Carrier mediated targeted delivery of drugs to endothelial cells in disease.

Jan A.A.M. Kamps, PhD

University Medical Center Groningen, Dept. Pathol. & Medical Biology, Medical Biology section

Laboratory for Endothelial Biomedicine & Vascular Drug Targeting research

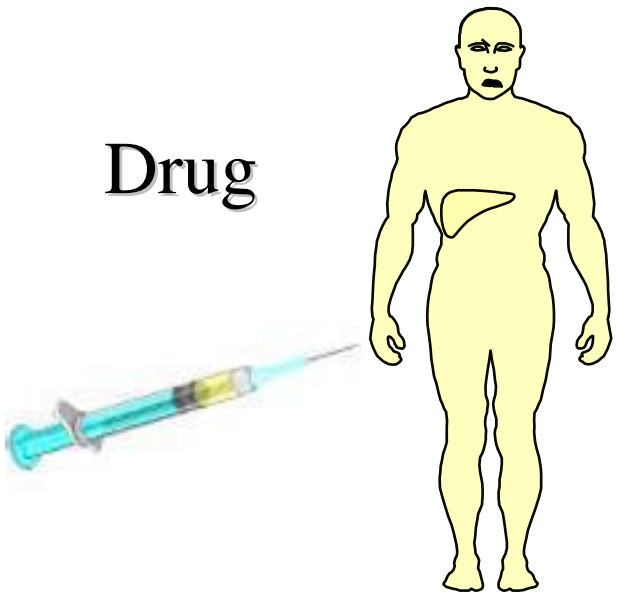
1st International Conference on Sustainable Pharmacy

24-25 April 2008

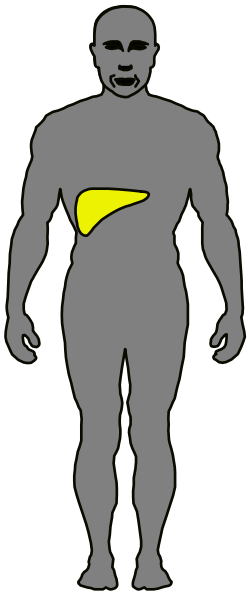
Osnabrück, Germany

university of groningen / university medical center groningen

Drugtargeting



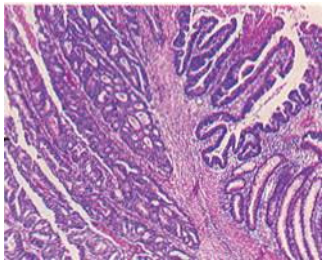
Without targeting, whole body distribution of the drug



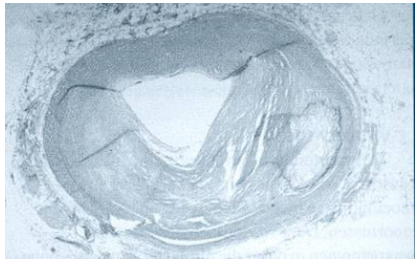
With targeting selective delivery of the drug at the site (organ/cell) of the disease

- Higher concentration of the drug at the site of disease
- Less unwanted side effects

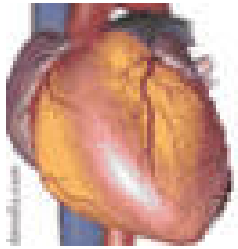
Drug delivery: toward versatile formulation technology for broad application to existing drugs/NME



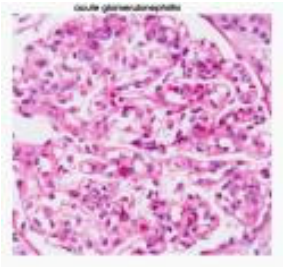
cancer



atherosclerosis



MI infarction



Diabetes type-2 assoc renopathy

Rheumatoid arthritis

"The synthesis of the medicine is only one part of the drug. Without delivery you just won't have a successful treatment"

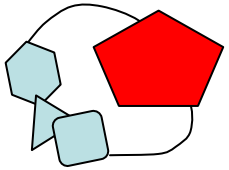
Bob Langer / MIT, FDA - 2003

Table 2. Examples of DDS that have received regulatory approval. Years given are for the United States, unless otherwise specified. Table S1 gives a more comprehensive listing for products in Phase II or later clinical trials.

Drug or therapeutic agent (trade name), manufacturer(s)	Indication	Year of approval	Reference
Liposomal amphotericin B (AmBisome), Gilead, Fujisawa	Fungal infections Leishmaniasis	1990 (Europe), 1997 2000	(*44*)
PEG-adenosine deaminase (Adagen), Enzon	Severe combined immunodeficiency disease	1990	(*45*)
Styrene maleic acid and neocarzinostatin copolymer in Ethiodol (SMANCS/Lipiodol, Zinostatin stimalamer), Yamanouchi	Hepatocellular carcinoma	1993 (Japan) 1996 (Japan)	(*46, 47*)
Stealth (PEG-stabilized) liposomal doxorubicin (Doxil/Caelyx), ALZA, Schering Plough	Kaposi's sarcoma Refractory ovarian cancer Refractory breast cancer	1995 1999 2003 (Europe, Canada)	(*10, 48*)
Liposomal cytosine arabinoside (DepoCyt), SkyePharma	Lymphomatous meningitis Neoplastic meningitis	1999 Phase IV	(*25, 49*)
Denileukin diftitox or interleukin 2–diptheria toxin fusion protein (ONTAK), Seragen	Cutaneous T-cell lymphoma	1999	(*50*)
Liposomal doxorubicin (Myocet), Elan	Metastatic breast cancer in combination with cyclophosphamide	2000 (Europe)	(*51*)
Gemtuzumab ozogamicin or anti-CD33–linked calicheamicin (Mylotarg), Wyeth-Ayerst	$CD33^+$ relapsed acute myeloid leukemia	2000	(*52*)
Liposomal verteporfin (Visudyne), QLT, Novartis	Wet macular degeneration in conjunction with laser treatment	2000 2001 2003 (Japan)	(*30*)
PEG-interferon α-2b (PEG-Intron), Enzon, Schering-Plough	Hepatitis C	2001	(*53*)
PEG–granulocyte colony stimulating factor or pegfilgrastim, (Neulasta), Amgen	Reduction of febrile neutropenia associated with chemotherapy	2002	(*54*)
^{90}Y-ibritumomab tiuxetan or ^{90}Y anti-CD20 (Zevalin), IDEC	Relapsed or refractory non-Hodgkin's lymphoma	2002	(*55*)
^{131}I-tositumomab (anti-CD20) (Bexxar), Corixa, GlaxoSmithKline	$CD20^+$ relapsed non-Hodgkin's lymphoma	2003	(*56*)

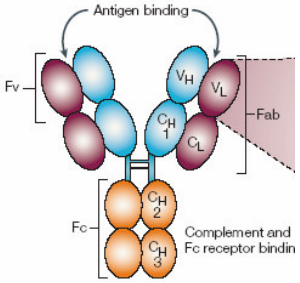
Allen & Cullis (2004), Science **303**, 1818

Carriers for (vascular) drug targeting

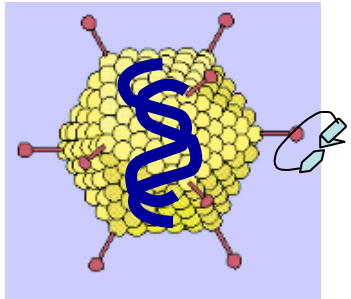


Peptides
(doxorubicin, apoptosis inducing ligands)

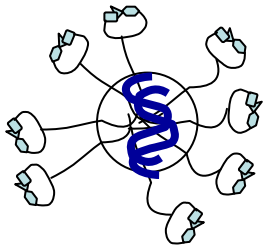
Growth factors
(toxins)



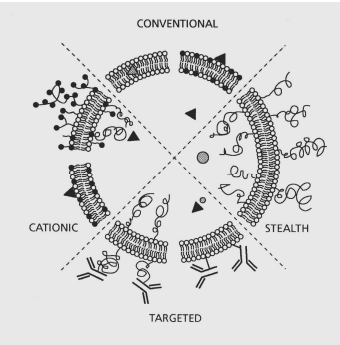
Antibodies
(toxins, toxic drugs, radioisotopes)



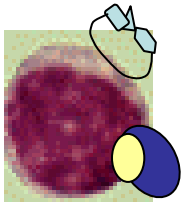
Viruses
(therapeutic genes)



Polymer based nanoparticles
(therapeutic genes, toxic drugs)



Liposomes
(toxic drugs)



Immune effector cells
(cytolytic activity)

Drug carrier requirements

- Stability in the blood circulation
- Efficient homing (accessibility of target organ/cells)
- dissociation carrier/drug (intracellular release)
- Intracellular homing

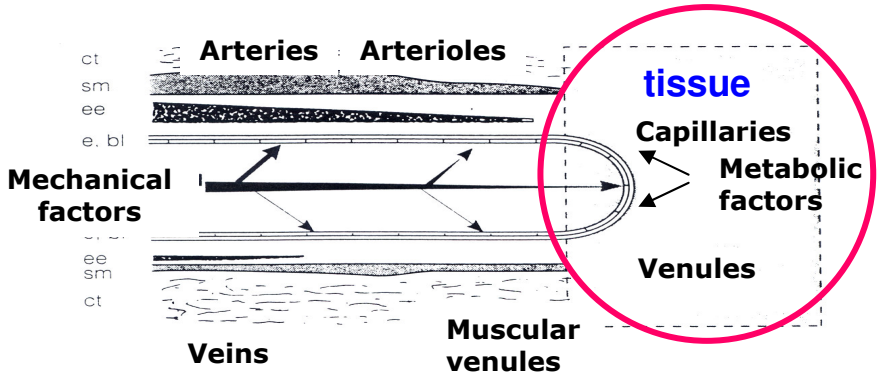
Molema G., In: Angiogenesis: an integrative approach from science to medicine (Eds. Figg WD, Folkman J). Springer, 2008 - in press.

Innovation focus drug delivery:

Targeted drug delivery systems based on materials that are biocompatible, can contain pharmacologically effective NCEs, and posess intracellular release modalities

Laboratory for Endothelial Biomedicine and Vascular Drug Targeting research

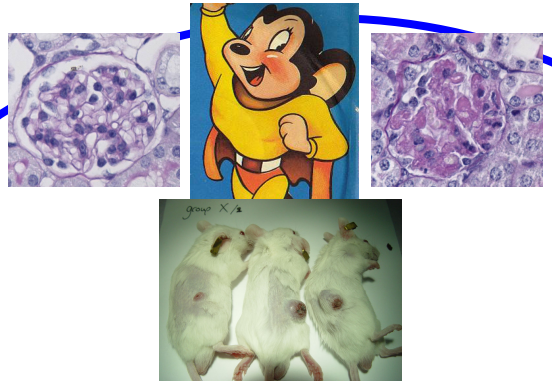
Dept. Pathology & Medical Biology, Medical Biology section, UMCG

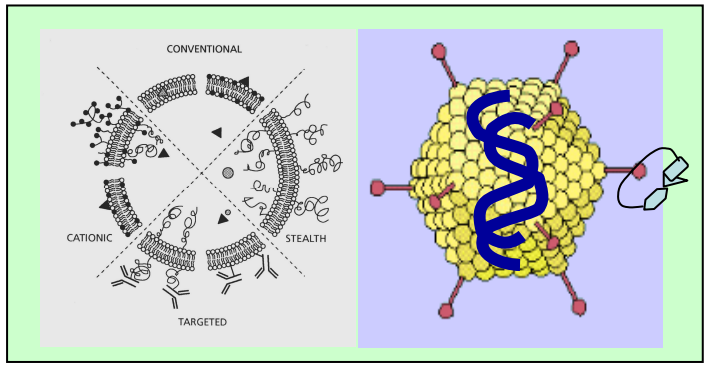


Microvascular endothelial cells as target:

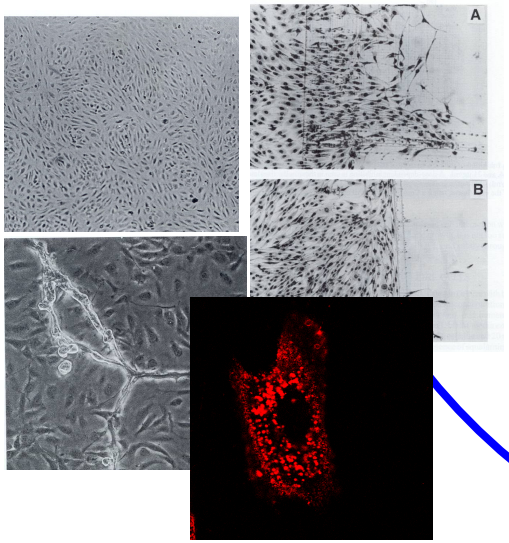
- control disease activity
- easily accessible for nanomedicines
- new technologies enable *in vivo* studies on pharmacological efficacy of targeted drug delivery systems → animal and human studies

Mouse models



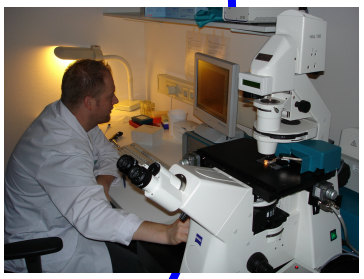


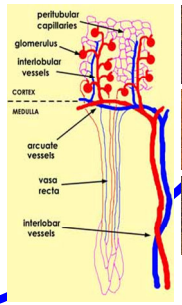
in vitro cell systems and advanced read out systems

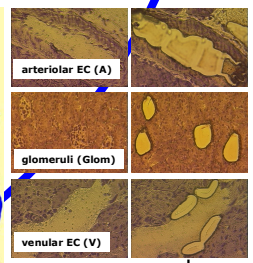


UMCG EC facility

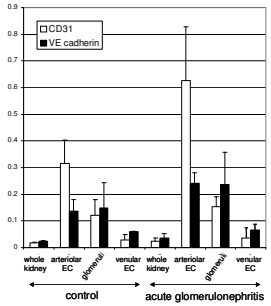
Advanced in vivo pharmacology read out systems







qRT-PCR



Endothelial cells: Targets for selective liposome mediated drug delivery

- Involvement in patho-physiological processes
- Accessibility for substances transported by the blood
- Endothelial cell heterogeneity, allowing for organ specific and/or disease specific drug delivery strategies

E.g. Endothelial cells express or over-express a variety of adhesion molecules during inflammation

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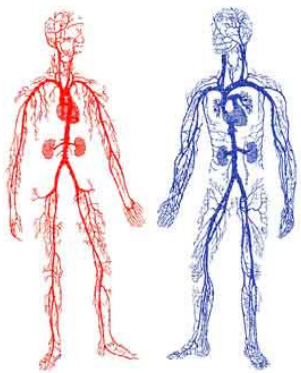
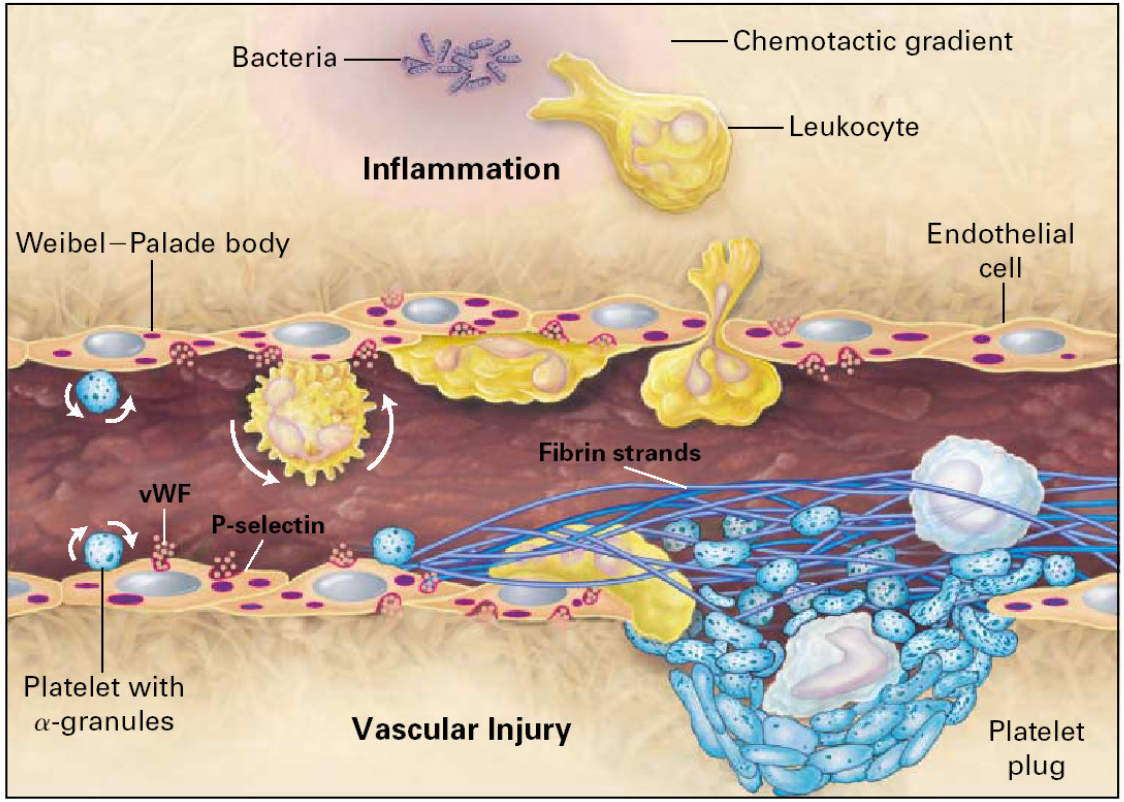
Endothelial cells



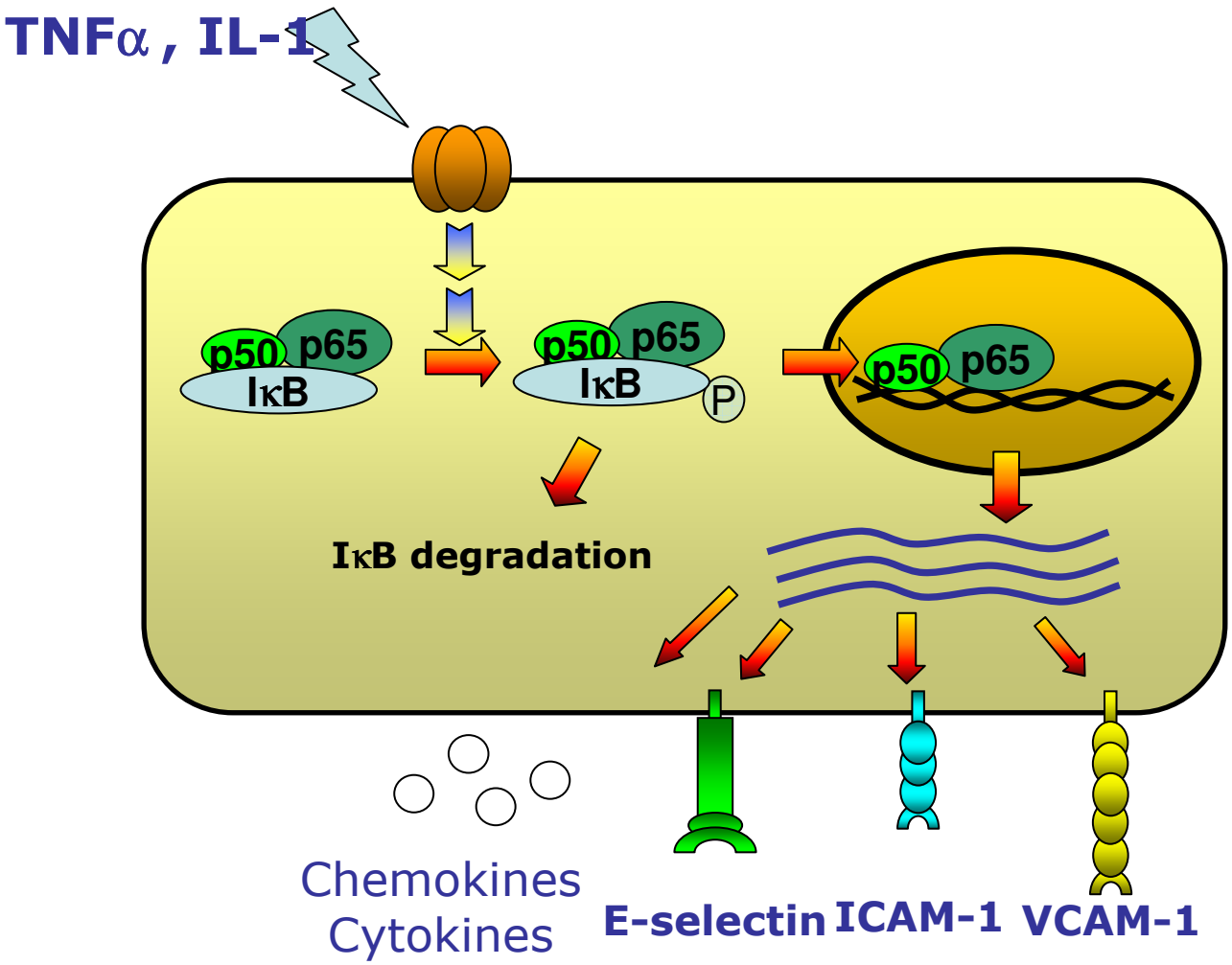
- Covering the inside of the bloodvessels
- Surface 350 m^2; 1.10^{13} cells



Functions:

- Transport of substances from the blood to underlying tissue
- Blood coagulation
- Inflammation
- Angiogenesis

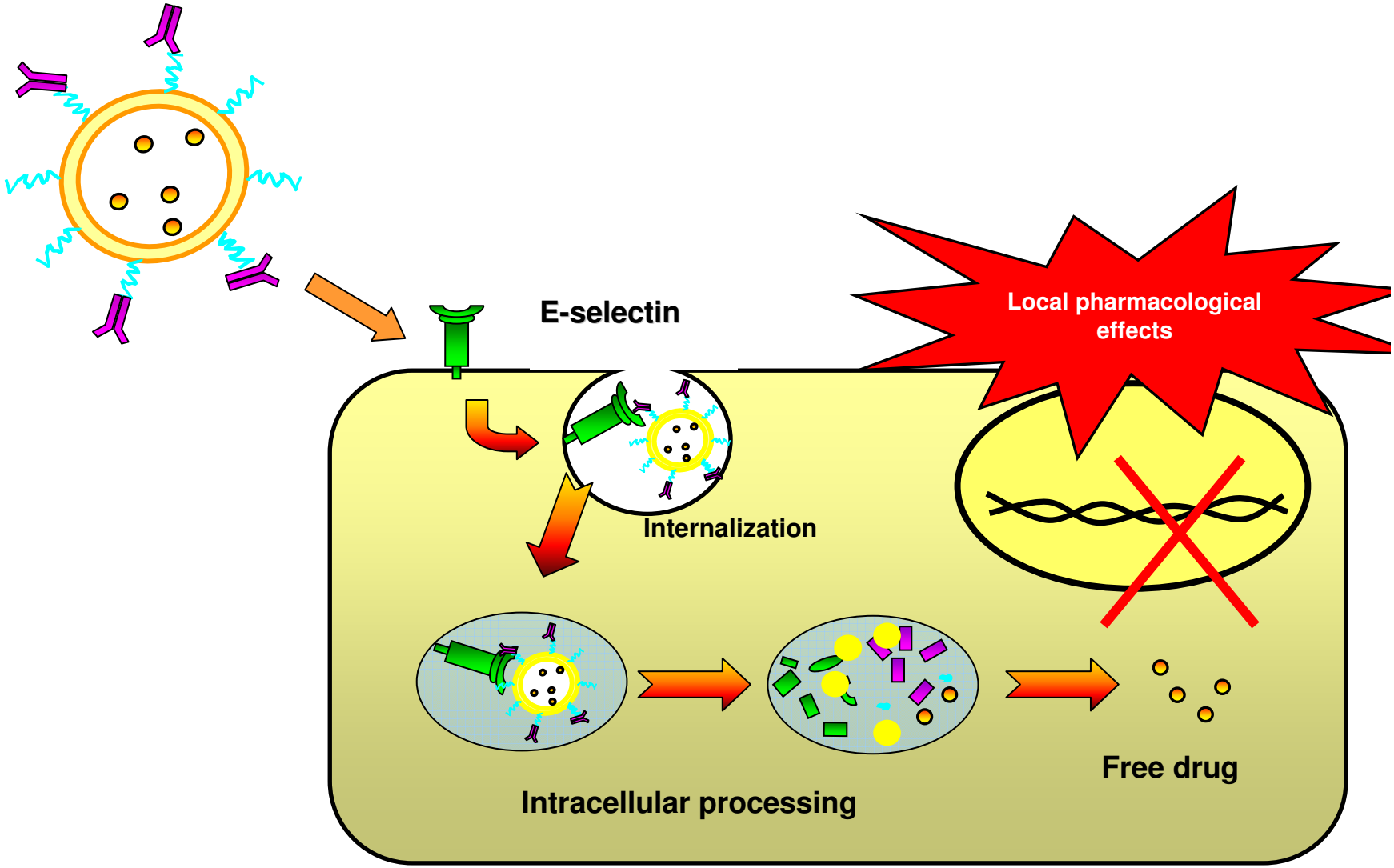
Endothelial cell activation: a key step in inflammatory response



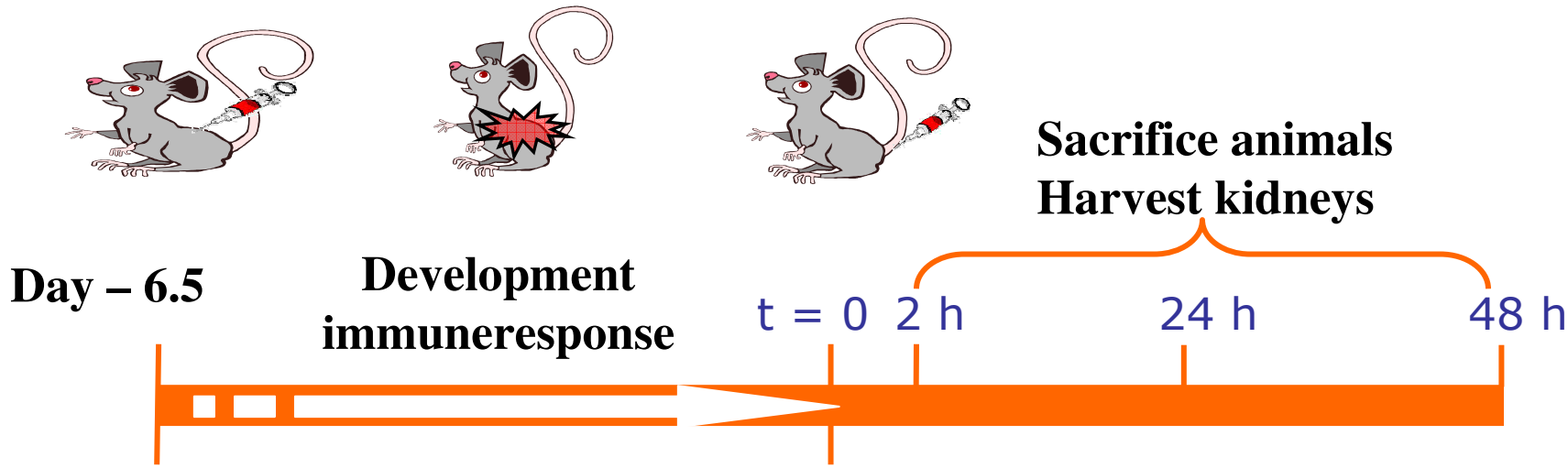
Adhesion molecules: Targets for selective *liposome* mediated drug delivery in inflammation

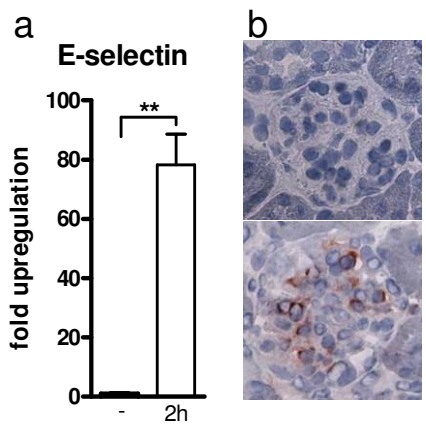
Targeting of immunoliposomes in glomerulonephritis

Drug targeting to inflamed endothelium via E-selectin: anti-E-selectin immunoliposomes

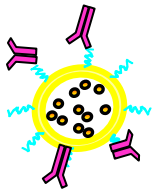


Targeting of immunoliposomes in glomerulonephritis

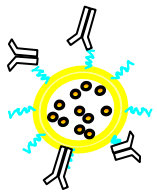




(b) + MES1-dexa-liposome (0.4 µmol lipid)



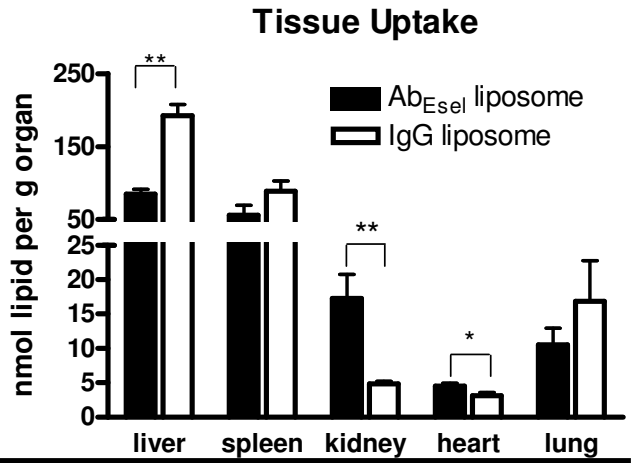
(c) + IgG-dexa control liposome (0.4 µmol lipid)



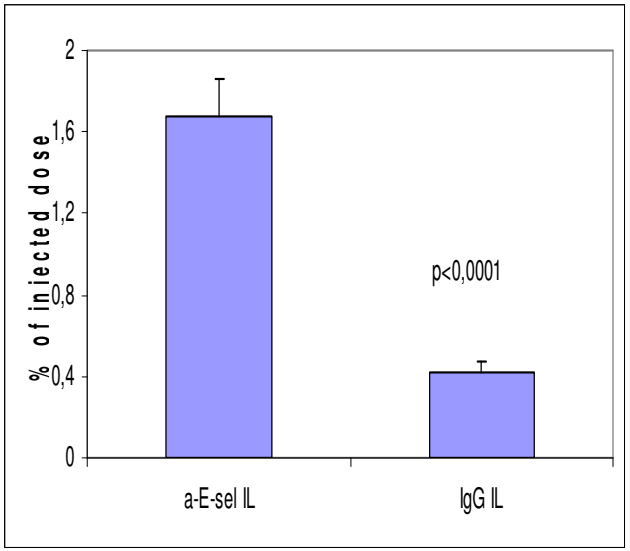
(d) + free dexa

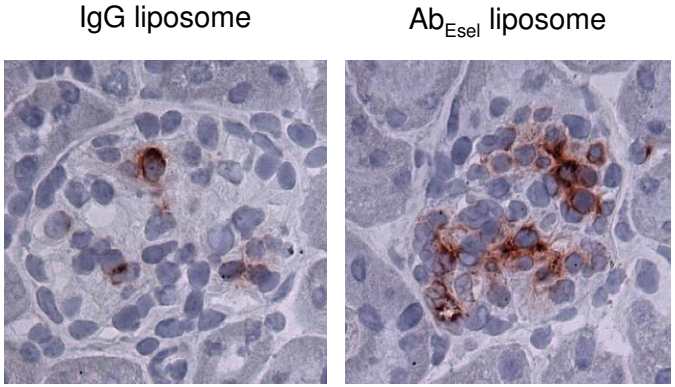
Ásgeirsdóttir, Kamps et al, Mol. Pharmacol. 2007, 72: 121

Kidney uptake of AbEsel - immunoliposomes is four fold higher compared to non-targeted immunoliposomes 24 h after i.v. injection

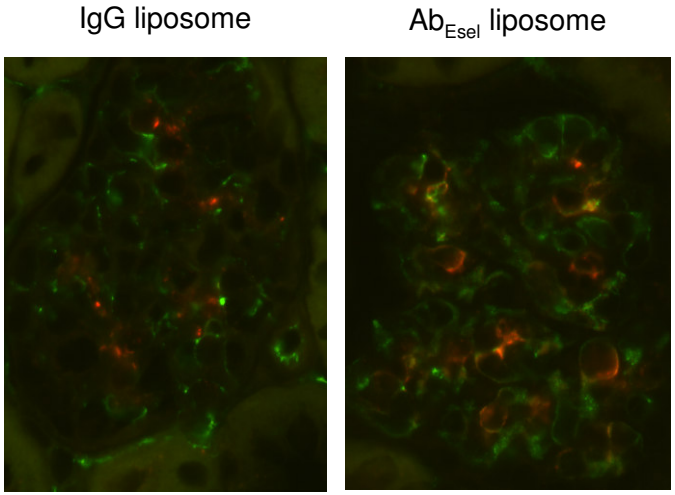


Targeting index	0.4	0.6	3.6	1.5	0.6





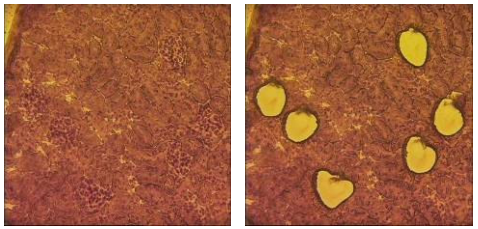
b

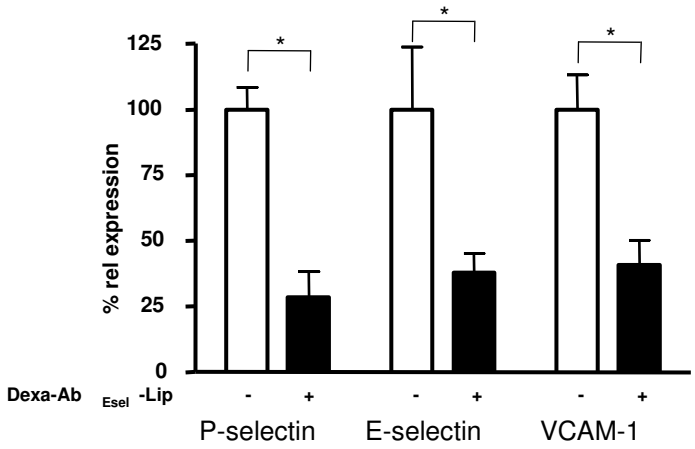


Ásgeirsdóttir et al, Am J Physiol Renal Physiol. 2008;294:F554-61.

AbEsel-immunoliposomes containing dexamethasone down-regulate adhesion molecule expression only in glomerular endothelium

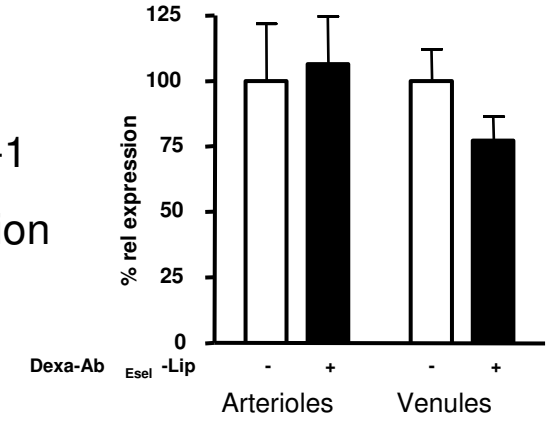
LDM





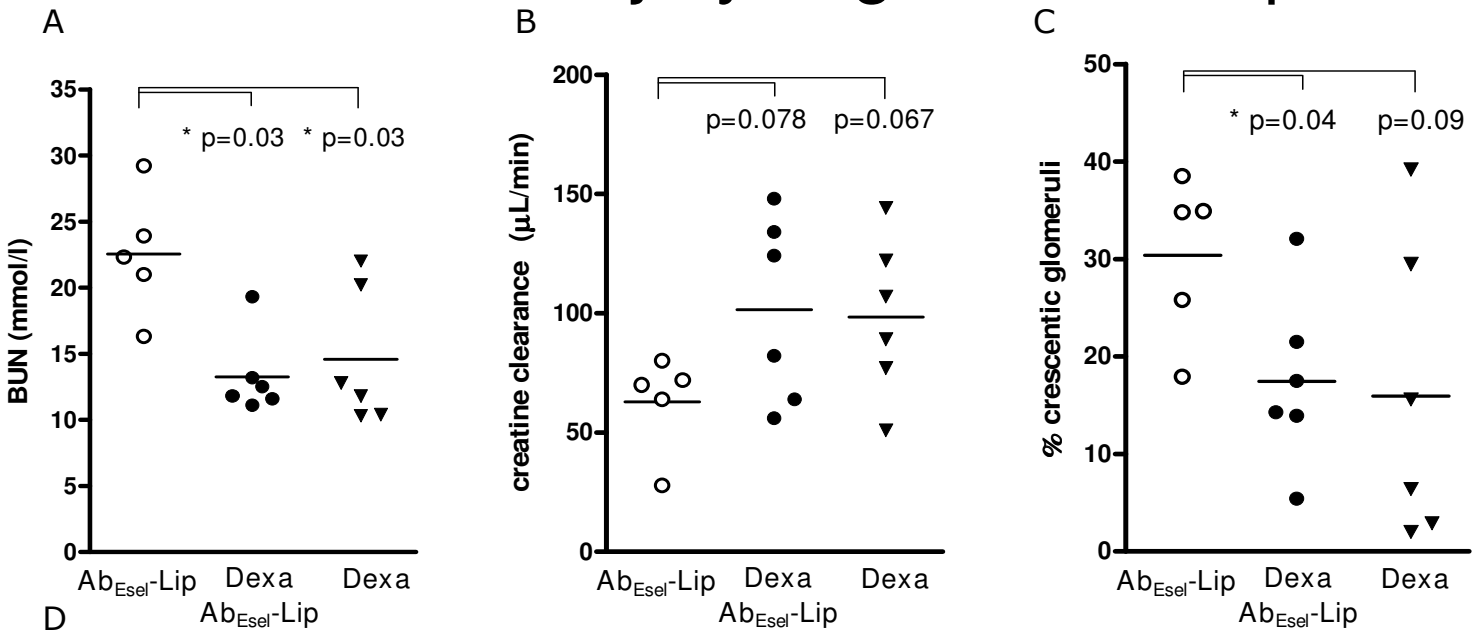
Glomeruli

VCAM-1 expression

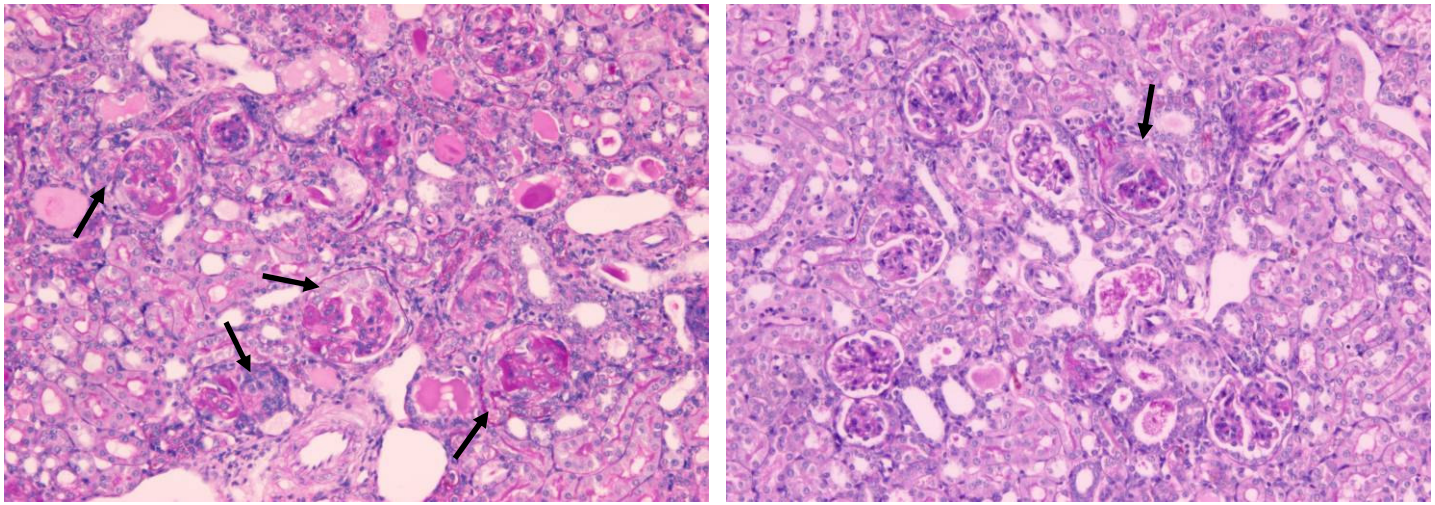


Aterioles and venules

AbEsel-immunoliposomes containing dexamethasone reduce renal injury in glomerulonephritis



D



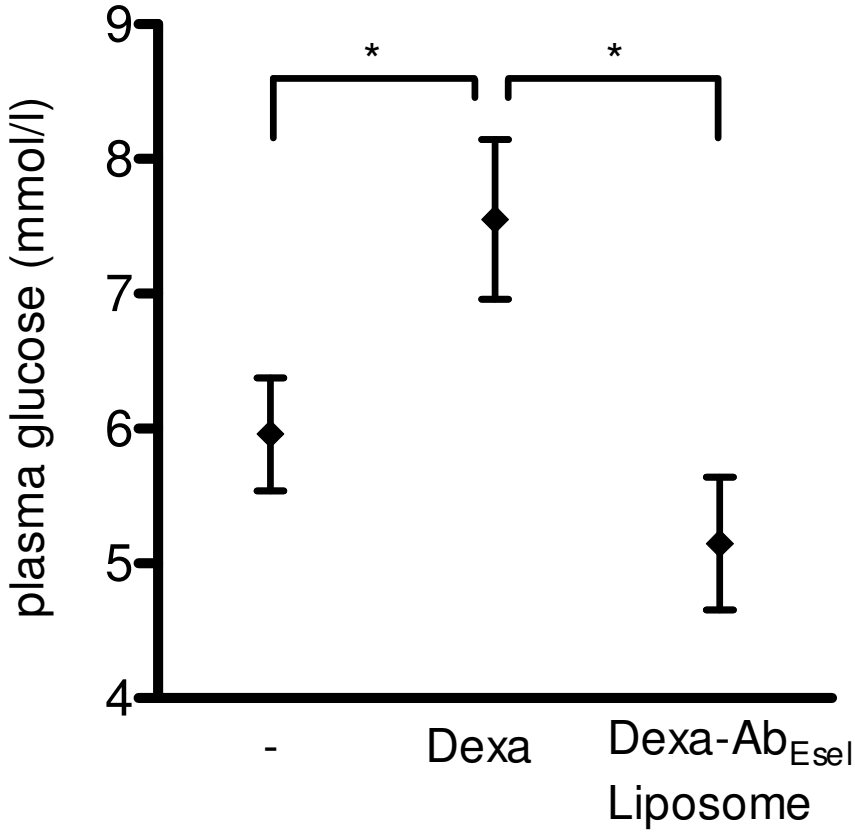
empty Ab$_{Esel}$ liposome

Dexa-Ab$_{Esel}$-liposome

Ásgeirsdóttir Kamps et al, Mol. Pharmacol. 2007, 72: 121

Targeted dexamethasone was devoid of systemic side effects

- Upper body obesity with thin arms and legs
- Buffalo Hump
- Red, Round Face
- High Blood Sugar
- High Blood Pressure
- Vertigo
- Blurry Vision
- Acne
- Female Balding
- Water Retention
- Menstrual Irregularities
- Thin Skin and Bruising
- Purple Striae
- Poor Wound Healing
- Hirsutism
- Severe Depression
- Cognitive Difficulties
- Emotional Instability
- Sleep Disorders
- Fatigue



Conclusion

► Targeted delivery of dexamethasone using anti-E-selectin IL leads to ***local effects*** on gene expression, ***diminished side effects*** and ***reduced progression*** of glomerulonephritis

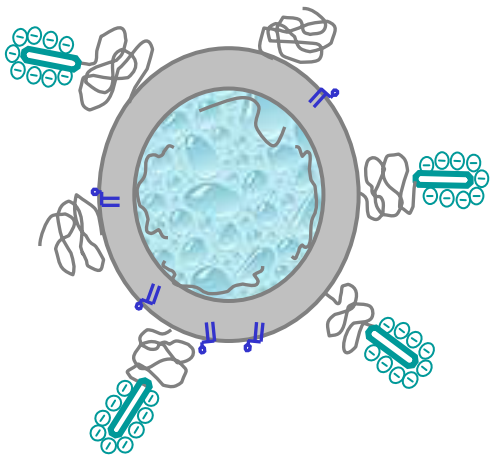
Sustainable Pharmacy

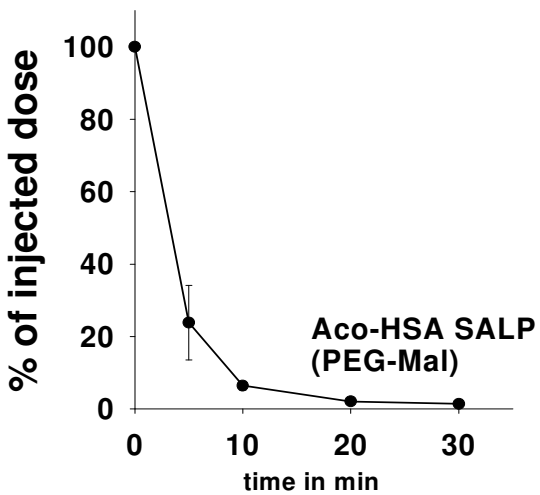
Drug targeting: Reduction of administration of pharmaceutically active compounds?

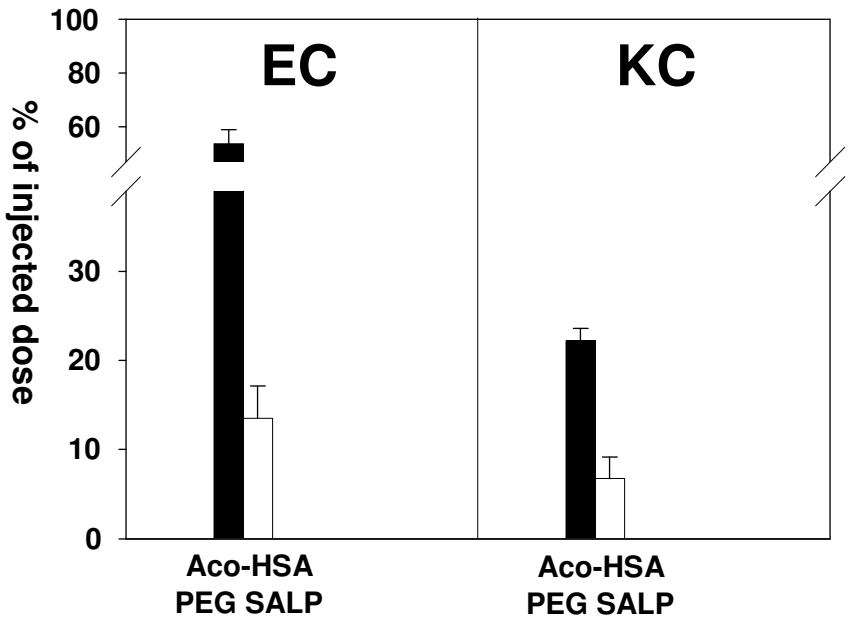
More/new drugs?

Reduction of environmental emissions?

60% of the injected dose of Aco-HSA liposomes disappear fast from the blood and are taken up by liver endothelial cells







Bartsch et al. Mol. Pharmacol. 2005

Kamps et al. PNAS 1997

University Medical Center Groningen, Dept. Pathol. & Medical Biology, Medical Biology section

Laboratory for Endothelial Biomedicine & Vascular Drug Targeting research

Sigridur A. Ásgeirsdóttir

Joanna E. Adrian

Peter Heeringa

Henriëtte Morselt

Peter J. Zwiers

Henk E. Moorlag

Jan A.A.M. Kamps

Grietje Molema

Synvolux therapeutics

Marcel Ruiters

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