Self-assembling Nanomedicine for Oncology

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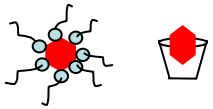
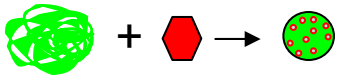
Injectable drug delivery for oncology

First generation – solution (classical injectable)
(for water-insoluble drug, forcible solubilization into water using solubilizer, eg. surfactants, cyclodextrins)



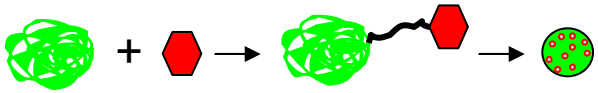
If drug is not soluble in any injectable solvent/solubilizer

Second generation – Drug physically encapsulated into nanoparticle carrier



If drug is released too rapidly after injection

Third generation – Drug chemically linked to nanoparticle carrier (Prodrug)



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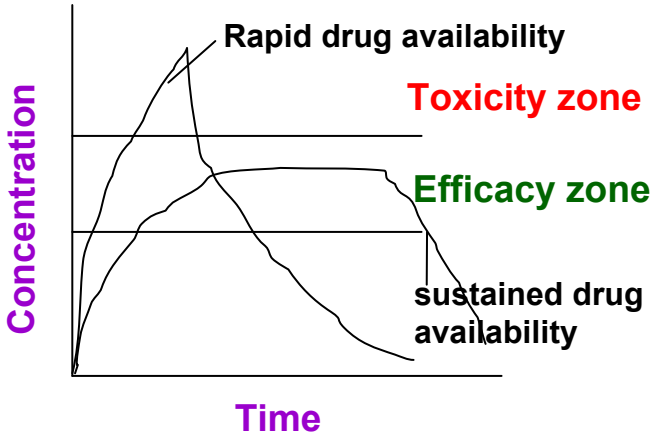
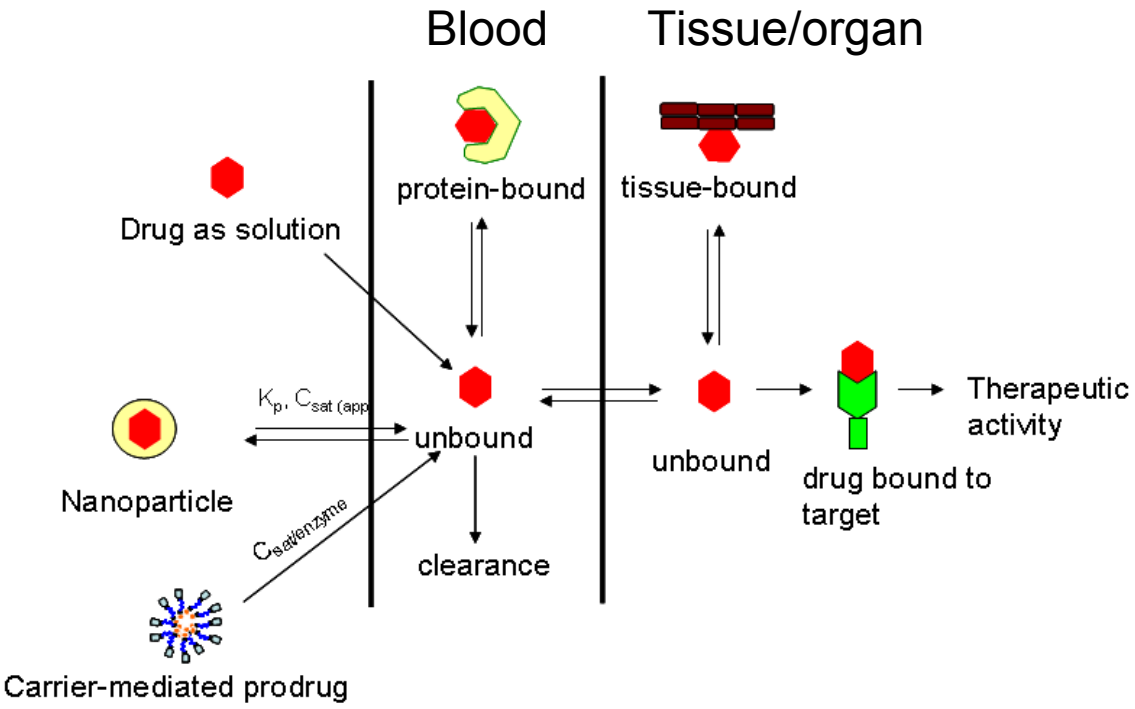
Factors influencing drug availability





How to modulate unbound drug concentration:

a) Minimizing the nanomedicine capture by RES (PEGylation),

b) sustained drug release from carrier (Prodrug approach)

Longer the blood residence time of drug, slower is the clearance, sustained/optimum unbound drug conc, and better is the therapeutic activity and safety

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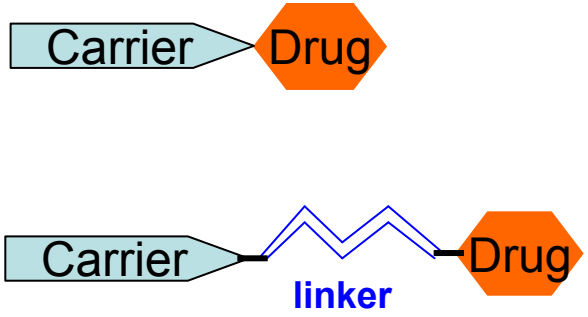
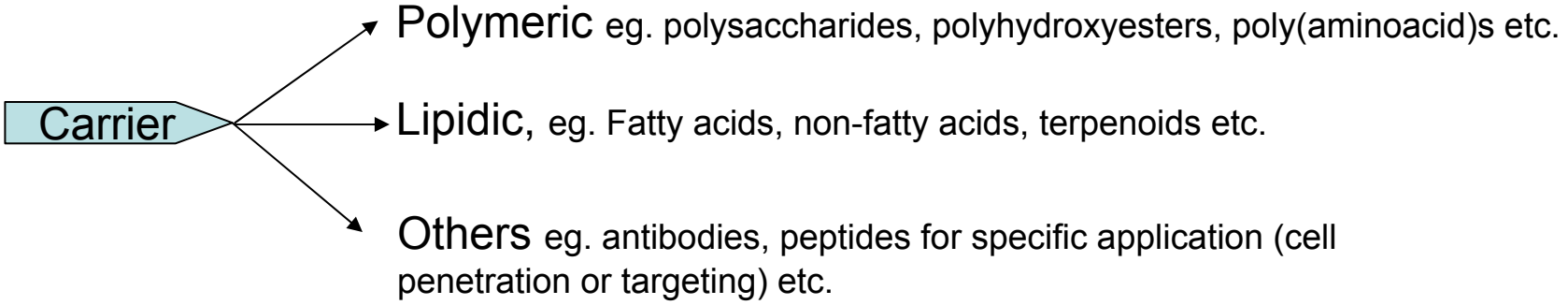
Carrier-mediated prodrugs





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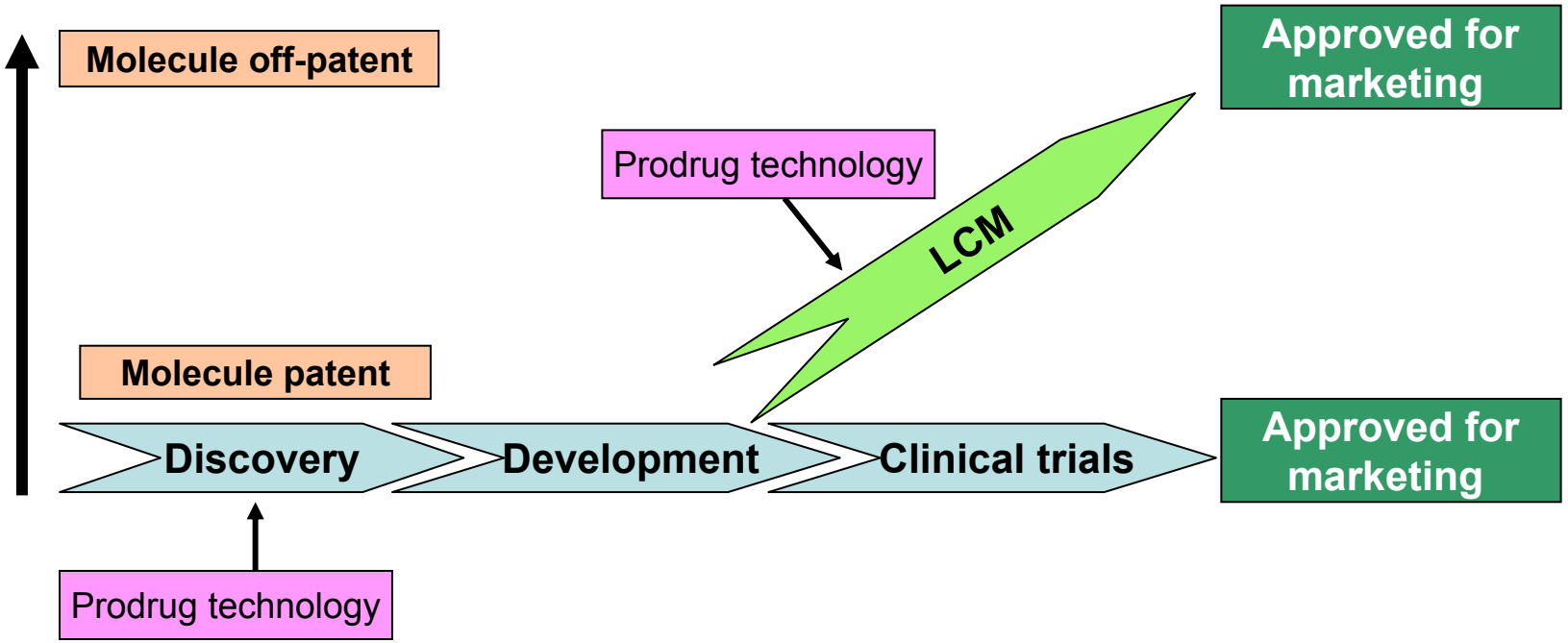
Carrier-mediated prodrugs

- Advantages:
  - Sustained drug release, hence improved pharmacokinetic profile
  - Protect drugs from rapid metabolic inactivation
  - Reduced non-specific biodistribution, selective activation inside the tumor
  - Improved transport to the tumor site
  - Improved efficacy and safety

- Limitations:
  - Solubility-related issues, necessitating their encapsulation into delivery carriers
  - New Chemical Entity – needs full development program

Carrier-mediated prodrug technology in pharmaceutical development



LCM – Life Cycle Management

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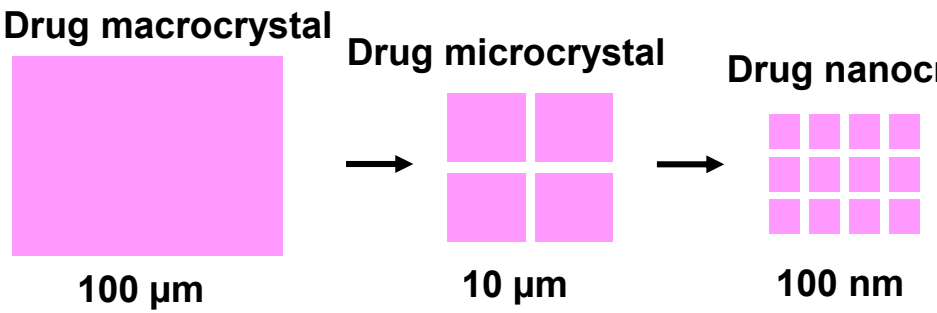
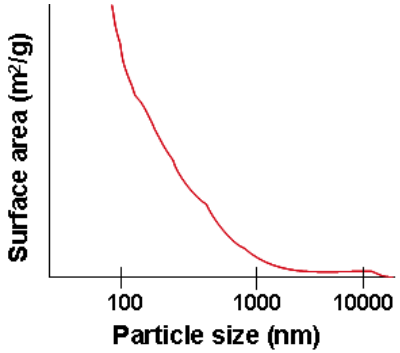
Factors influencing engineering of prodrug nanomedicine

- Chemical purity
- Physical nature (crystalline/amorphous)
- Solubility in organic solvents
- Stability in organic solvents
- Stability at process conditions (light/temperature/sonication etc.)

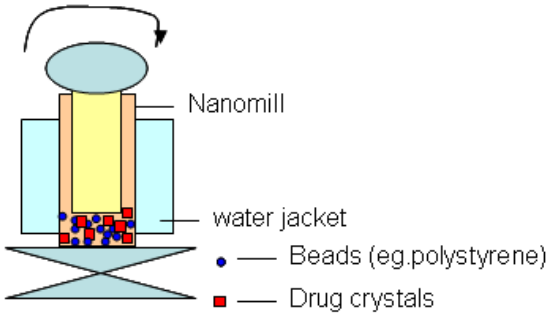
Manufacture of prodrug nanomedicine

1. Top down technique – size reduction of drug crystals





- Limitations:
  - Non-crystalline prodrugs cannot be milled (eg. some lipidic/polymeric prodrugs
  - Issues with temp-sensitive prodrugs



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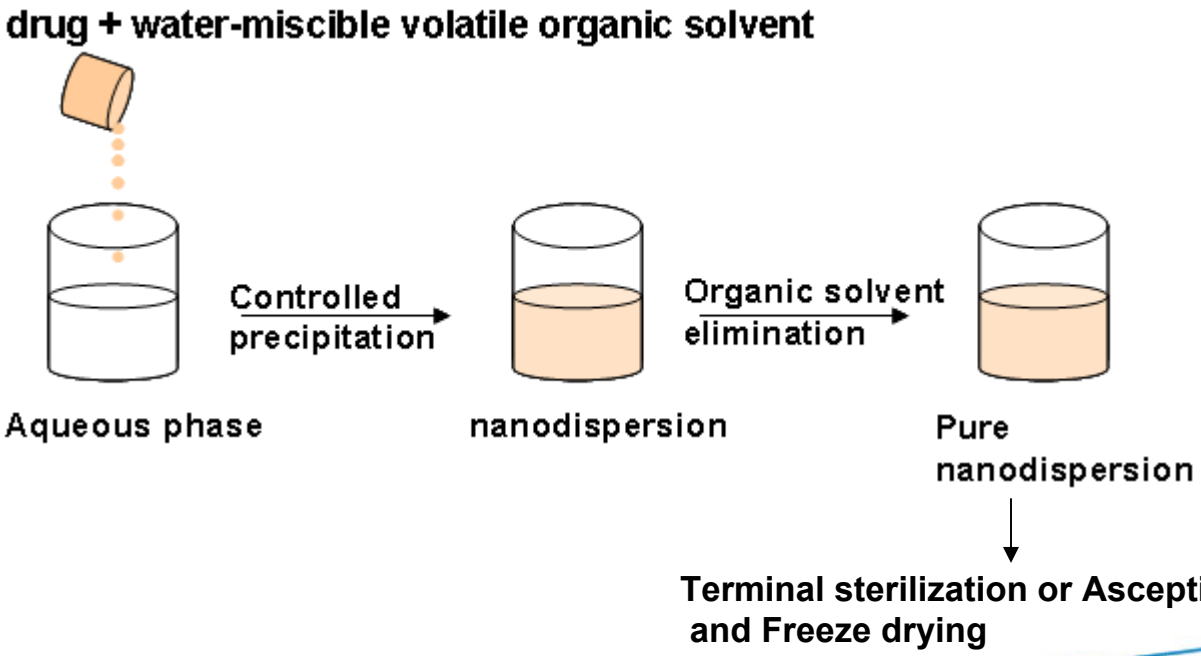
Manufacture of prodrug nanomedicine

2. Bottom-up technique(s) – controlled precipitation in aqueous medium

a) Nanoprecipitation



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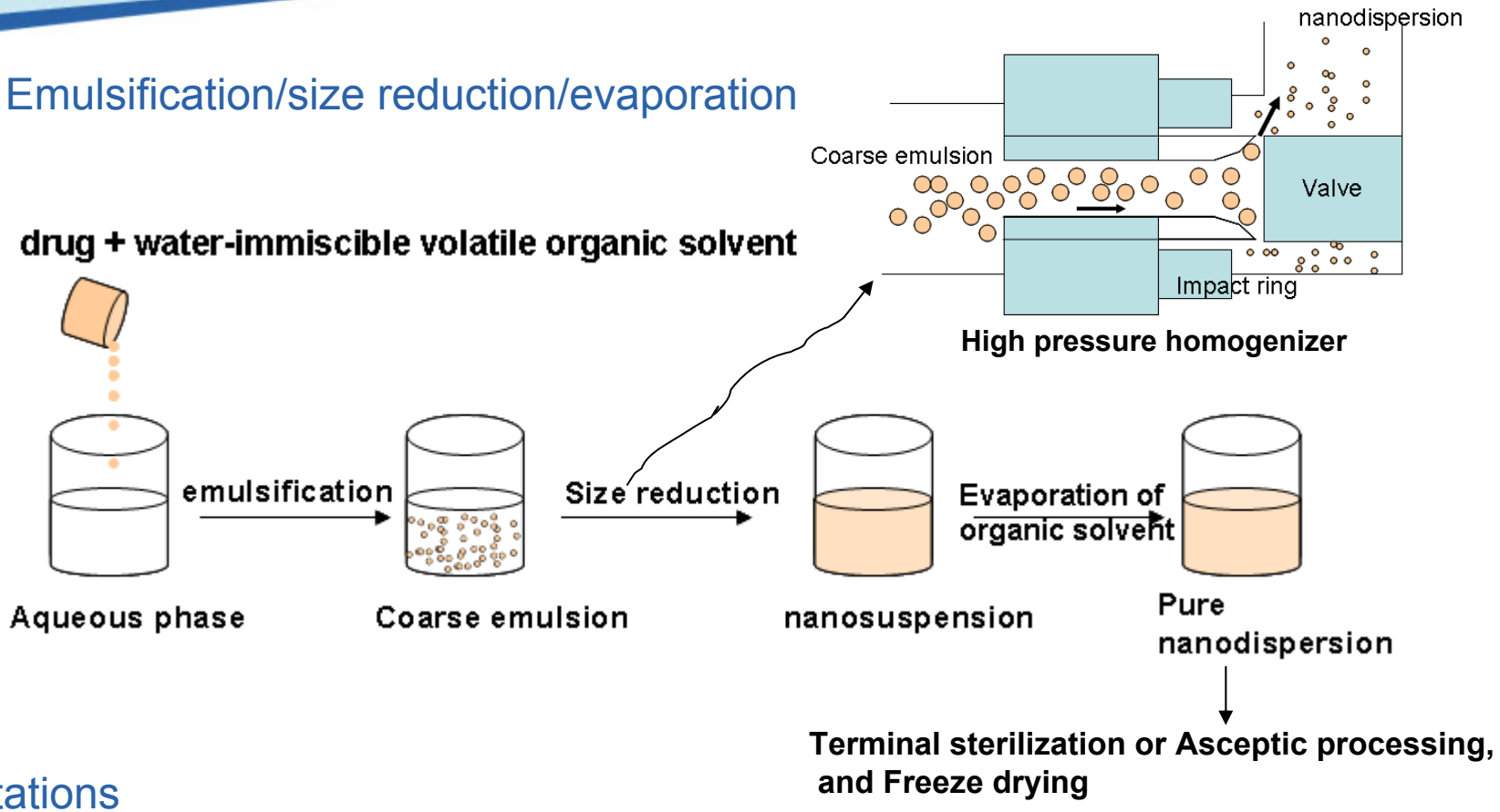
Manufacture of prodrug nanoparticles

b) Emulsification/size reduction/evaporation



Limitations

- Prodrugs insoluble in organic solvents could not be processed
- Safety issues associated with the use of organic solvents

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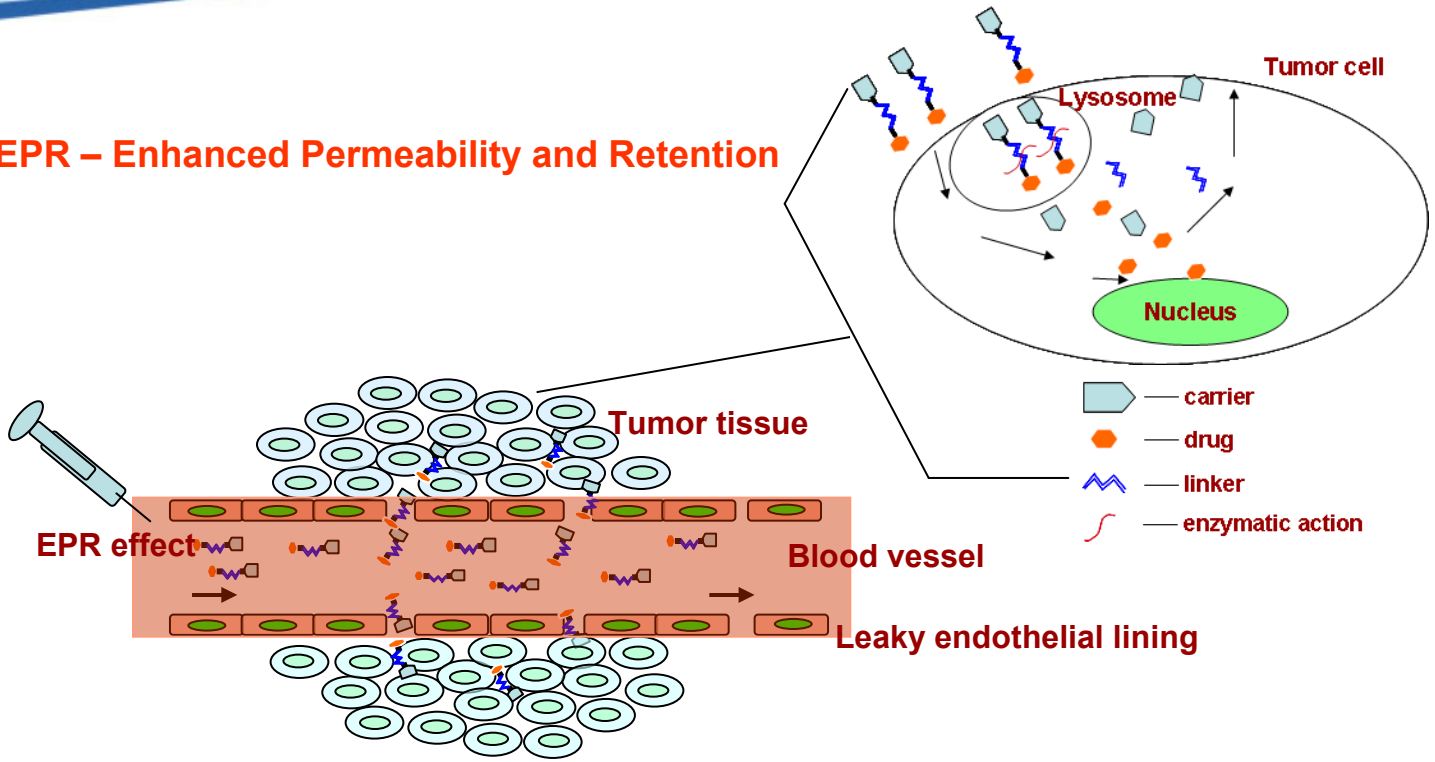
Biofate of prodrug nanomedicine

EPR – Enhanced Permeability and Retention



The leaky endothelial vasculature in tumor affected areas facilitate the infiltration of prodrug nanoparticles into tumors. This phenomenon is called EPR effect

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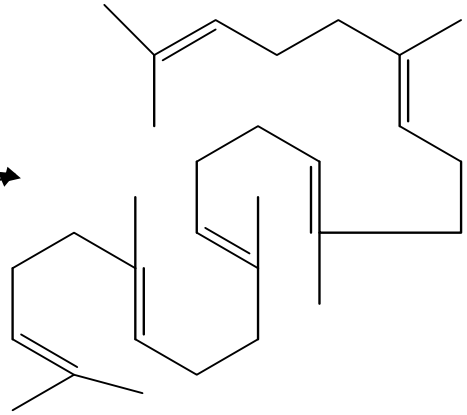
Squalenoyl prodrug nanomedicines -a lipidic prodrug approach

Shark

Olives



$C_{30}H_{50}$

Squalene - a biological lipid

(precursor of CHOL biosynthesis)

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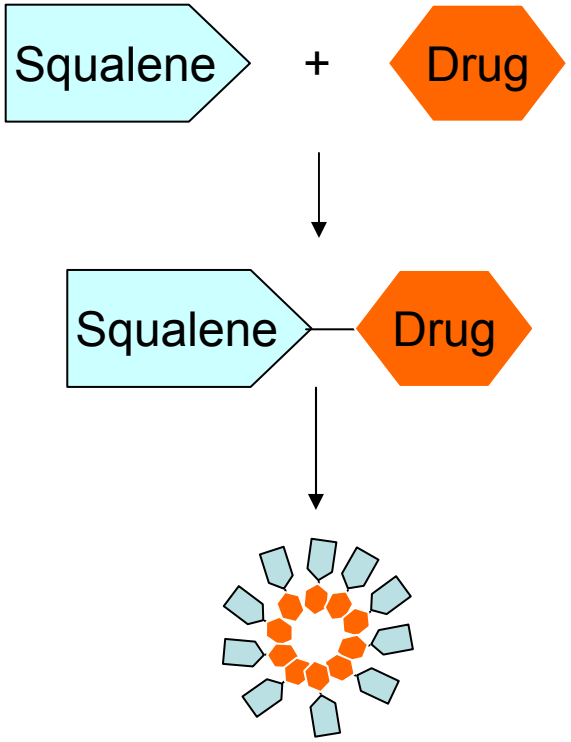
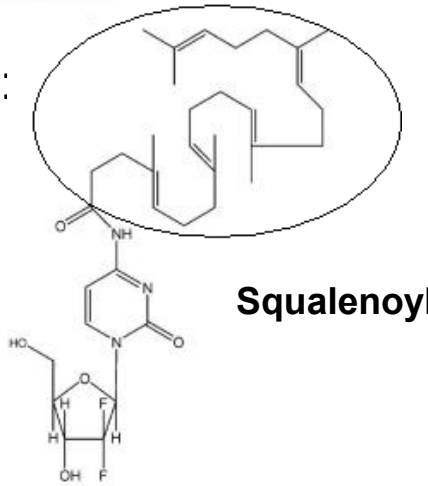
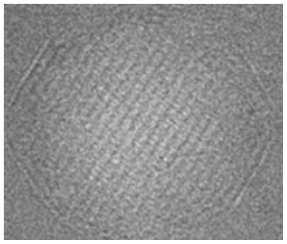
Squalenoyl prodrug nanomedicines



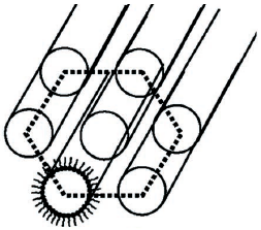
Example:

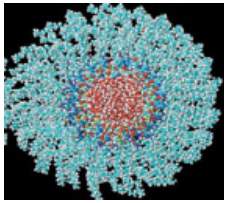


Squalenoyl gemcitabine



CryoTEM (130nm)





Molecular modeling

Couvreur et al. NanoLett 2006, Small 2008

- **Squalenoyl prodrugs assemble into nanoparticles in water**
- **Enhanced drug loading could be achieved with squalenoyl prodrug approach (squalene being a small molecule)**

Couvreur et al. Nano Lett 2006, Small 2008, Dosio et al. Bioconj Chem 2010

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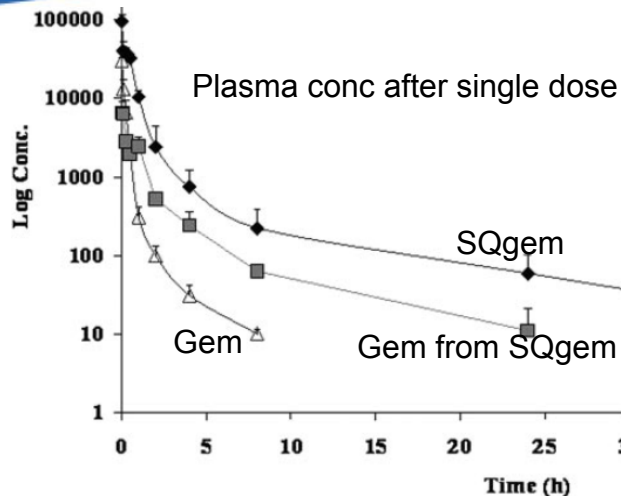
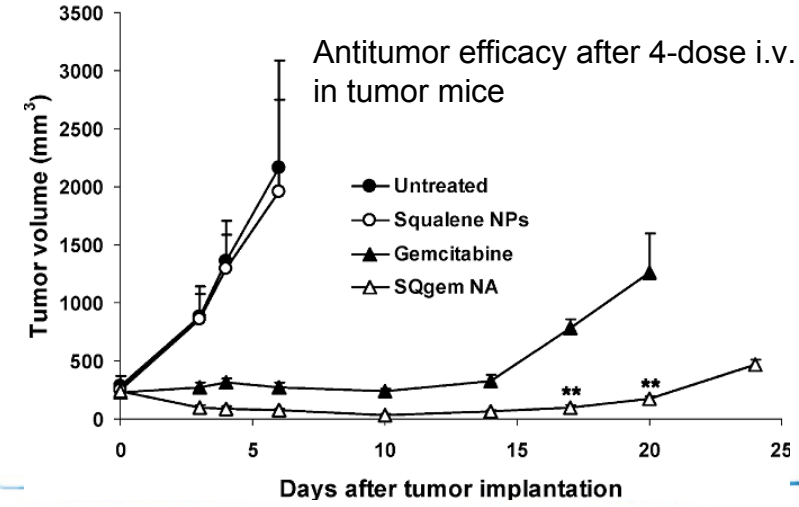
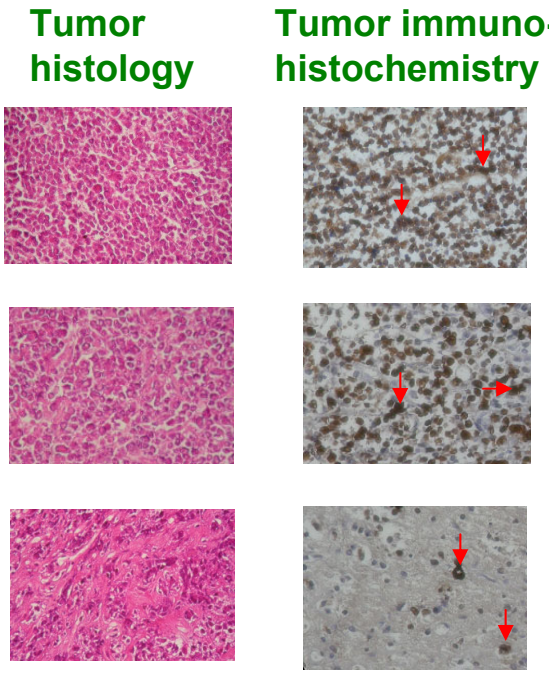
Pharmacokinetics & anticancer activity of Squalenoyl gemcitabine







Reddy et al. J Cont Rel 2007, J PET 2008, Drug Met Disp 2008, Mol Pharm 2009

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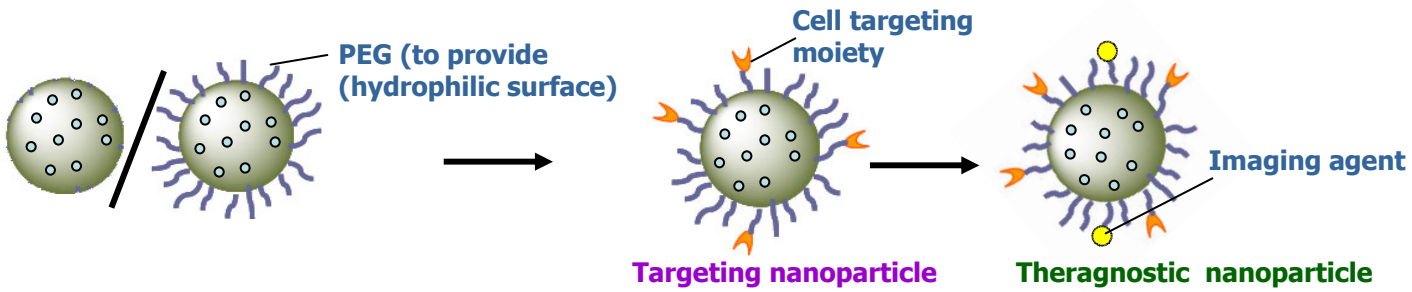
Future of prodrug nanomedicines



Toward personalized medicine

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Conclusion & prospective

- self-assembling prodrugs could be an effective tool to deliver potent but water-insoluble new molecules at discovery stage or for LCM of commercialized drugs to offer improved biopharmaceutical profile
- this approach offers opportunity for developing efficient and safer medicines
- the clinical reach of various oncology prodrugs like Opaxio, Taxoprexin, Elacytarabine, AP5346 (HPMA copolymer–DACH platinate analogue) etc. has renewed considerable interest in this area and hence more prodrugs could be expected in pipeline
- development of multifunctional self-assembling prodrug nanomedicines that possess both drug targeting and imaging /diagnostic functionalities are expected to provide opportunities for personalized therapy.

Back-up slides

Carrier-mediated anticancer prodrugs approved or in clinical development

Prodrug/conjugates	Company/name	Indication	Status
Polymeric			
PEG-asparaginase	Enzon (Oncospar)	AML	Approved in 1990
Styrene Maleic Anhydride-Neocarzinostatin (SMANCS)	Yamanouchi (Zinostatin Stimaler)	Hepatocellular carcinoma	Approved in 1990 in Japan
Poly(glutamic aicd-paclitaxel)	Cell Ther (Opaxio)	NSCLC	Filed EMEA
PEGylated-anti VEGFR2 Fab fragments as angiogenesis inhibitor	UCB Pharma (CDP 791)	NSCLC	Phase II
HPMA-DACH platinate analogue	Access Pharma (AP5346)	Solid tumours	Phase II
PEG-poly(Aspartic Acid)-Doxorubicin Micelles	NK911	Solid tumours	Phase II
HPMA copolymer–GFLG–doxorubicin	FCE 28068	Solid tumours	Phase I/II
HPMA copolymer–GFLG–doxorubicin–galactosamine	FCE 28069	Solid tumours	Phase I/II
HPMA copolymer–carboplatinate analogue	AP5280	Solid tumours	Phase I/II

Carrier-mediated anticancer prodrugs approved or in clinical development

Prodrug/conjugates	Company/name	Indication	Status
Polymer–cyclodextrin nanoparticle–camptothecin	Calando Pharma (IT-101)	Solid tumours	Phase I/II
Polymer–cyclodextrin nanoparticle-siRNA	Calando Pharmaceutical (CALAA-01)	Solid tumours	Phase I
Polyglutamic acid-Gly-Camptothecin	Cell Ther (CT-2106)	Solid tumours	Phase I (Phase II delayed)
PEG–docetaxel (intravenous)	Nektar (NKTR-105)	Solid tumours incl. hormone-refractory prostate cancer	Phase I
Lipidic			
Elaidic acid-cytarabine	Clavis pharma (Elacytarabine)	AML	Phase II-III
Elaidic acid-gemcitabine	Clavis Pharma (CP-4126)	Pancreatic cancer	Phase II
DHA-paclitaxel	Protarga (Taxoprexin)	Sloid tumors	Phase II