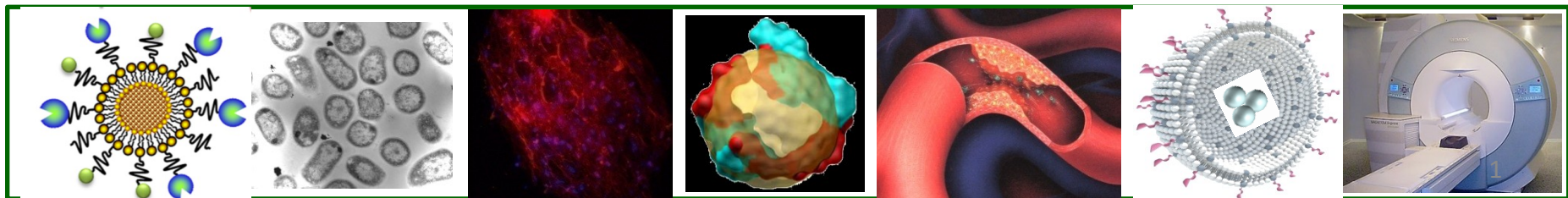


Liposomale Wirkstoffträgersysteme Vom Konzept bis zur klinischen Anwendung

Ruth Prassl

10. Thüringer Biomaterial – Kolloquium

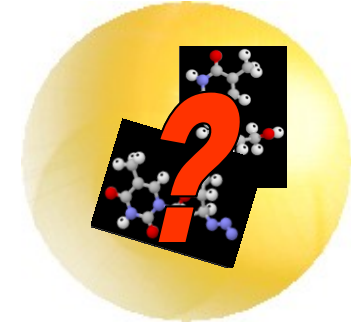
17. September 2015



Drug Delivery Systeme - Wirkstoffträger

Wozu überhaupt Wirkstoffträger ?

- Schutz des Wirkstoffes vor enzymatischen Abbau
Erhöhung der Löslichkeit des Wirkstoffes
- Geschützter Transport an den Wirkort und
gezielte Freisetzung des Wirkstoffes vor Ort (targeted drug delivery)



Erwartete Vorteile:

- Reduktion der verabreichten Wirkstoffmenge
- Reduktion der Toxizität von Wirkstoffen
- Reduktion unerwünschter Nebenwirkungen
- Langzeitwirkung durch verlangsamte Freisetzung (Retardeffekt)

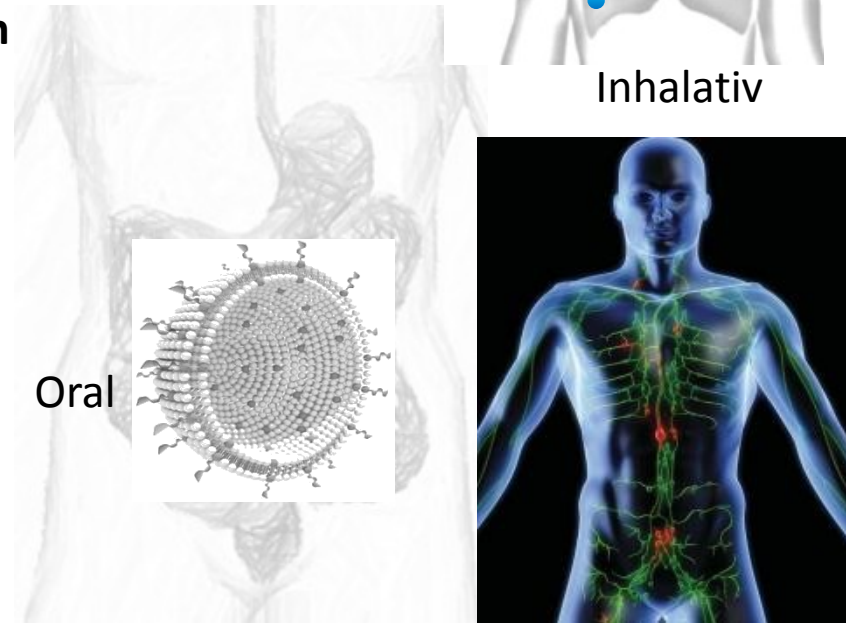
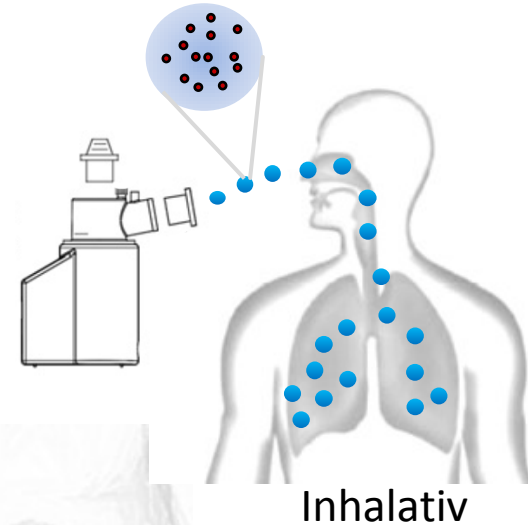


Drug Delivery Systeme - Wirkstoffträger

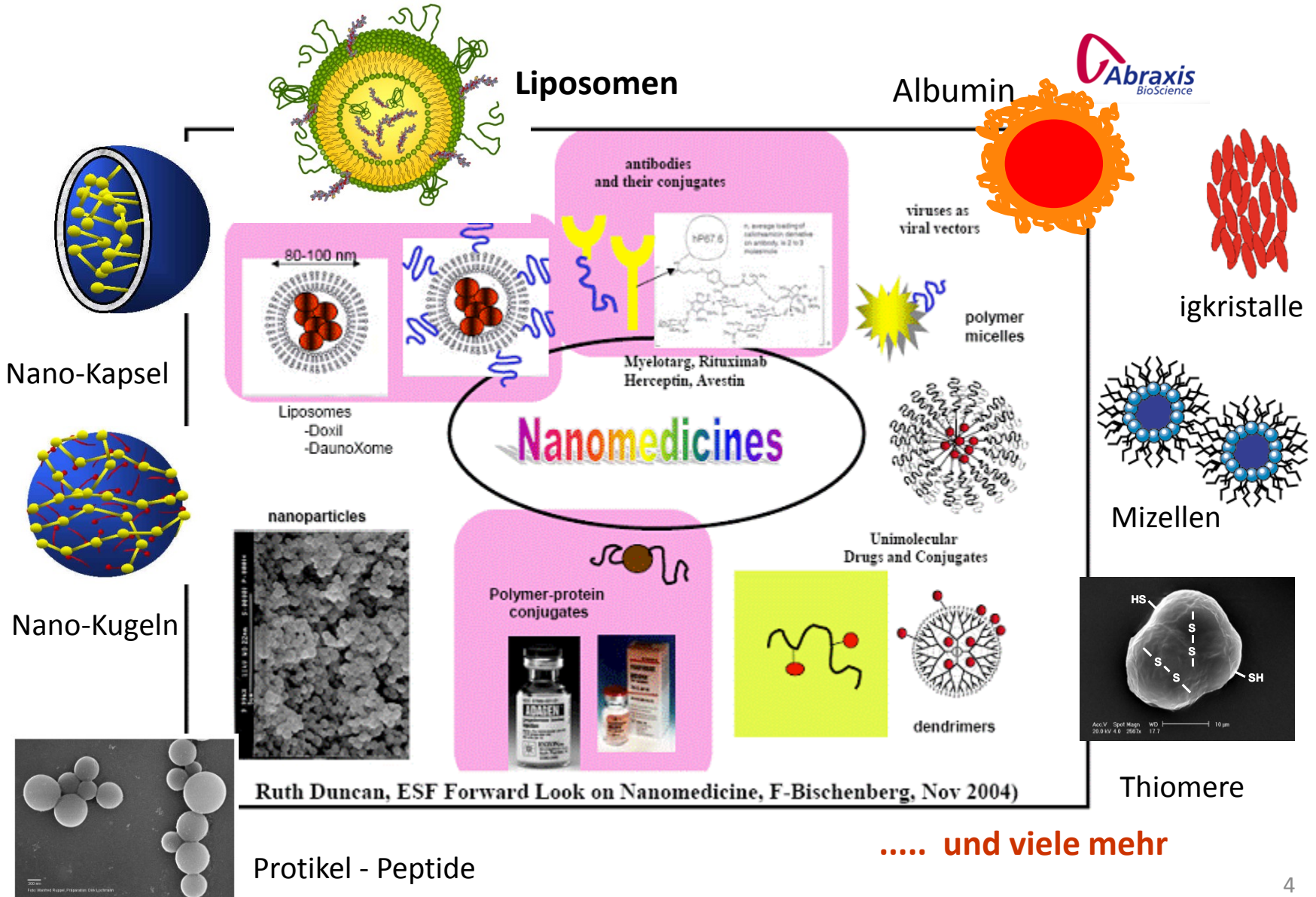
Herausforderungen:

- Biologische Verträglichkeit
- Beladbarkeit des Wirkstoffträgers
- Lagerungsstabilität
- Stabilität im Körper, Aufnahme von den Zellen
- Freisetzung des Wirkstoffes

- Reproduzierbarkeit im Herstellungsverfahren
- Up-scaling (Herstellung großer Mengen)
- Regulatorische Hürden
- Kosten



Nanotechnologie Plattform für Wirkstoffträger



Geschichte – Liposomen als Wirkstoffträger

1965



Alec Bangham (1921-2010)

1970

FEBS Lett. 1973 Nov 1;36(3):292-6.

Drug entrapment in liposomes.

Gregoriadis G.

review article

Nature 265, 407 - 411 (03 February 1977); doi:10.1038/265407a0

Targeting of drugs

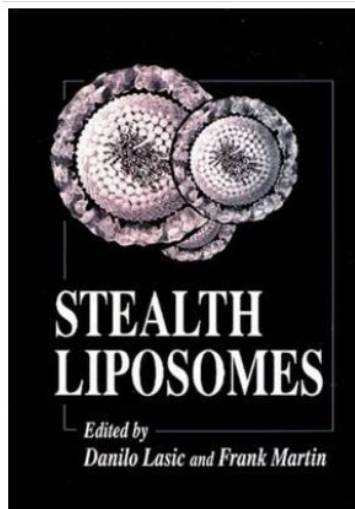
GREGORY GREGORIADIS*

*Division of Clinical Investigation, Clinical Research Centre, Watford Road, Harrow, Middx. HA1 3UJ, UK.



Gregory Gregoriadis

1990

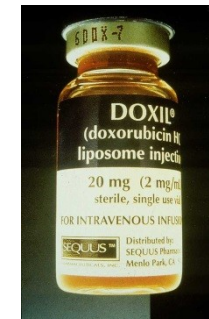


Danilo Lasic
Demetrios Papahadjopoulos



Yechezkel „Chezy“ Barenholz

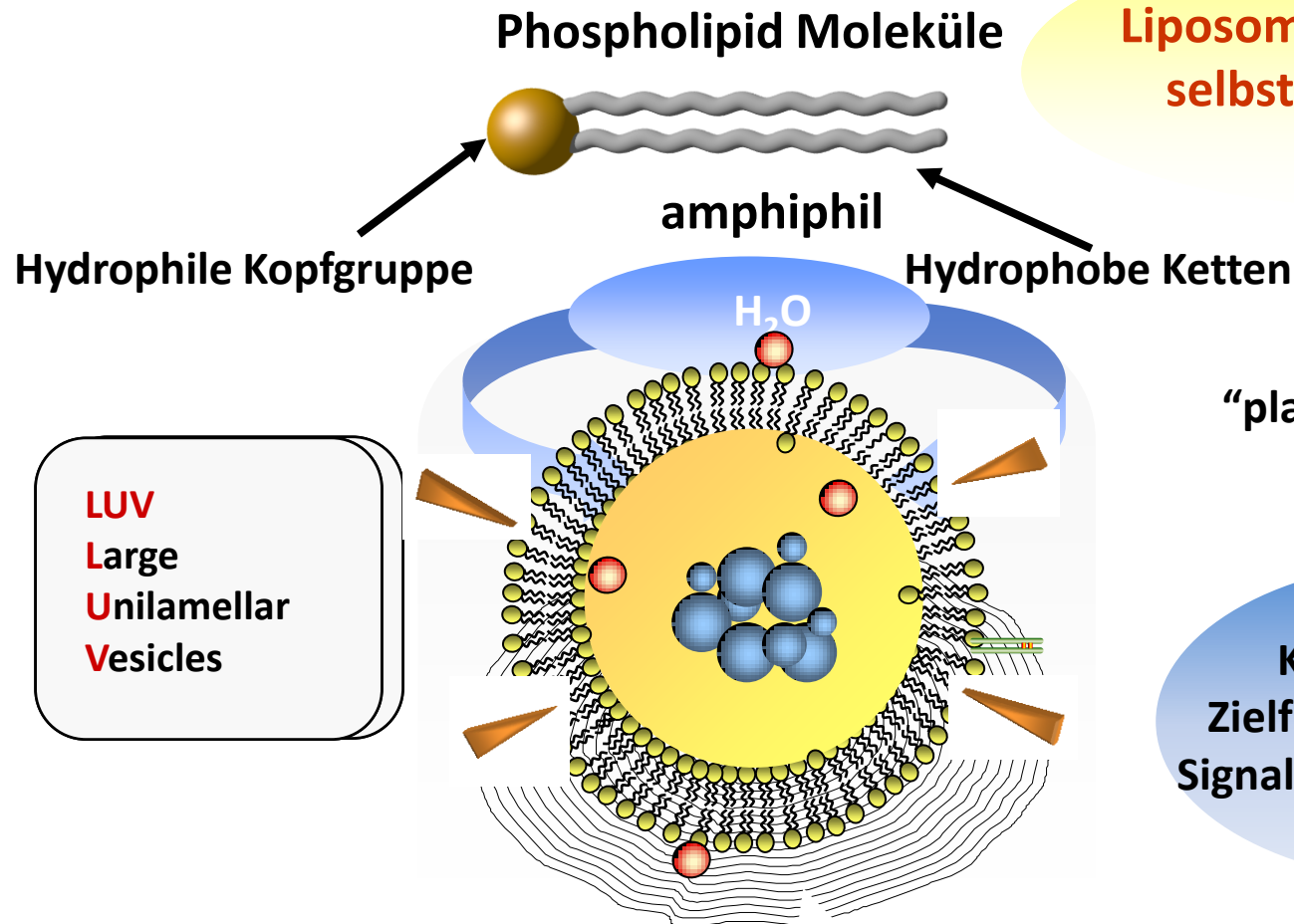
Liposomal Doxorubicin
FDA approved 1995



Liposomen als Wirkstoffträgersysteme

Warum Liposomen ?

Liposomen sind modulare selbstassemblierende Systeme



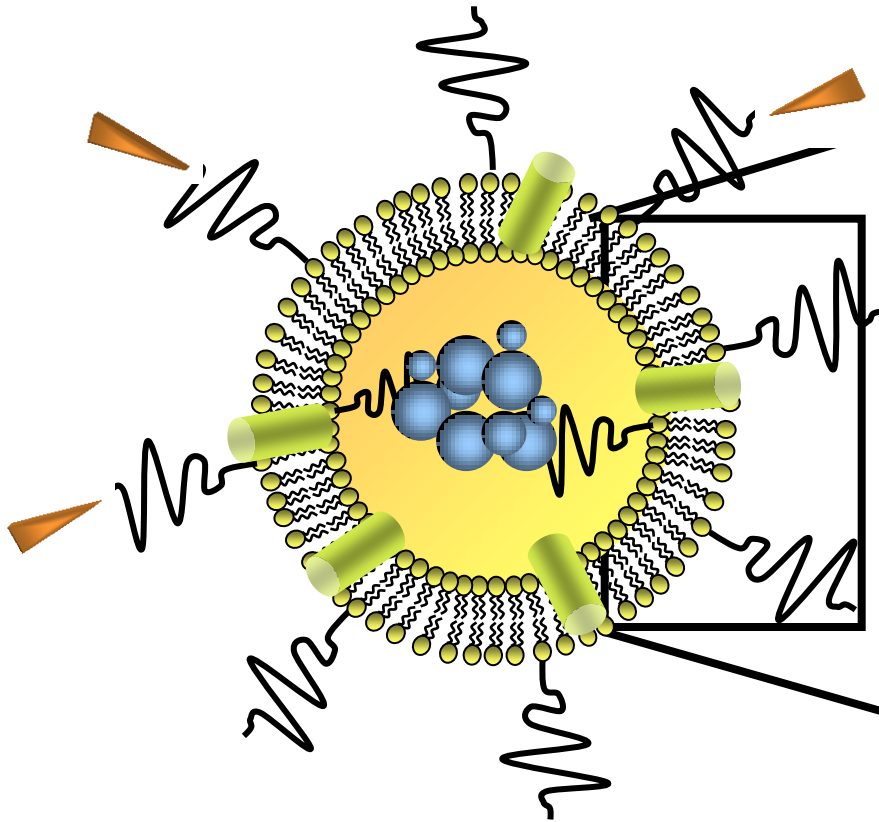
“plain” Liposomen

Wirkstoffe
Kontrastmittel
Zielfindungsmoleküle
Signalgebende Moleküle

Polymer Oberflächen⁶

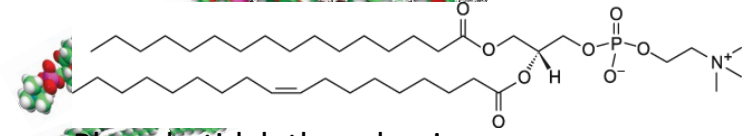
Sterisch stabilisierte Liposomen

Polymer Ummantelung

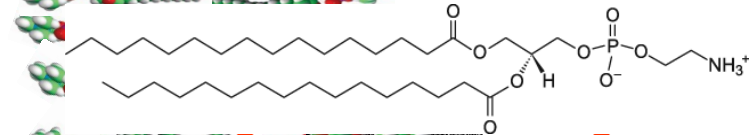


Phospholipide:

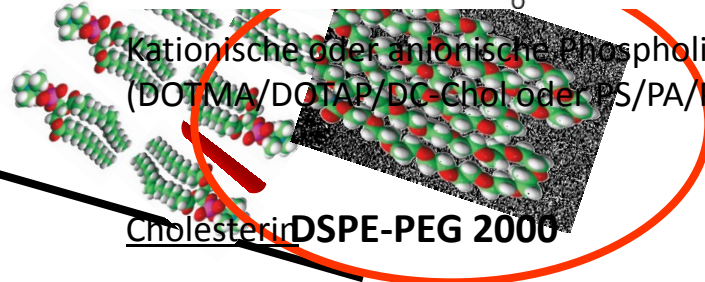
Phosphatidylcholine – Lecithin
(EggPC, SoyPC, POPC, DPPC...)



Phosphatidylethanolamin -
(DPPE, DOPE.....)



Kationische oder anionische Phospholipide
(DOTMA/DOTAP/DC-Chol oder PS/PA/PG...)



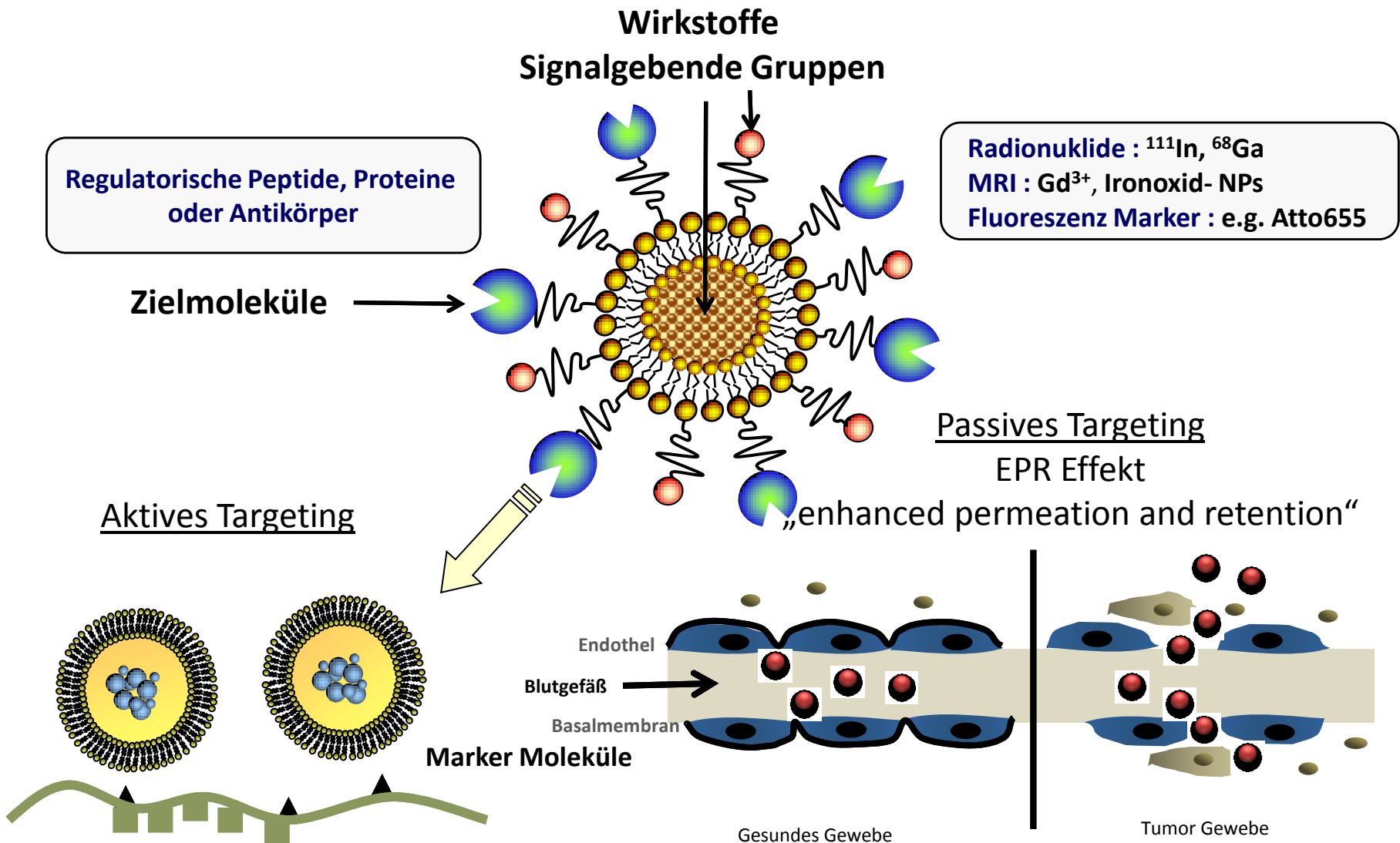
Cholesterin **DSPE-PEG 2000**

PEGyliertes Phosphatidylethanolamin
(3-5 mol % DSPE – PEG2000)

„Stealth Liposome“

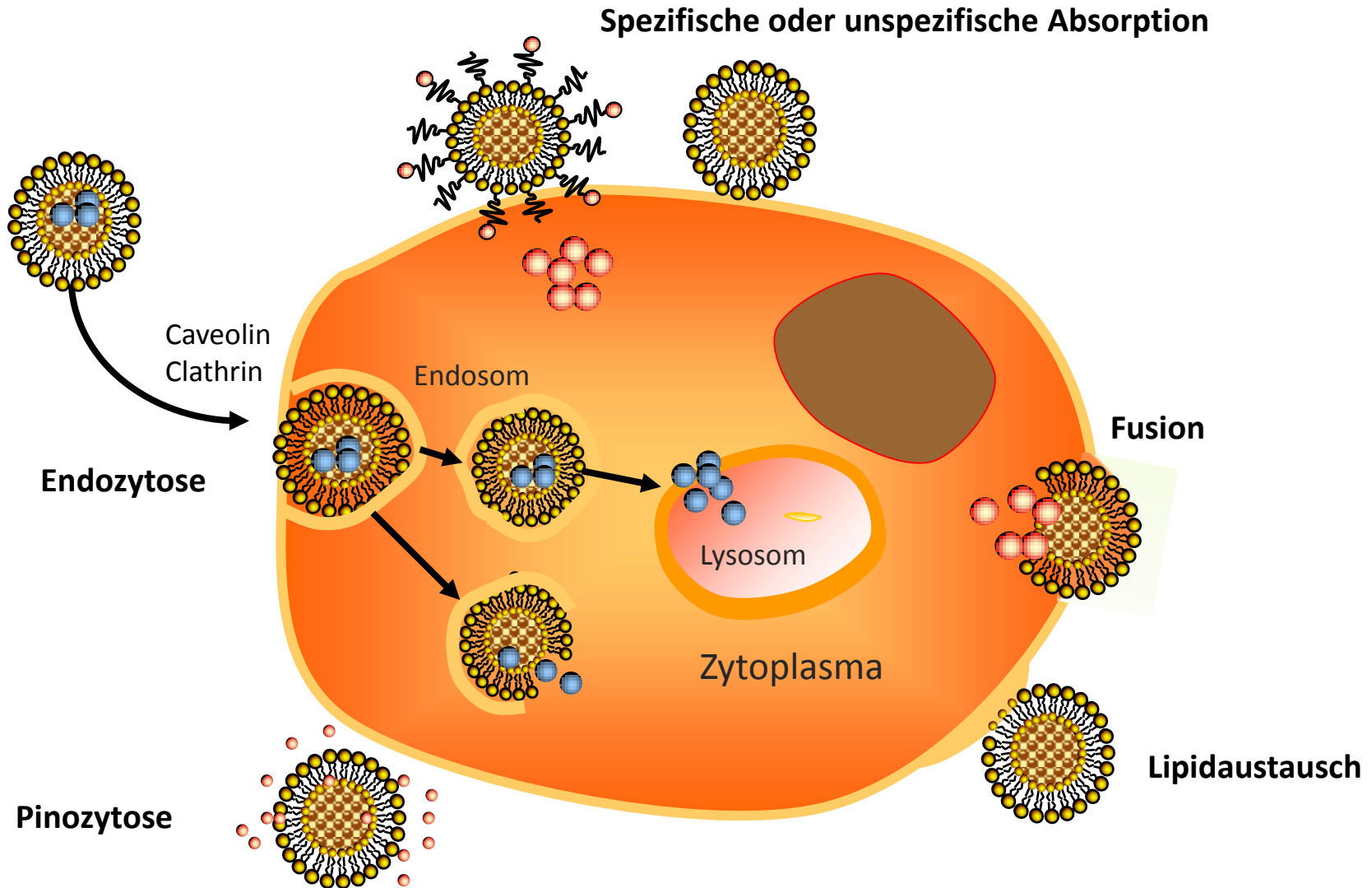
**Wirkstoffbeladung
&
„targeting“**

Funktionalisierte sterisch-stabilisierte Liposomen



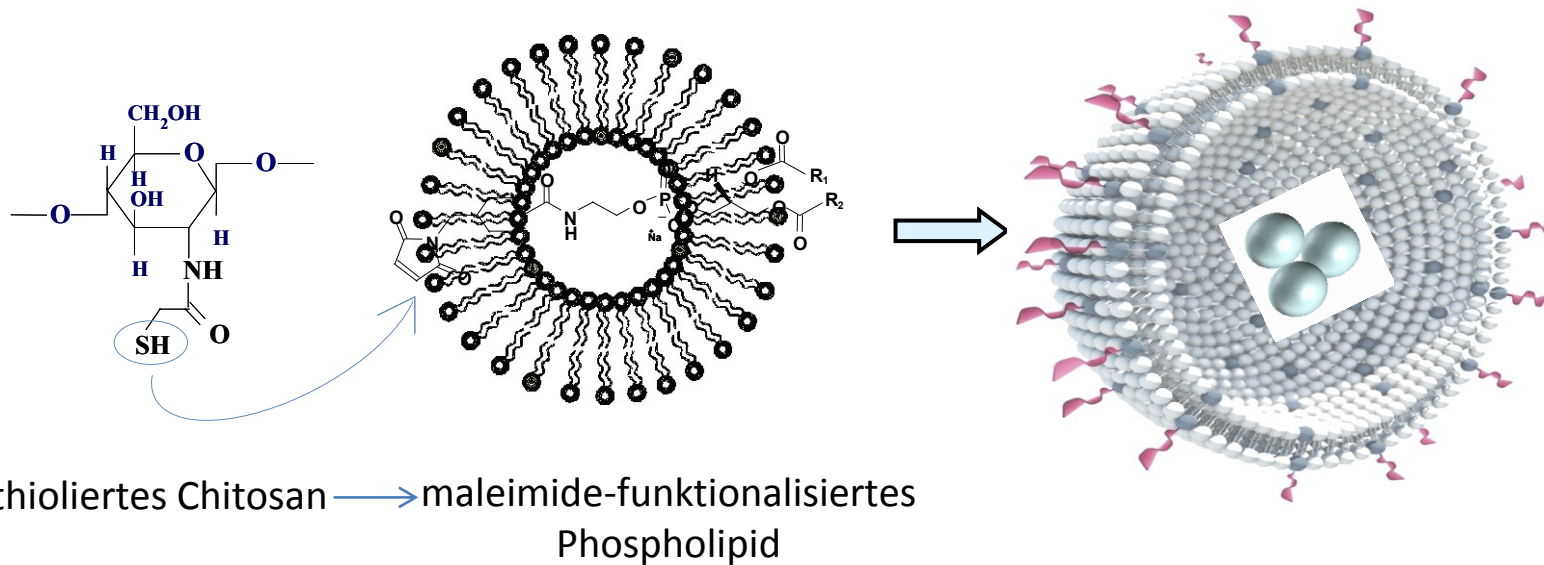
Erkranktes Gewebe: Tumor, atherosklerotischer Plaque....

Zelluläre Aufnahme von Liposomen



Polymer Coating: Thiomer gecoatete Liposomen

Kopplung von thiolierten Polymeren an funktionalisierte Liposomen



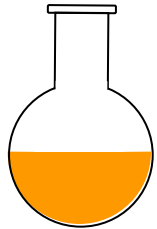
➤ **Orale Applikation:**

- verbesserte mucoadhäsive Eigenschaften erhöhen die orale Bioverfügbarkeit von Wirkstoffen

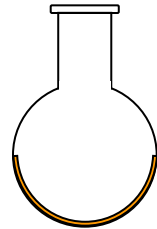
Herstellungsmethoden von Liposomen

Lipide, funktionalisierte Lipide
Markermoleküle

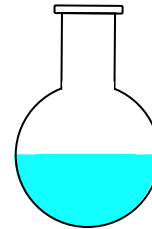
Beladung / Labelling



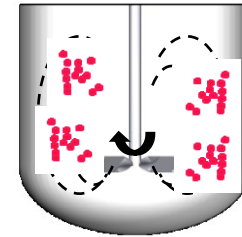
Abdampfen
N₂-Strom



Hydratation
& Vortex



Dispersion



Suspension

Liposomen
unterschiedlicher
Größe in Puffer

Freeze/thaw

Lipidmischungen in
organischen
Lösungsmittel
Chloroform/Methanol

Trockener Lipidfilm
Vakuumtrocknung

Homogenisieren - Beschallen



Größenextrusion



Membranfilter mit definierter
Porengröße
z.B. sequentiell
400 nm, 200 nm, 100 nm Filter

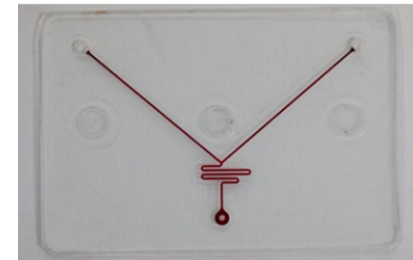
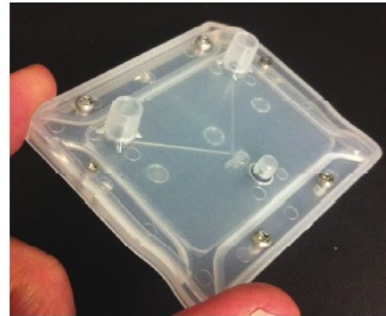
Herstellungsmethoden von Liposomen

Reversed phase separation, Ethanolinjektion

Mikrofluidics - schnelles Mischen



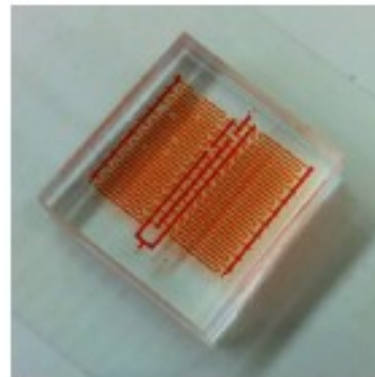
NanoAssemblr™ Benchtop Instrument



Einschrittsynthese

Flussraten 2-12 ml/min

Scale-up



NanoAssemblr®

Reinigung und Charakterisierung von Liposomen

Reinigung :

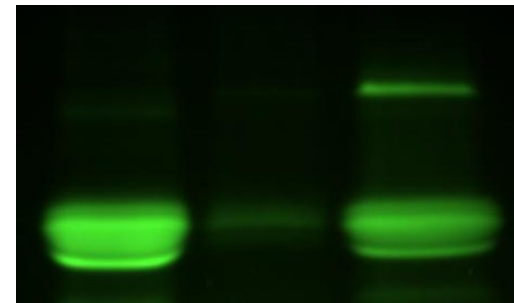
- Dialyse
- Zentrifugation
- Chromatographische Methoden

Charakterisierung :

Chemische Charakterisierung

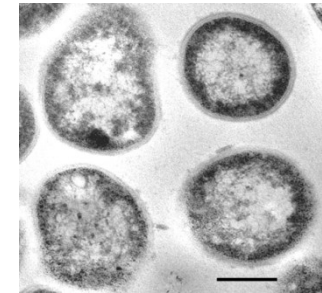
- Lipid Zusammensetzung / Lipid Integrität
Dünnschichtchromatographie
- Lipidquantifizierung
Enzymatische Assays, Anorganischer Phosphor
- Wirkstoff / Markerkonzentration
HPLC/MS, Fluoreszenz
- Elektrophoresen

Liposome Suspension

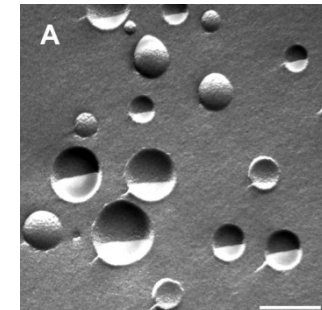
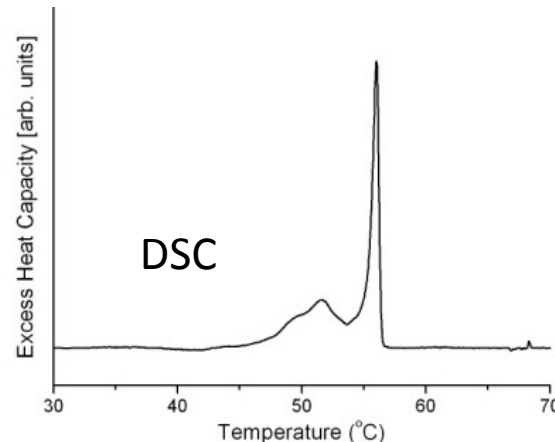
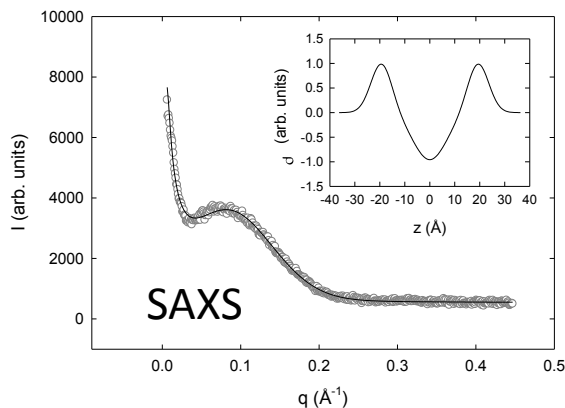


Biophysikalische Charakterisierung

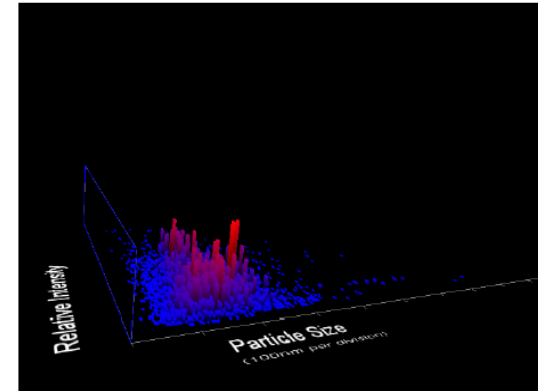
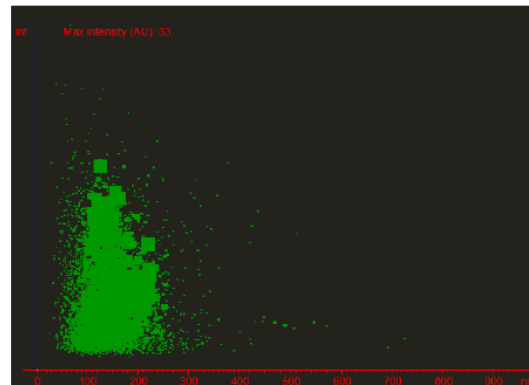
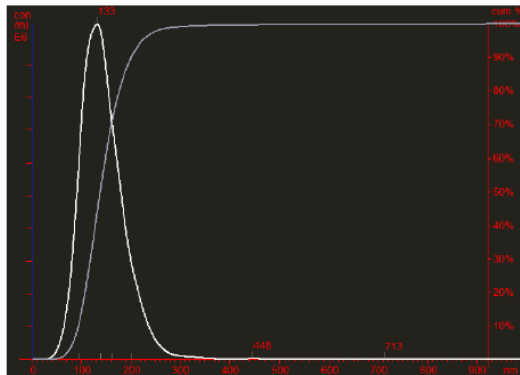
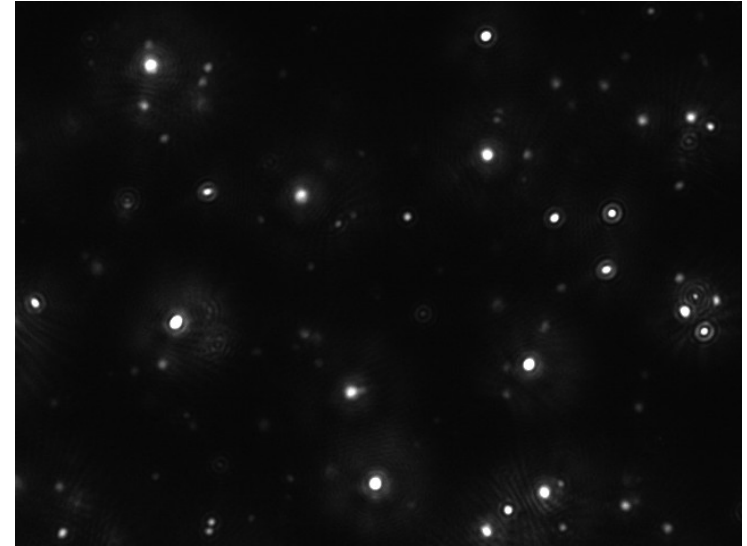
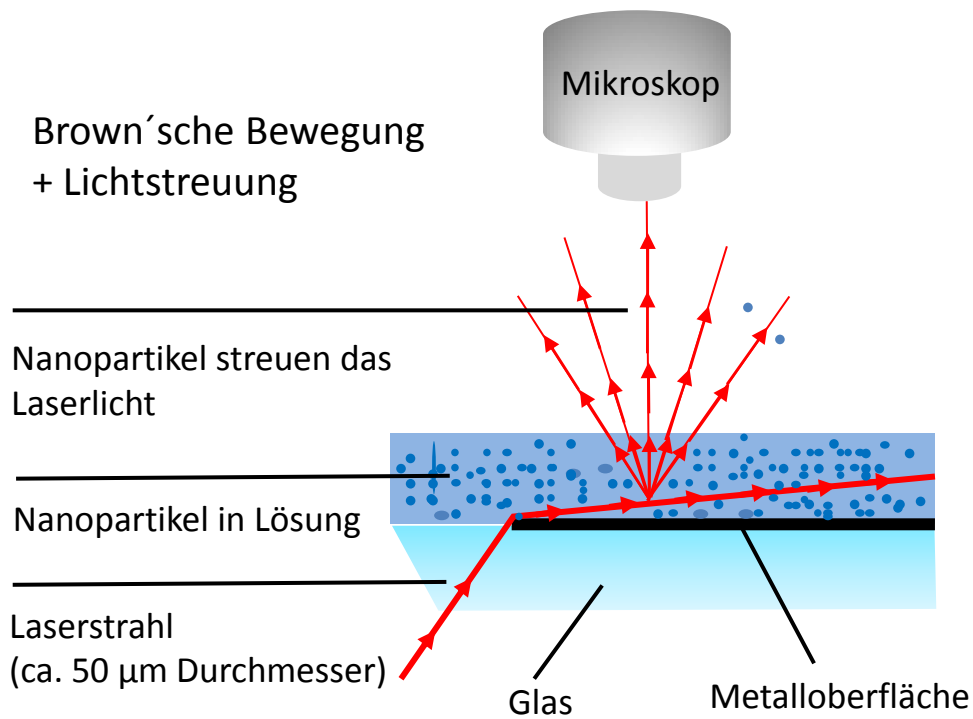
- Größenmessung – Photonenkorrelationspektroskopie
Dynamische Lichtstreuung (Malvern Instruments)
- Oberflächenladung – Zetapotential
- Morphologie – Elektronenmikroskopische Methoden
- Morphologie / Form – Röntgenkleinwinkelstreuung
(Small Angle X-ray Scattering, SAXS)
- Thermisches Verhalten – Differentielle Mikrokolorimetrie
(Differential Scanning Calorimetry, DSC)



TEM



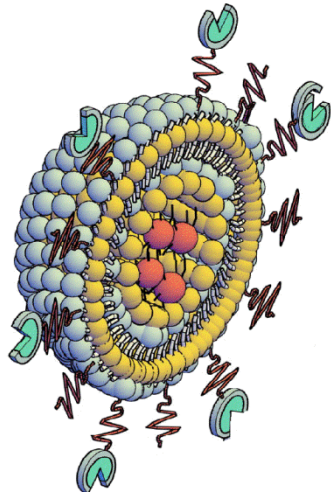
Nanopartikel Tracking Analyse - NTA



Pharmazeutische Entwicklung

- Stabilität, Beladungseffizienz, Freisetzungsverhalten, Wirkung
- Zellkultur, Biologische Barrieren, Proteincorona, zelluläre Aufnahme

Gezielte Freisetzung des Wirkstoffes

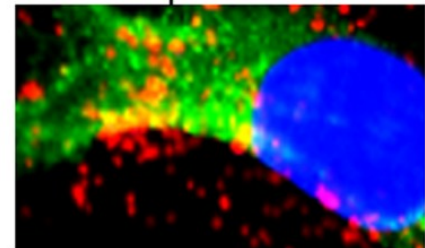
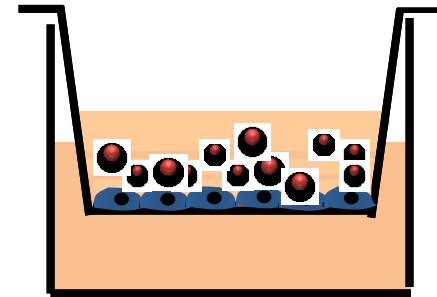


pH sensitive Lipide

Temperaturerhöhung

Photoaktivierung

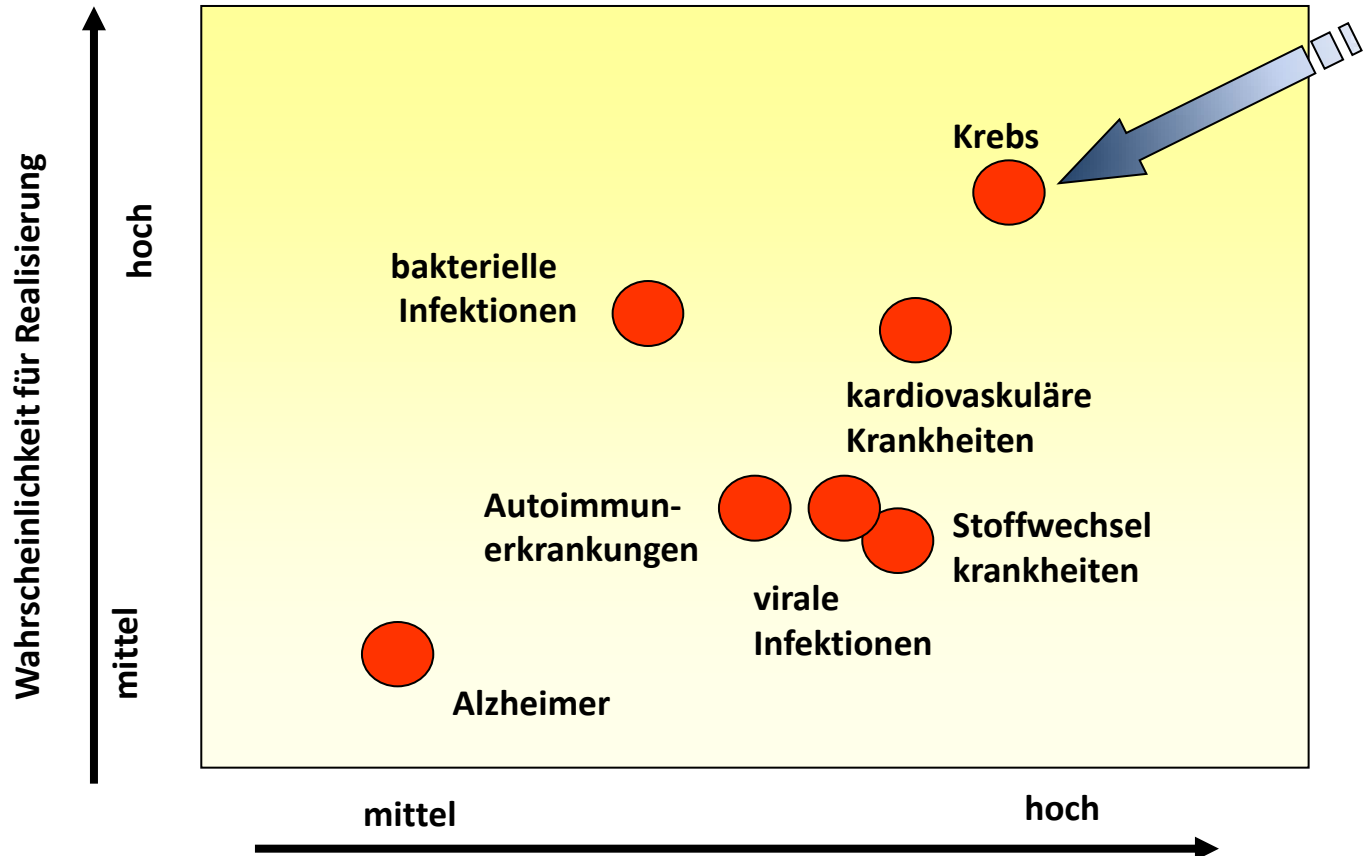
Ultraschall



- Präklinische Validierung – geeignetes Tiermodell



Anwendungsbereiche & Umsetzung



Potential

Baumgartner und Jäckli, 2007

Teilweise in klinischer Phase und erste Produkte schon am Markt

Product name	Drug	Indication	Route of injection	Nanoscale dimensions (nm)	Status
Lipovaxin-MM	Vaccine	Melanoma	Intravenous	240	Investigational
Liprostin	Prostaglandin	Peripheral vascular disease	Intravenous	100–200	Investigational
L-MTP-PE	L-MTP-PE	Osteosarcoma	Intravenous	710	Investigational
Marqibo	Vincristine	Solid tumors	Intravenous	100	Investigational
MBP-426	Oxaliplatin	Solid tumors	Intravenous	180	Investigational
MBP-Y003	Methotrexate	Lymphoma	Intravenous		Investigational
MBP-Y004	Docetaxel	Solid tumors	Intravenous		Investigational
MBP-Y005	Gemcitabine	Solid tumors	Intravenous		Investigational
MCC-465	Doxorubicin	Stomach cancer	Intravenous	143	Investigational
Myocet	Doxorubicin citrate	Breast cancer	Intravenous	190	Investigational
Nanocort	Prednisolone	Rheumatoid arthritis	Intravenous	<150	Investigational
NanoVNB	Vinorelbine	Colon cancer	Intravenous	95, 2	Investigational
ONCO-TCS™	Vincristine	Solid tumors	Intravenous	120	Investigational
OSI-211	Lurtotecan	Solid tumors	Intravenous	100–200	Investigational
PEP02	Irinotecan	Solid tumors	Intravenous	100	Investigational
PNT2258	Oligonucleotide	Cancer	Intravenous	100	Investigational
RVCLUV	Ropivacaine	Anesthetic	Intravenous	130	Investigational
SapC-DOPS	Saposin C	Solid tumors	Intravenous	190	Investigational
S-CKD602	Camptothecin analog	Advanced malignancies	Intravenous	100	Investigational
Stimuvax	BLP25 vaccine	Solid tumors	Intravenous	150–580	Investigational
ThermoDox	Doxorubicin, lyso-thermosensitive	Solid tumors	Intravenous	175	Investigational
TKM-ApoB	siRNA	Hypercholesterolemia	Intravenous	120	Investigational
TKM-Ebola	siRNA	Ebola	Intravenous		Investigational
TKM-PLK I	siRNA	Solid tumors	Intravenous		Investigational

Dimericine	T4N5	Precancerous condition	Topical	200	Investigational
Lip glucantime	Meglumine antimoniate	Cutaneous leishmaniasis	Topical	400	Investigational
NanoDOX™	Doxycycline monohydrate	Foot ulcer, diabetic	Topical	200–350	Investigational
T4N5 liposomal lotion	Bacteriophage T4 endonuclease 5	Skin cancers	Topical		Investigational
AeroLEF	Fentanyl	Pain relief	Aerosol		Investigational
Arikace	Amikacin	Cystic fibrosis	Aerosol	375	Investigational
L9NC	L9NC	Solid tumors	Aerosol	100–300	Investigational
VaxiSome	Vaccine	Influenza	Intramuscular		Investigational
CAF01	Vaccine	Tuberculosis	Intramuscular	450	Investigational
RTS S/AS02	FMP2.1/AS02A	Malaria	Intramuscular	20	Investigational
CFTR gene liposome	CFTR gene	Cystic fibrosis	Nasal		Investigational
OX-NLA	Cetirizine HCl	Allergic rhinitis	Nasal		Investigational
pGT-I gene liposome	pGT-I gene	Cystic fibrosis	Nasal		Investigational
DPX-0907	Cancer vaccine	Neoplasms	Subcutaneous		Investigational
I L-2 LI PO	Interleukin 2	Melanoma	Subcutaneous		Investigational
PLCLUV	Prilocaine	Dental anesthesia	Interstitial	400	Investigational
L-CsA	Cyclosporine	Bronchiolitis obliterans	Interstitial	40–50	Investigational
Telintra	TLK199 HCl	Myelodysplastic syndromes	Oral		Investigational

2015

1584 studies found for: liposome

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[List](#) | [By Topic](#) | [On a Map](#) | [Search Details](#)

+ Show Display Options

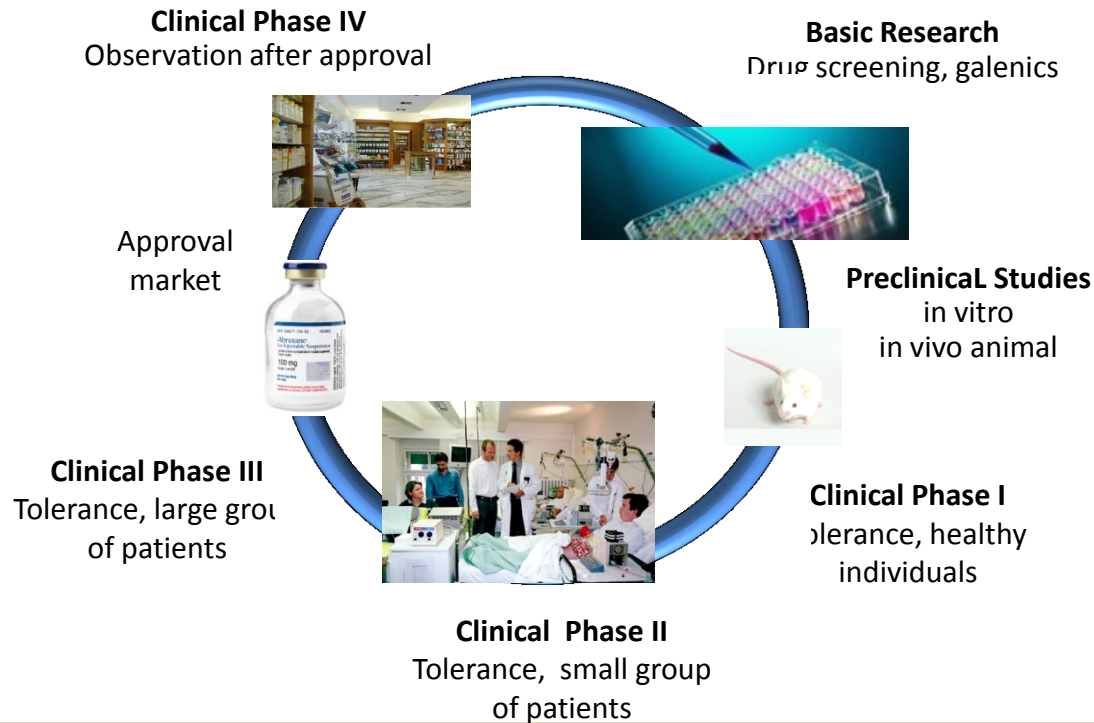
[Download](#) | [Subscribe to RSS](#)

Include only open studies Exclude studies with Unknown status

Rank	Status	Study
1	Active, not recruiting	Intravesical Liposomes for Interstitial Cystitis/Painful Bladder Syndrome (IC/PBS) Conditions: Interstitial Cystitis; Pelvic Pain Intervention: Biological: Liposomes
2	Recruiting	Dose Escalation and Pharmacokinetic Study of Paclitaxel Liposome Injection in Treating Patients With Advanced Solid Tumor After Failure From Conventional Treatments Condition: Solid Tumors Interventions: Drug: Paclitaxel liposome injection; Drug: Paclitaxel injection
3	Not yet recruiting	Vincristine Sulfate Liposome in Treating Patients With Relapsed or Refractory Acute Myeloid Leukemia Condition: Recurrent Adult Acute Myeloid Leukemia Interventions: Drug: Vincristine Sulfate Liposome; Other: Laboratory Biomarker Analysis
4	Active, not recruiting	AMG386 Comb w. Either Pegylated Liposomal Doxorubicin or Topotecan Subjects w. Advanced Recurrent Epithelial Ovarian CR Conditions: Cancer; Carcinoma; Fallopian Tube Cancer; Gynecological Malignancies; Metastases; Oncology; Ovarian Cancer; Solid Tumors; Tumors Interventions: Drug: A1: AMG 386 10 mg/kg + Liposomal doxorubicin; Drug: A3: AMG 386 15mg/kg + Liposomal doxorubicin; Drug: B1: AMG 386 10 mg/kg + Topotecan; Drug: B3: AMG 386 15mg/kg + Topotecan
5	Recruiting	Assess Bioequivalence of Two Formulations of Doxorubicin Hydrochloride Liposome in Female Patients With Ovarian Cancer Condition: Ovarian Cancer Intervention: Drug: Doxorubicin hydrochloride liposome
6	Recruiting	Intravesical Instillation of Liposome Encapsulated Botulinum Toxin A (Lipotoxin) in Treatment of Interstitial Cystitis Condition: Interstitial Cystitis Interventions: Drug: Liposome encapsulated BoNT-A; Drug: BOTOX 200U in normal saline; Drug: Normal saline
7	Completed	Phase I and Pharmacokinetic Study of Mitoxantrone Hydrochloride Liposome Injection Condition: Neoplasms Interventions: Drug: Mitoxantrone Hydrochloride Liposome; Drug: Mitoxantrone

Nanomedizin von „bench to bedside“

Vom Labor zur Klinik bis zum Market rechnet man mit 10-16 Jahren



Search /Optimization
of a drug

Preclinical
Phase

Clinical
Phase I

Clinical
Phase II

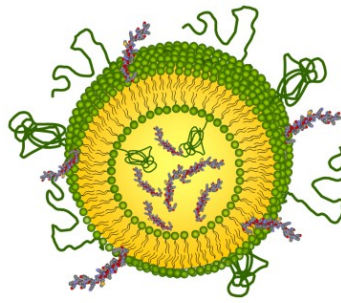
Clinical
Phase III

Marketing
Production

Nanomedicine Start-ups

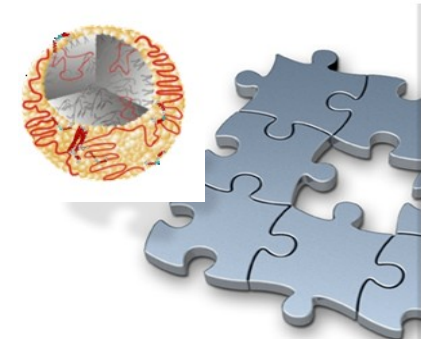
Pharmaceutical Industry

Acknowledgements



Medical University of Graz

NANO MEDICINE
INSTITUTE OF BIOPHYSICS



OAW
Austrian Academy
of Sciences

FWF

nano
HEALTH



FFG

