronic administration

Already in Clinical Development

poly glutamic acid

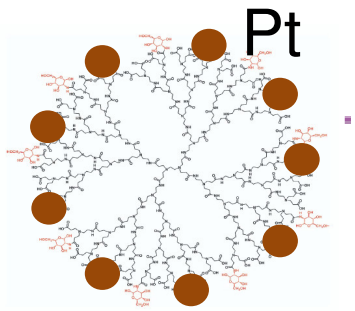
polysialic acid

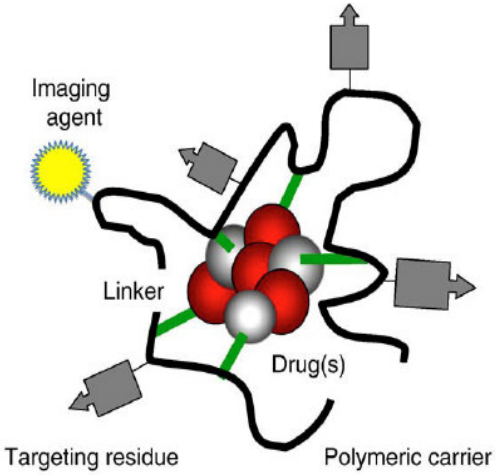
Others

dextrin

polyoxazolines

Polymer-Drug Conjugates – Main Objec

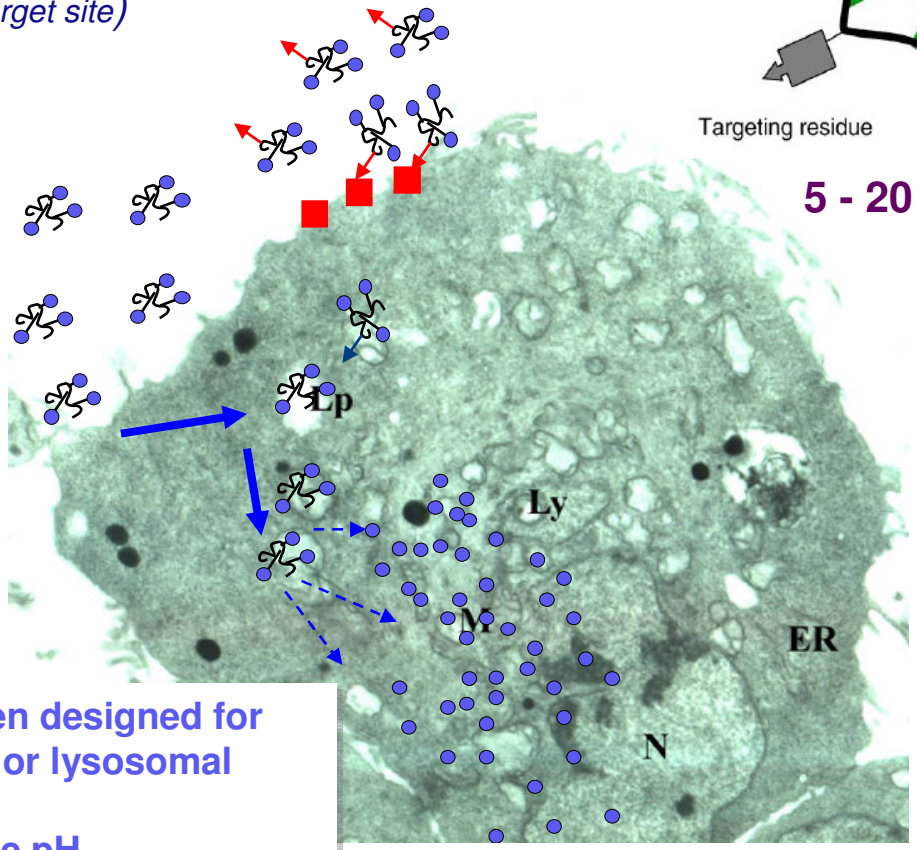




- Increasing drug solubility
- Enhancing disease specific targeting
  (with subsequent controlled release at the target site)
- Reducing drug toxicity

5 - 20 nm size range

- Promoting transport across biological barriers
- Optimising access to target Intracellular compartments



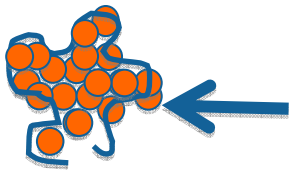
Linkers often designed for endosomal or lysosomal release

- acidic pH
- * cathepsin B

Polymer-Drug Conjugates – Anticancer Agents

XYOTAX®
OPAXIO™

Polyglutamic acid-paclitaxel

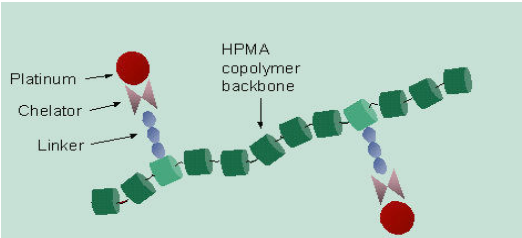


cathepsin B

PHASE II/III Programme

- Chemotherapy-naive advanced non-small cell lung cancer (NSCLC) in women with estradiol greater than 25 pg/mL
- Advanced ovarian cancer
- Oesophageal cancer + Radiation

http://www.celltherapeutics.com



Prolindac®

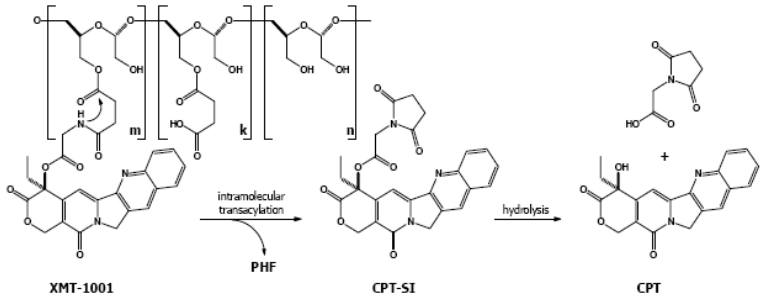
PHASE II

http://www.accesspharma.com/

HPMA copolymer-DACH platinate

- Ovarian cancer (montherapy and in combination)

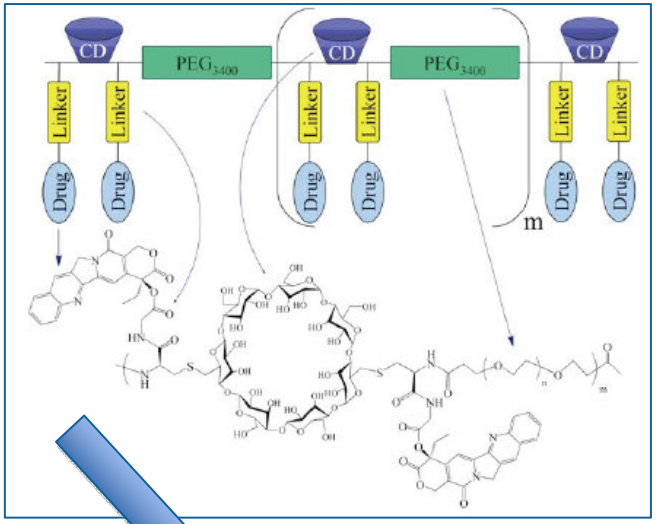
http://www.mersana.com



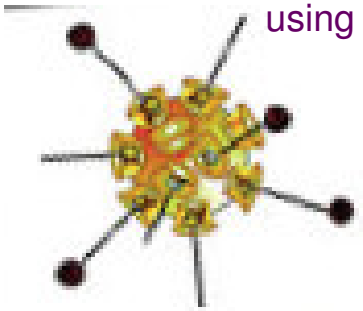
PHASE I

Biodegradable polymer-CPT conjugate

Polymer-Conjugates ..... self assembled into nanosized particles



potential for targeting
using transferrin



self-assembled into
nano-sized particles

http://www.calandopharma.com/

PHASE I

CALAA-01
polymer-cyclodextrin-siRNA

http://ceruleanrx.com

PHASE I

IT-101
polymer-cyclodextrin-camptothecin

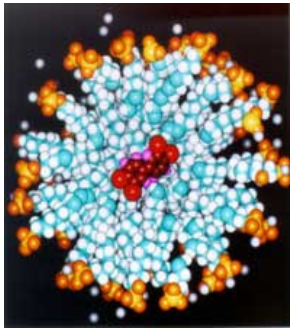
Polymer-Conjugates ..... self assembled into block copolymer micelles

PHASE II

SP1049C

Supratek Pharma Inc.

FDA has granted orphan drug designation to SP1049C for the treatment of gastric cancer.



Pluronic micelles - Doxoruicin

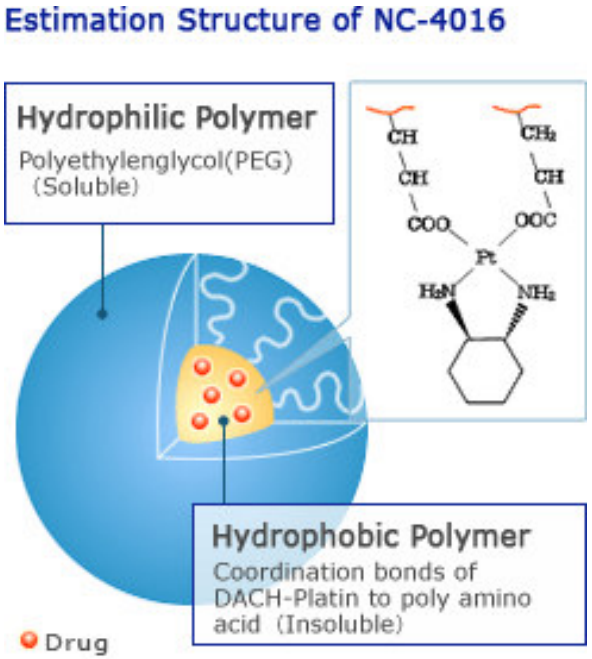
PHASE I

NanoCarrier®
Considering the Future of Drugs

NC 6004 – Nanoplatin

NK 105 – Paclitaxel

NC-4016 - Oxaliplatin



The Regulatory Process

Agencies make an integrated assessment

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

The risk-benefit balance

'quality'

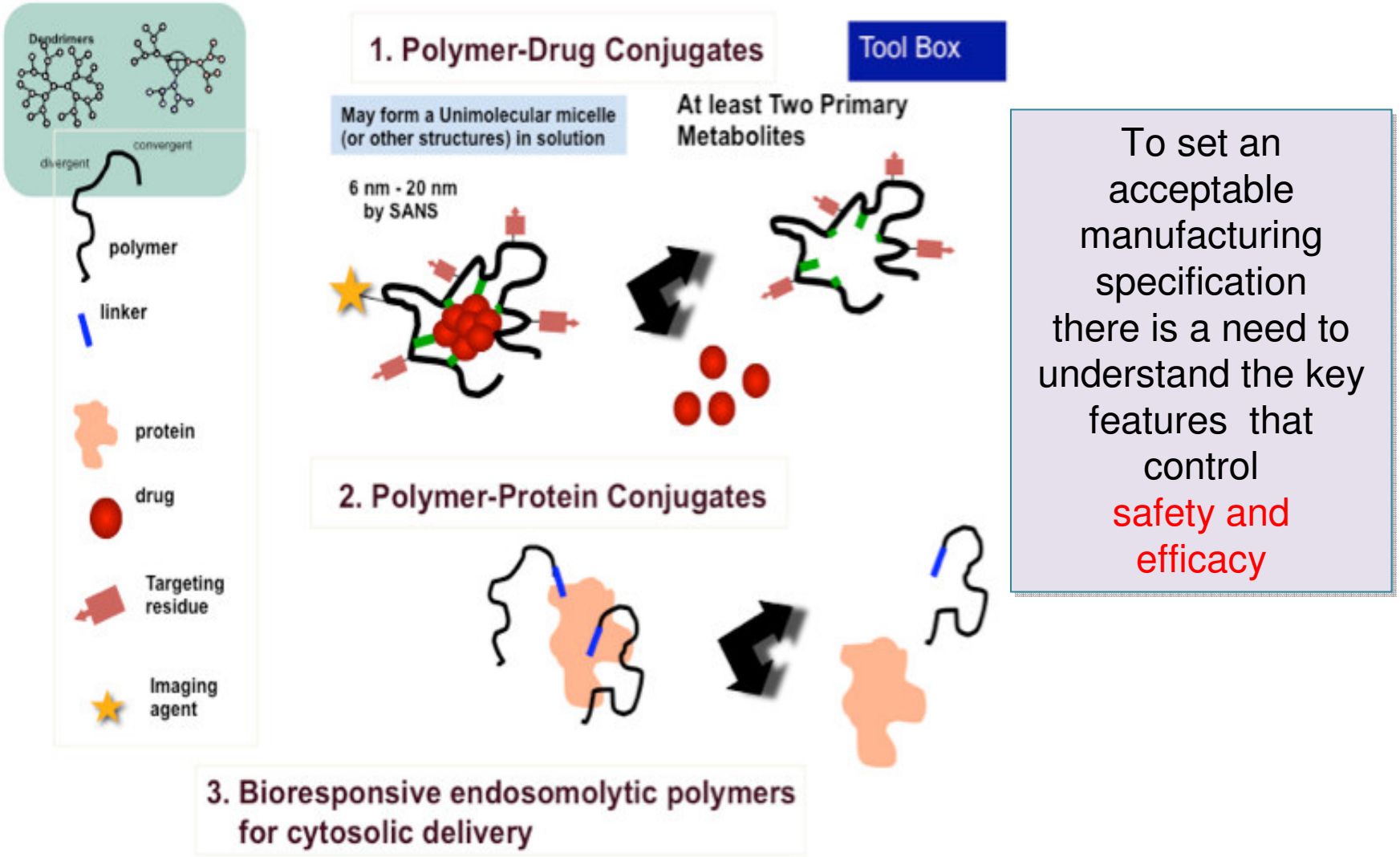
Carry out rigorous post-market surveillance('pharmacovigilance')

safety **efficacy**

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.

Polymer-Drug Conjugates – Multicomponent Complex Systems

Need to understand the reality of the cartoons – complexity/heterogeneity



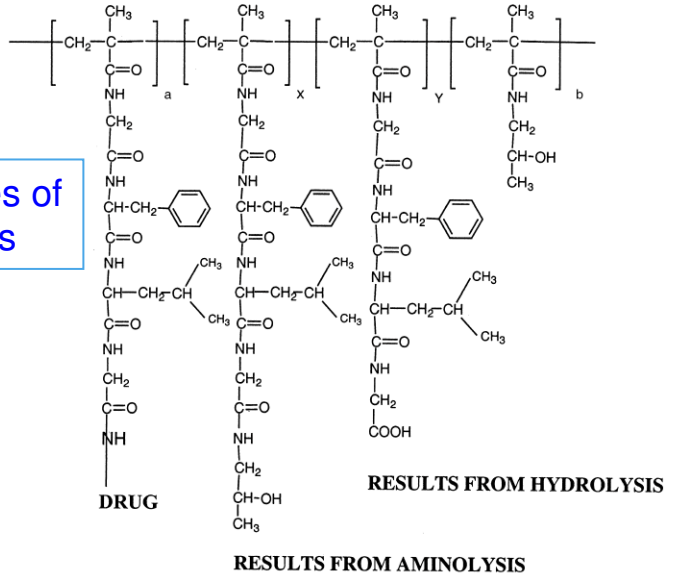
To set an acceptable manufacturing specification there is a need to understand the key features that control safety and efficacy

Manufacture, characterisation and control of 'Quality'

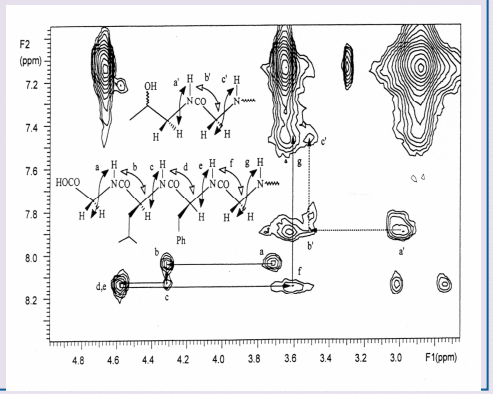
Challenges for reproducible manufacture on large scale

Validated techniques for determination of
- **product identity**
- **impurities**
- **strength**
- **Mw and polydispersity**

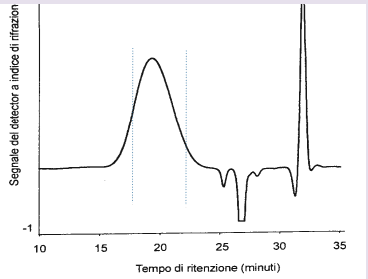
New types of impurities



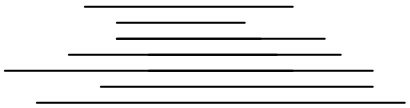
2D NOESY/TOCSY NMR



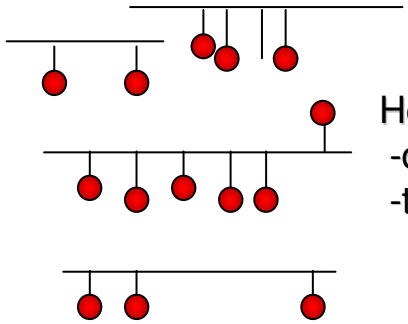
GPC + Universal Calibration



Heterogeneity
-need for specification
relevant to Safety/Efficacy



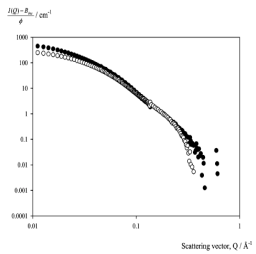
Polydispersity

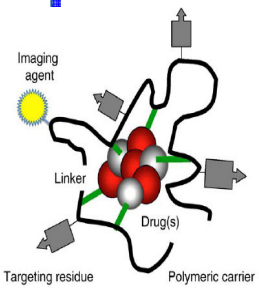


Heterogeneity
-drug
-targeting residues

HPLC
– free and bound drug
- free and bound targeting residue

Small Angle Neutron Scattering solution conformation





Pharmaceutical Development

Injectable drugs

- methods of sterilisation
- lyophilised formulations for reconstitution with water
- as ready to use solutions for injection

Perception of doses/labelling should make consideration of total formulation composition

- Important for Regulatory and Clinical Colleagues to Understand

Cavallo, Adami M, Magrini R, et al. PK1/PK2 lyophilised formulations. HPMA doxorubicin conjugates with potentially improved antitumour activity. *Proceedings of the 1st World Meeting APGI/APV.* Budapest; 1995:843.

HPMA Copolymer Dox lyophilised formulation contain

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

• Solutions of 30 - 50 mg/mL conjugate filter sterilised freeze dried

• Lyophilised cake reconstituted with water for injection or NaCl dissolution occurred in ~ 2 min.

In the case of polymer-drug conjugates, **the integral solubilising and bulking agent properties** of the polymeric carrier often replace the need for some of these ingredients.

Preclinical Safety

Many of materials are not suitable for proposed use

Understanding cellular fate and toxicity of new materials *in vitro*

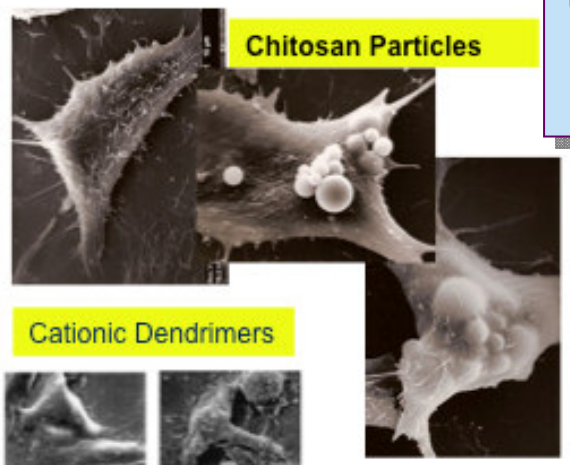
Understanding biodistribution, long term fate and immuno-toxicity *in vivo*

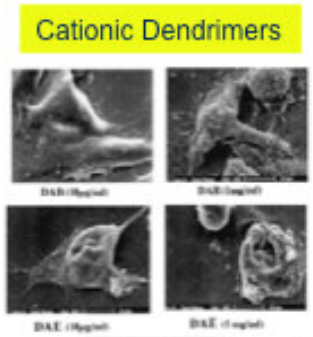
Considerations

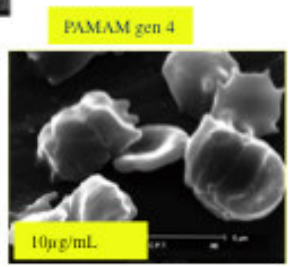
– route of admin
- dose
- frequency of dosing
- (payload)
-- clinical setting

GLP

Preclinical Toxicological testing of candidate polymer therapeutics Tailored to proposed use





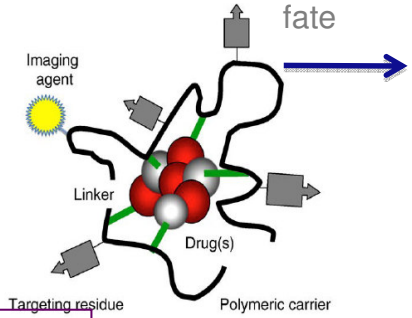


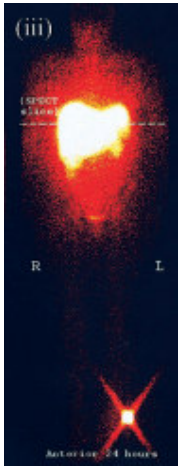
Gaspar & Duncan Adv. Drug Del. Rev. (2009)

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 Rihova, B et al., *Biomaterials, 10 335-342, (1989)*

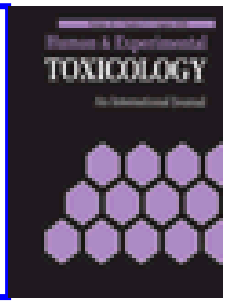
Immunogenicity of protein-N-(2-hydroxypropyl)methacrylamide copolymer conjugates measured in A/J and B10 mice. Flanagan, P.A.et al. J. Bioact. Compat. Polymers 5, 151-166 (1990)

Blanka Rihova Biocompatibility of biomaterials: hemocompatibility, immunocompatiblity and biocompatibility of solid polymeric materials and soluble targetable polymeric carriers *Adv. Drug Del. Rev., 21, (1996) 157-176*





Preclinical toxicology of a novel polymeric antitumour agent: HPMA copolymer doxorubicin (PK1) R Duncan, J K Coatsworth, and S Burtles *Human and Experimental Toxicology, Feb 1998; vol. 17: pp. 93 - 104*



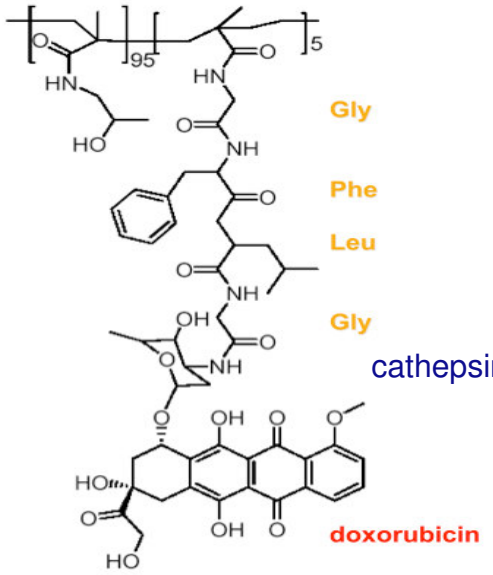
Clinical Development

Duncan, R. Development of HPMA Copolymer Anticancer Conjugates: Clinical Experience And Lessons Learnt (2009. Adv. Drug Del. Rev.61, 1131-1148.

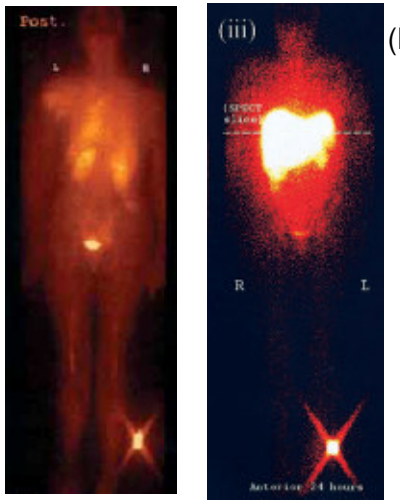
Duncan R. and Vicent, M. J. (2010) Do HPMA copolymer conjugates have a future as clinically useful nanomedicines? A critical overview of current status and future opportunities. Adv. Drug Del. Rev., 62, 262-272.

FCE28068/FCE28069 (+gal)

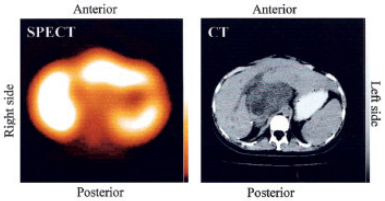
HPMA Copolymer Anticancer Conjugates and Imaging agents **(Theranostics)**



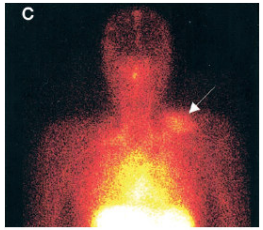
New, non-degradable polymeric carrier – never before used in man



liver hepatocytes
15-20% dose
(hepatoma 12-50 fold targeting)



Seymour et al. *J. Clin. Oncol. 20, 2002,1668-1676*



1140 *R. Duncan / Advanced Drug Delivery Reviews 61 (2009) 1131–1148*

Table 1
Characteristics of the HPMA copolymer conjugates that have entered early clinical trials as anticancer agents.

Code	Composition	Status	~Mw (g/mol)	~Total drug Content (wt.%)	Free Drug (% total)	Principal mechanism of drug release
FCE 28068	HPMA copolymer–GFLG–doxorubicin	Phase II	30,000	8.5	<2	Enzymatic (cathepsin B)
FCE 28069	HPMA copolymer–GFLG–doxorubicin–galactosamine	Phase I/II	25,000	7	<2	Enzymatic (cathepsin B)
PNU166945	HPMA copolymer–paclitaxel	Phase I[a]	NS[b]	5	NS[b]	Hydrolysis
MAG-CPT, PCNU166148	HPMA copolymer–camptothecin	Phase I[a]	18,000	10	<0.01 (wt.%)	Hydrolysis
AP5280	HPMA copolymer–carboplatinate analogue	Phase I/II	25,000	8.5	NS[b]	Hydrolysis
AP5346	HPMA copolymer–DACH platinate analogue	Phase II	25,000	10	NS[b]	Hydrolysis

[a] Stopped after Phase I trial.
[b] NS - not stated.

Phase I/II Clinical Trials Committee Cancer Research Campaign (CRC)

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[1]

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

Table 1 Patient population

Characteristic	No. of patients
Total no. of patients	36
No. of males/no. of females	20/16
Mean age, yr (range)	58.3 (34–72)
Performance status	
0–1	31
2	5
Previous medical treatment for malignancy	
Chemotherapy and radiotherapy	12
Chemotherapy[a]	28
Radiotherapy	14
Hormones/immunomodulators	8
No prior therapy	6
Tumor type	
Colorectal	8
Adenocarcinoma, unknown primary[b]	5
Breast	3
Ovary	3
Biliary tract	3
Pancreas	3
Urinary tract	3
Head/neck	3
NSCLC	2
Mesothelioma	2
Stomach	1

[a] Six were treated previously with anthracyclines: 4 with doxorubicin (200, 120, 80, and 50 mg/m^2 cumulative doses) and 2 with epirubicin (160, 480 mg/m^2 cumulative doses).

[b] One patient had coexisting soft tissue sarcoma of the lower limb, treated with radiotherapy.

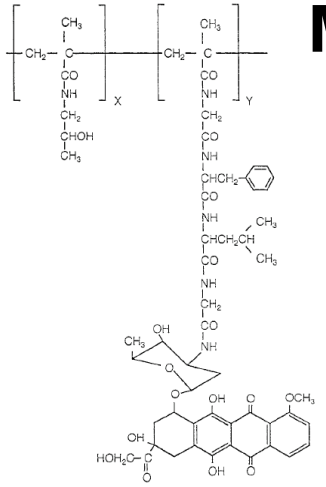


Fig. 1 Structure of PK1 (HPMA copolymer doxorubicin). The molecular weight of the compound is 28,000 [doxorubicin, 8.5% (w/w)].

once every 3 weeks

MTD = 320 mg/m^2 Dox equiv

~ 3 g/m^2 conjugate

Q administer by fixed conc or fixed bolus/infusion time ?

Table 2 Dose escalation scheme

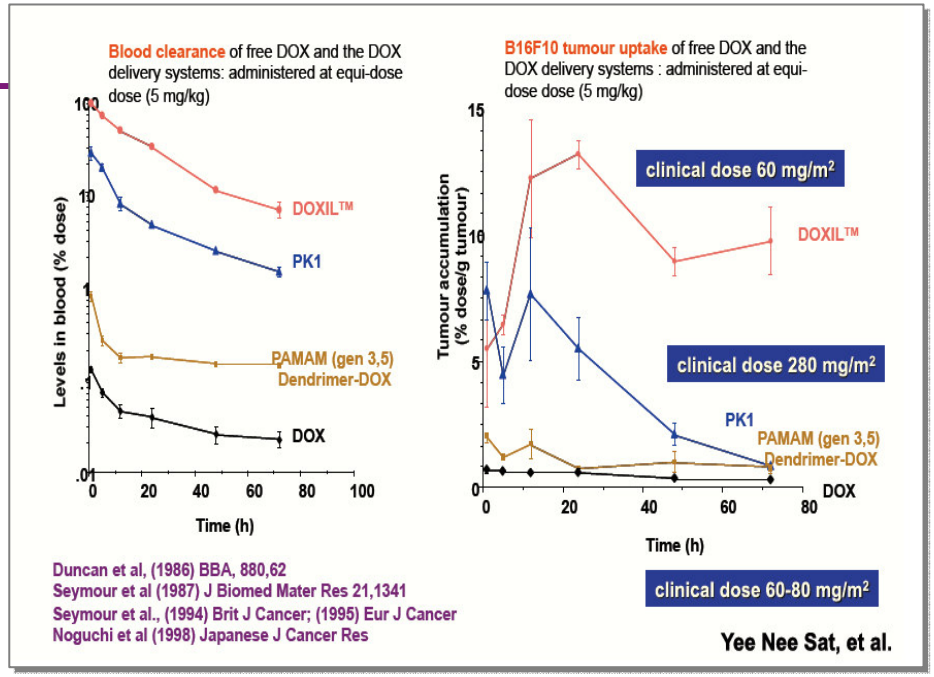
Dose (mg/m^2 doxorubicin equivalent)	No. of patients	No. of courses/ patient	Median cumulative dose, mg/m^2 (range)
20	3	2, 1, 3	40 (20–60)
40	3	2, 1, 1	40 (40–80)
80	3	6, 2, 4	320 (160–480)
120	3	7, 4, 7	840 (480–840)
180	6	1, 6, 1, 7, 1, 1	180 (180–1260)
240	6	1, 4, 2, 4, 2, 4[a]	480 (240–960)
280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

Challenges for Clinical Trial Design

Knowing Biodistribution % Dose

Optimising dosing schedules v comparators

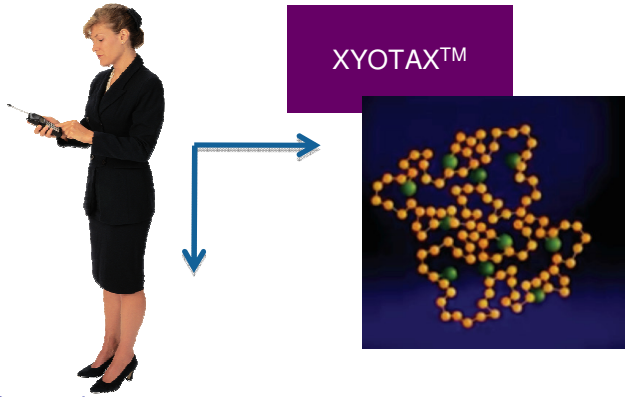


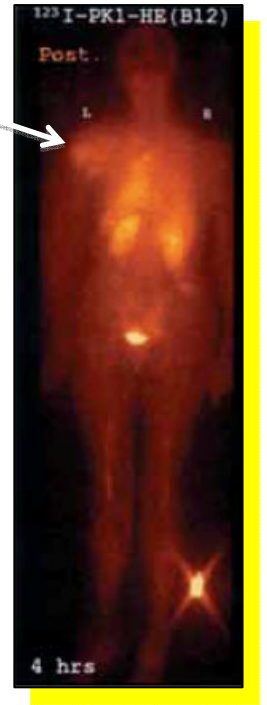
Patient Selection

– Most Relevant Biomarkers for efficacy/toxicity

according to levels of activating enzymes e.g. cathepsin B

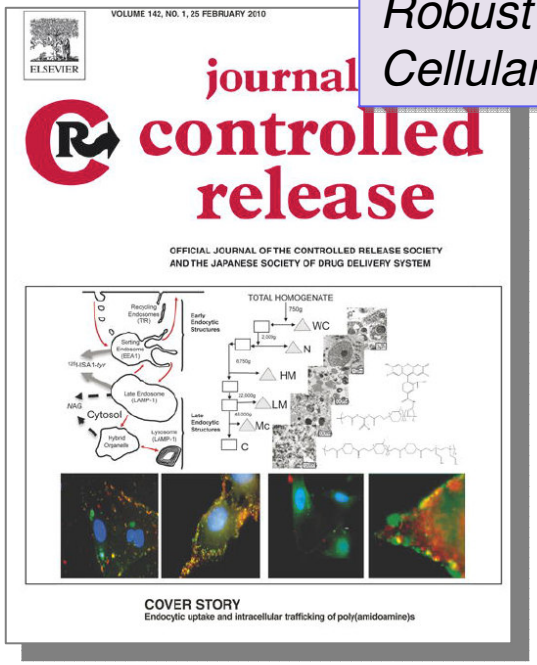
according to tumour vascular permeability

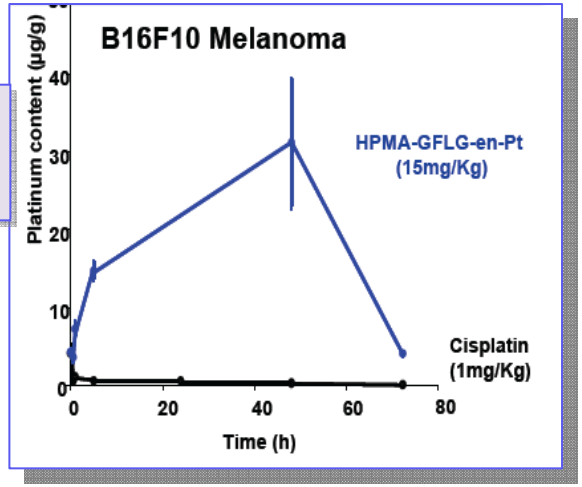




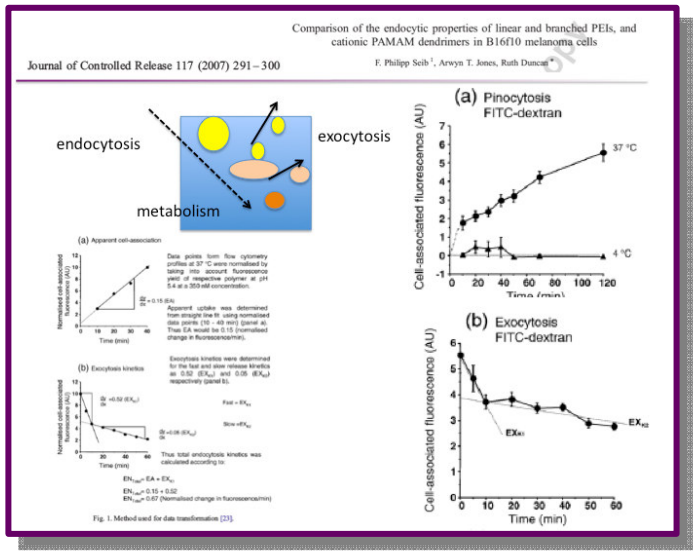
Preclinical Pharmacokinetics and Pharmacology

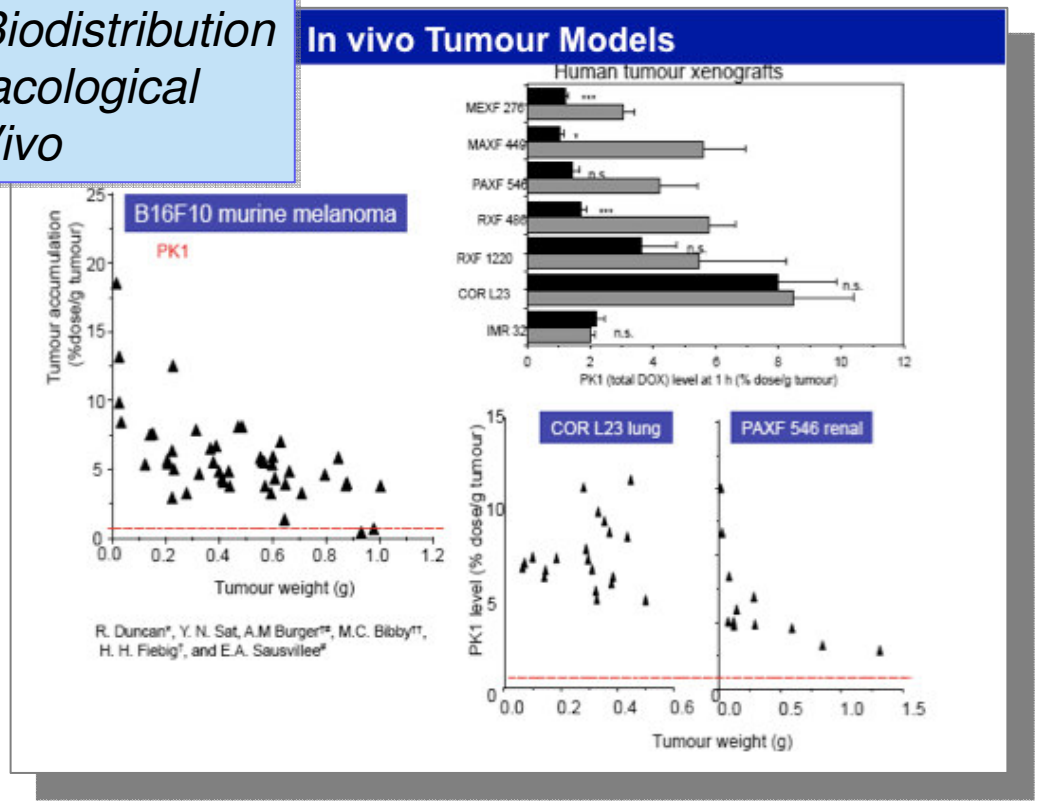
*Robust Techniques for **Quantitation of** Cellular Uptake and Drug Release In Vitro*





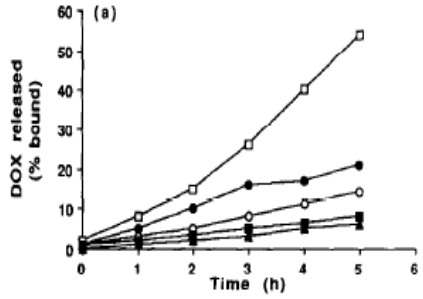
*Models for **Quantitation** of PK and Biodistribution and Pharmacological Activity In Vivo*

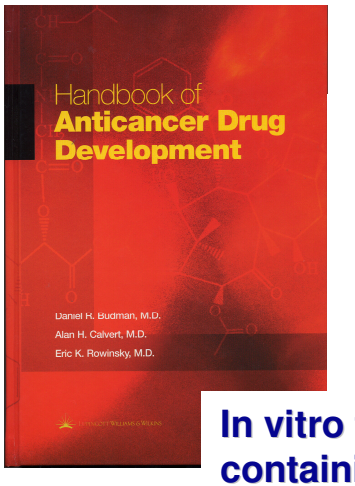


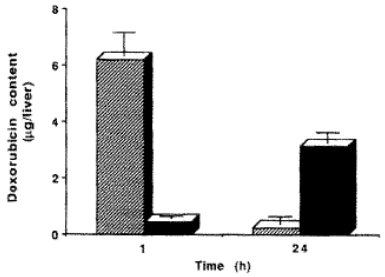


To define Efficacy must have validated models

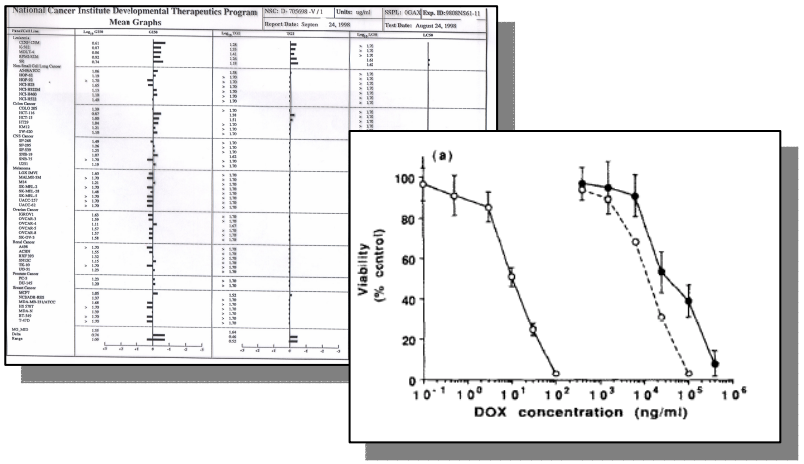
In vitro and in vivo drug release rates very important





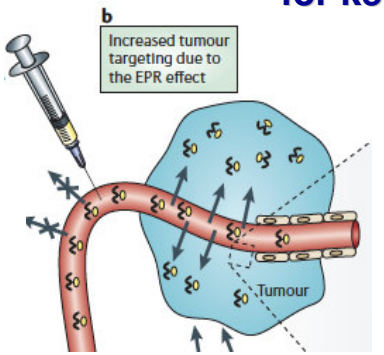


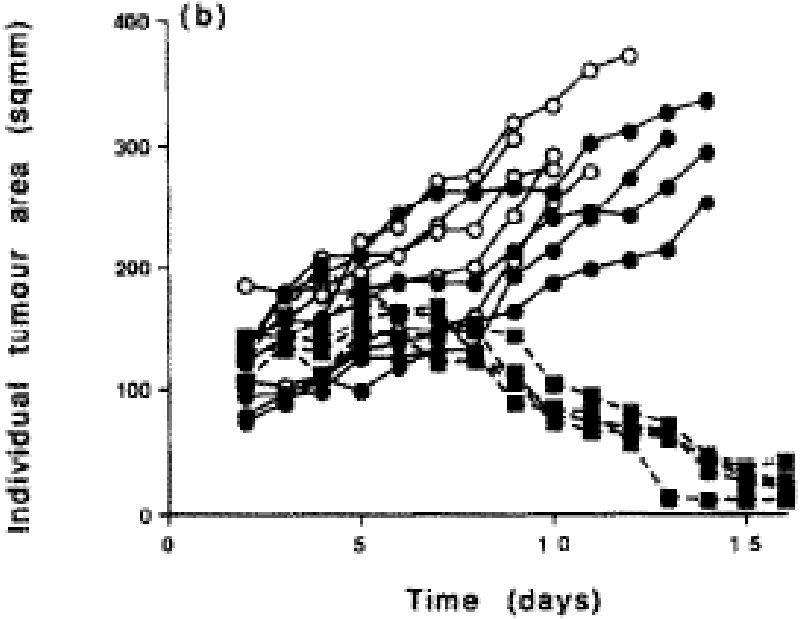
In vitro testing of systems containing potent anticancer cytotoxic drugs not helpful



In vivo models must be calibrated for key parameters e.g.

- EPR
- activating enzymes
- endocytosis/trafficking
- difficult to compare DDS and parent drug to different PK
- dose schedule that might mimic clinical situation





Pharmacokinetically-Guided Design - important to review when setting clinical protocols

- pharmacokinetics and biodistribution
- stability of linkers – in transit & at target
- potential to overcome traditional mechanisms of resistance but can give rise to new mechanisms of resistance

Nanomedicine Patient & Disease-Relevant Biomarkers

at the whole organism level

- poor EPR – clinical importance in all tumours ??
- EPR in other sites –potential for side effects

at the cellular level

- shut down of endocytosis
- wrong intracellular trafficking
- variations in activating enzyme level, pH etc

Conclusions and Future Opportunities

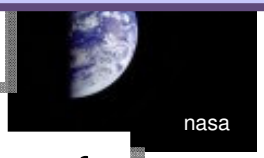
There are a growing number of polymer therapeutics **that are products** and also Entering clinical development as both novel treatments and imaging agents

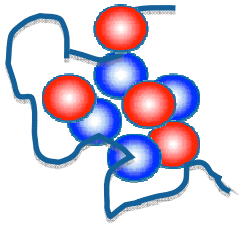
- *this is a global effort*

..... emergence as similars

.....in preclinical development

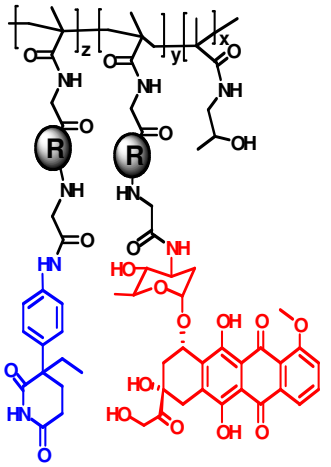
- polymer therapeutics against new molecular targets
- combination therapies
- new polymers/dendritic architectures
- theranonstics





- They are used as Nano-sized Medicines in the form of
  - individual agents or conjugates
  - as components of complex, self assembling nanoparticles and micelles
  - polymer technology is also used as a 'stealth coating'

HPMA-AGM-DOX



- There is a need for continued development of
  - validated analytical techniques for characterisation of these complex nano-sized medicines
  - validated methods for establishing preclinical safety
  - identification of the most relevant biomarkers for patient selection and optimised clinical trial design

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

For All

• Polymer therapeutics are complex multi-component, nano-sized constructs containing covalent linkages **in Routine Clinical Use since 1990** ..... growing number products in clinical development for different diseases

Reflections

avoid calling all a "nanoparticle" "nano-sized" or "nano object"

For Scientists

• Need for robust techniques for validated characterisation, biological evaluation and preclinical development. Need to justify the product specification (Quality) and safety evaluation scientifically, on **a case by case basis. Distinguish Research from Development**

Link emerging technologies to historical database

For Regulators

- Regulatory Agencies need appropriate technical expertise in-house, don't believe all you read
- Should continue to review all nano-sized medicines **(1-1000 nm)** on a **case by case basis**

• ***Polymers (linking chemistry)*** are increasingly used in innovative (nano) medicines.

• Need to ensure that **"All Committees"** contain experts with relevant **polymer chemistry expertise and also the cellular and whole body PK/biodistribution expertise**

• Need for awareness of emerging, new, nano-sized medicines, their drug combinations and 'nano' medicine/device/imaging combinations **AVOID GAPS**

• **Follow-on products (similars) are already emerging**