Jenseits von First in Man - herkömmliche und innovative Phase I Studien am Menschen

MEDICAL UNIVERSITY OF VIENNA

Markus Zeitlinger

Department of Clinical Pharmacology

PK/PD

Mass balance

Biosimilars

Dose-Response

Special population

ADME

Impaired excretion

DDI

Adverse event

Challenge Test

Biomarker

Come, let us go down and confuse their language so they will not understand each other.
Genesis 11,7

Definition Phase 1

Phase	Aim	Notes
Phase 0	Pharmacodynamics and pharmacokinetics in humans	Phase 0 trials are the first-in-human trials. Single subtherapeutic doses of the study drug or treatment are given to a small number of subjects (10 to 15) to gather preliminary data on the agent's pharmacodynamics (what the drug does to the body) and pharmacokinetics (what the body does to the drugs).[30] For a test drug, the trial documents the absorption, distribution, metabolization, and removal (excretion) of the drug, and the drug's interactions within the body, to confirm that these appear to be as expected.
Phase 1	Screening for safety.	Testing within a small group of people (20–80) to evaluate safety, determine safe dosage ranges, and begin to identify side effects. A drug's side effects could be subtle or long term, or may only happen with a few people, so phase 1 trials are not expected to identify all side effects.
Phase 2	Establishing the efficacy of the drug, usually against a placebo.	Testing with a larger group of people (100–300) to see if it is effective and to further evaluate its safety. The gradual increase in test group size allows less-common side effects to be progressively sought.
Phase 3	Final confirmation of safety and efficacy.	Testing with large groups of people (1,000–3,000) to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow it to be used safely.
Phase 4	Safety studies during sales.	Postmarketing studies delineate additional information, including the treatment's risks, benefits, and optimal use. As such, they are ongoing during the drug's lifetime of active medical use. (Particularly relevant after approval under FDA Accelerated Approval Program)

https://en.wikipedia.org/wiki/Clinical_trial

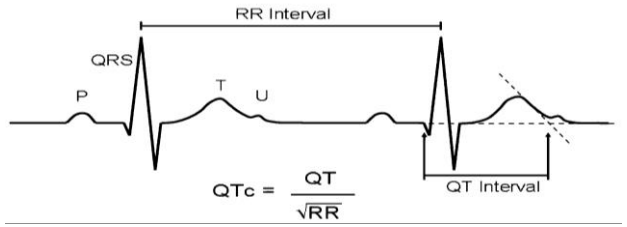
Definition Phase 1 cont.

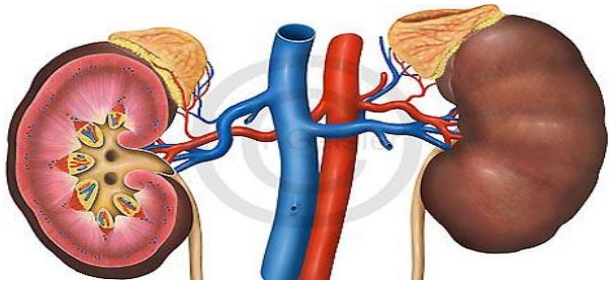
Summary of clinical trial phases					
Phase	**Primary goal**	**Dose**	**Patient monitor**	**Typical number of participants**	**Notes**
Preclinical	Testing of drug in non-human subjects, to gather efficacy, toxicity and pharmacokinetic information	unrestricted	A graduate level researcher (Ph.D.)	not applicable (*in vitro* and *in vivo* only)	
Phase 0	Pharmacodynamics and Pharmacokinetics particularly oral bioavailability and half-life of the drug	very small, subtherapeutic	clinical researcher	10 people	often skipped for phase I
Phase I	Testing of drug on healthy volunteers for dose-ranging	often subtherapeutic, but with ascending doses	clinical researcher	20-100	determines whether drug is safe to check for efficacy
Phase II	Testing of drug on patients to assess efficacy and safety	therapeutic dose	clinical researcher	100-300	determines whether drug can have any efficacy; at this point, the drug is not presumed to have any therapeutic effect whatsoever
Phase III	Testing of drug on patients to assess efficacy, effectiveness and safety	therapeutic dose	clinical researcher and personal physician	1000-2000	determines a drug's therapeutic effect; at this point, the drug is presumed to have some effect
Phase IV	Postmarketing surveillance – watching drug use in public	therapeutic dose	personal physician	anyone seeking treatment from their physician	watch drug's long-term effects

https://en.wikipedia.org/wiki/Phases_of_clinical_research

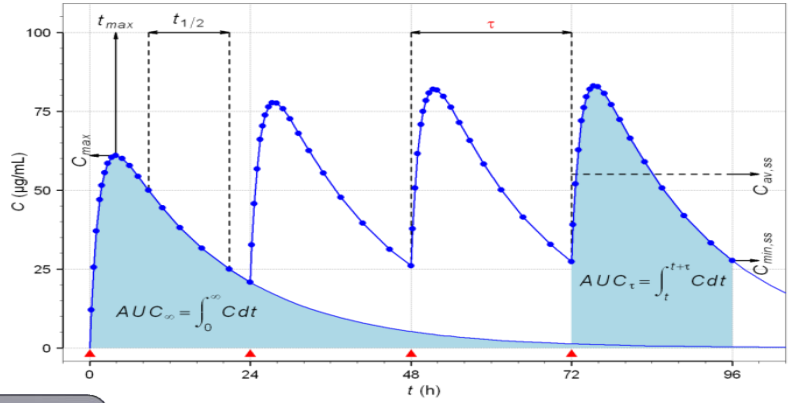
Arten von Phase 1 Studien

- FIM* Study
  - Single dose escalation
  - Multiple dose escalation
- Excretion and metabolism
  - Mass balance studies
  - Renal impairment
  - Hepatic impairment
- QTc study
- “Special PK studies”
- Drug interaction
  - With other drugs
  - With combination (BLI*)





Work flow in einer FIM studie



shipment

Study days Cohort 1

PK analysis

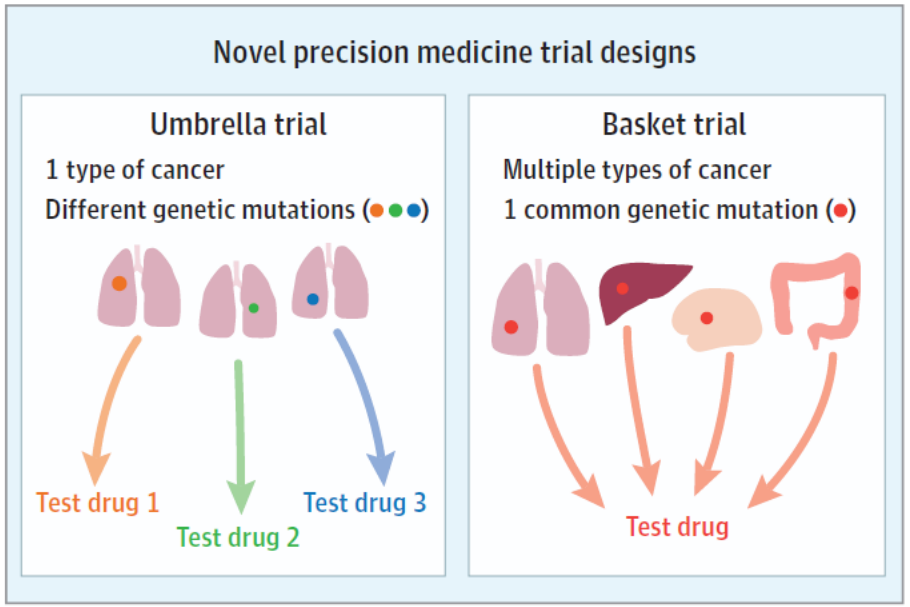
Data entry

Screening next subjects

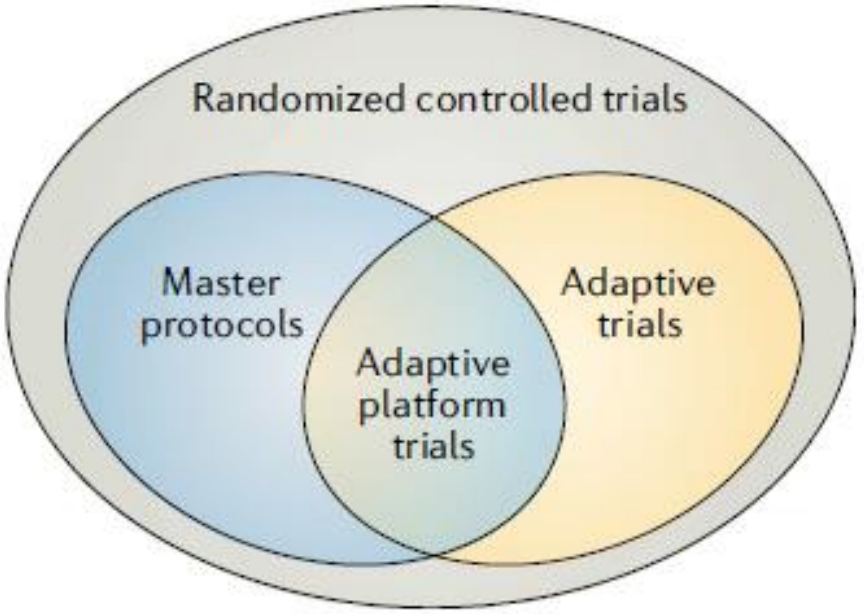
RBC

Study days Cohort 2

Komplexe Designs?



West H. JAMA Oncology 2017



Adaptive platform trials. Nature Reviews Drug Discovery 2019

Basket trial design for a first-in-human trial

- design that facilitates the transition from phase Ia in healthy volunteers to phase Ib in patients with rare complement-mediated disorders
- TNT009, a humanized monoclonal antibody directed against the C1s subunit of human complement
  - bullous pemphigoid
  - antibody-mediated rejection of organ transplants
  - cold agglutinin disease
  - warm autoimmune hemolytic anemia

Derhaschnig et al. Orphanet Journal of Rare Diseases (2016) 11:134

Basket trial design for a first-in-human trial

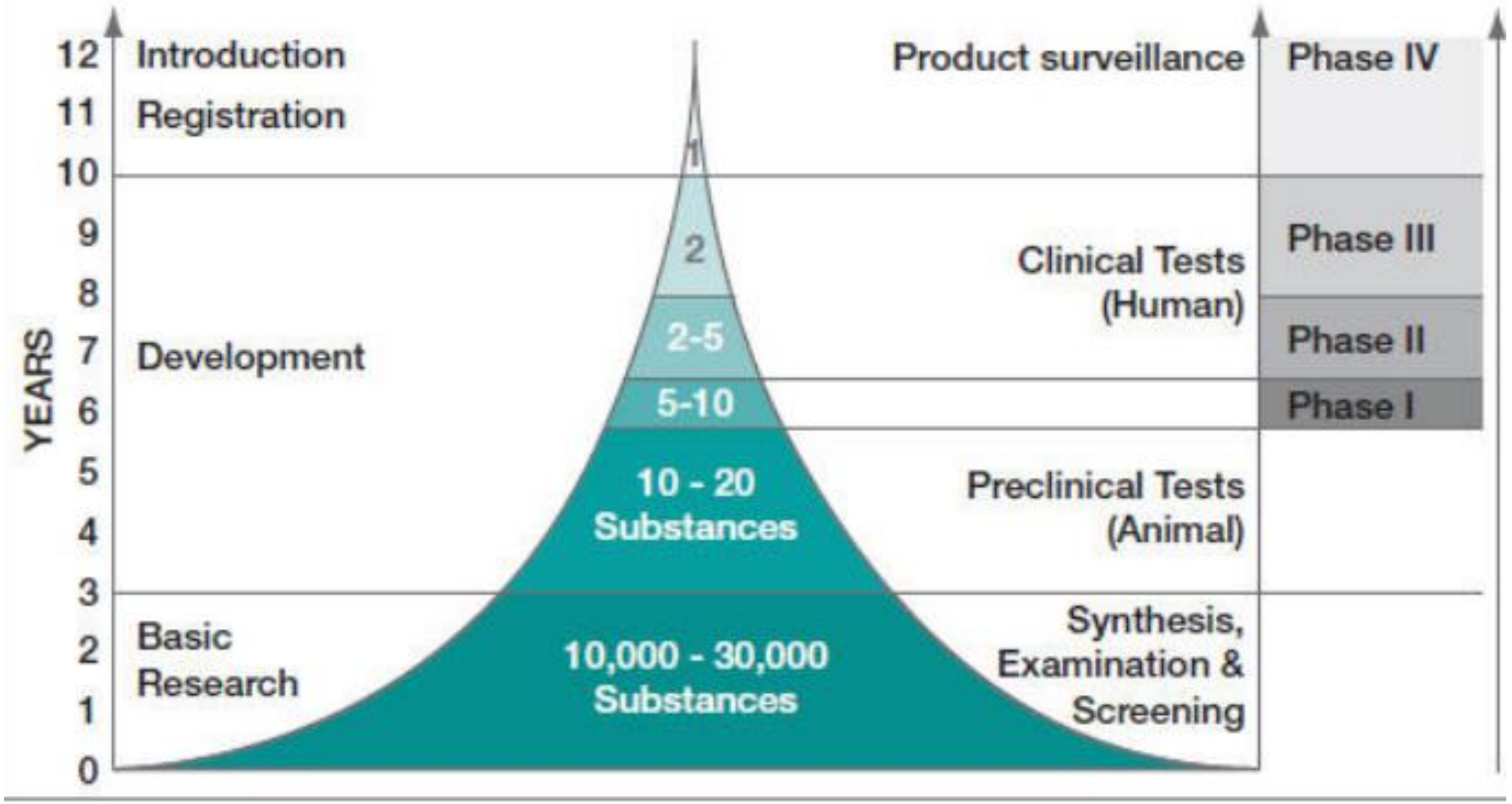
	Population	Cohort (mg/kg)	Dosed w/ TNT009	Dosed w/ Placebo
Ph 1a SAD	NHV	0.3	3	1
		1	3	1
		3	6	2
		10	6	2
		30	6	2
		60	6	2
		100	6	2
Ph 1a MAD	NHV	30, 30, 30, 30	6	2
		60, 60, 60, 60	6	2
Ph 1b MD	CAD	10, 60, 60, 60, 60	5	-
	wAIHA	10, 60, 60, 60, 60	0	-
	BP	10, 60, 60, 60, 60	4	-
	Late AMR	10, 60, 60, 60, 60	7	-

- basket trials may not be limited to single genetic aberrations
- but pathway specificity is a viable paradigm for defining baskets

Derhaschnig et al. Orphanet Journal of Rare Diseases (2016) 11:134
Mühlbacher et al. Transplantation. 2017 Oct;101(10):2410-2418.

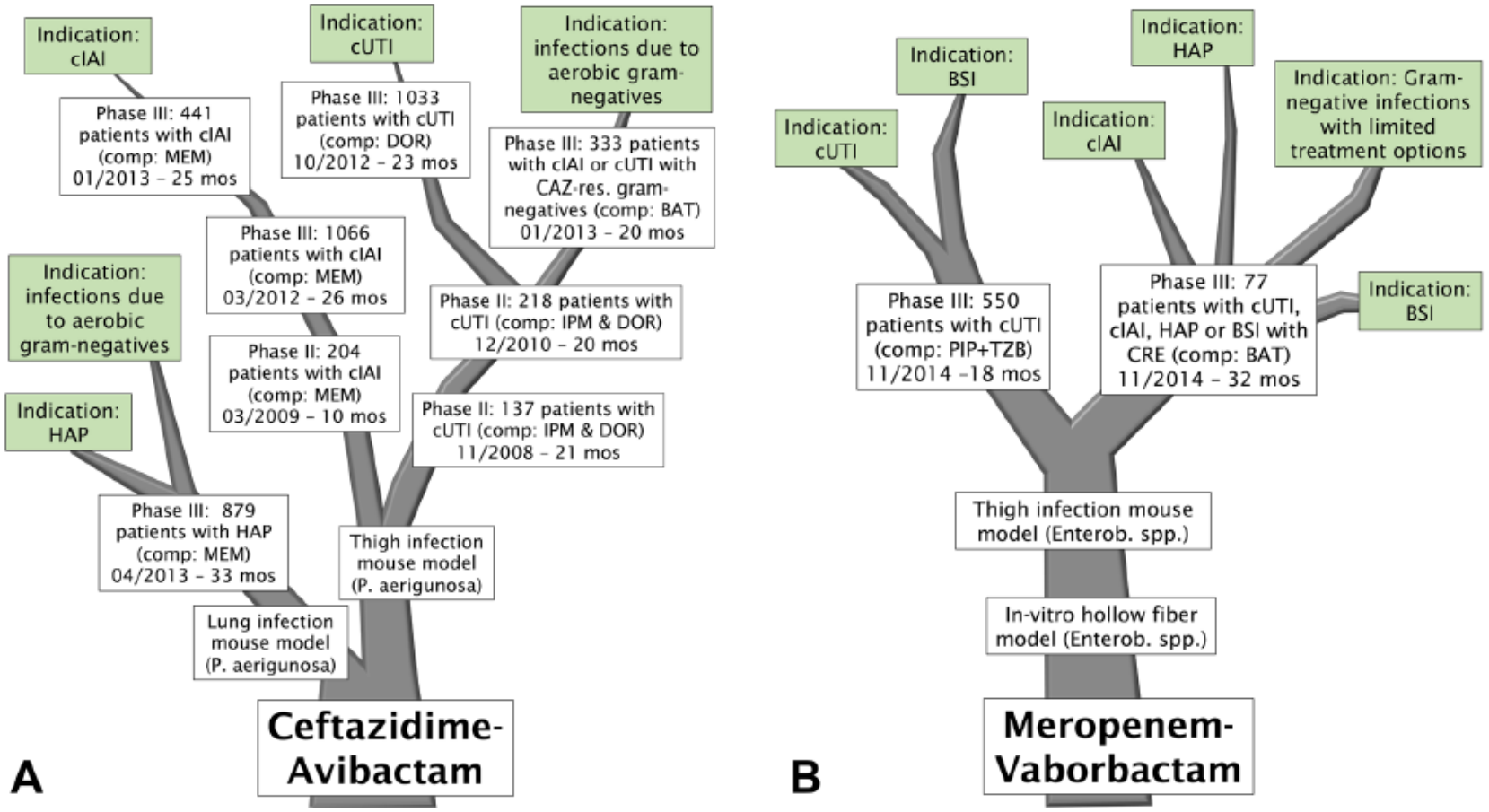
- Backbone der Zulassung
- Topische Phase 1 Studien
- Bioequivalenz spezial
- Imaging als PK und PD tool

Backbone der Zulassung



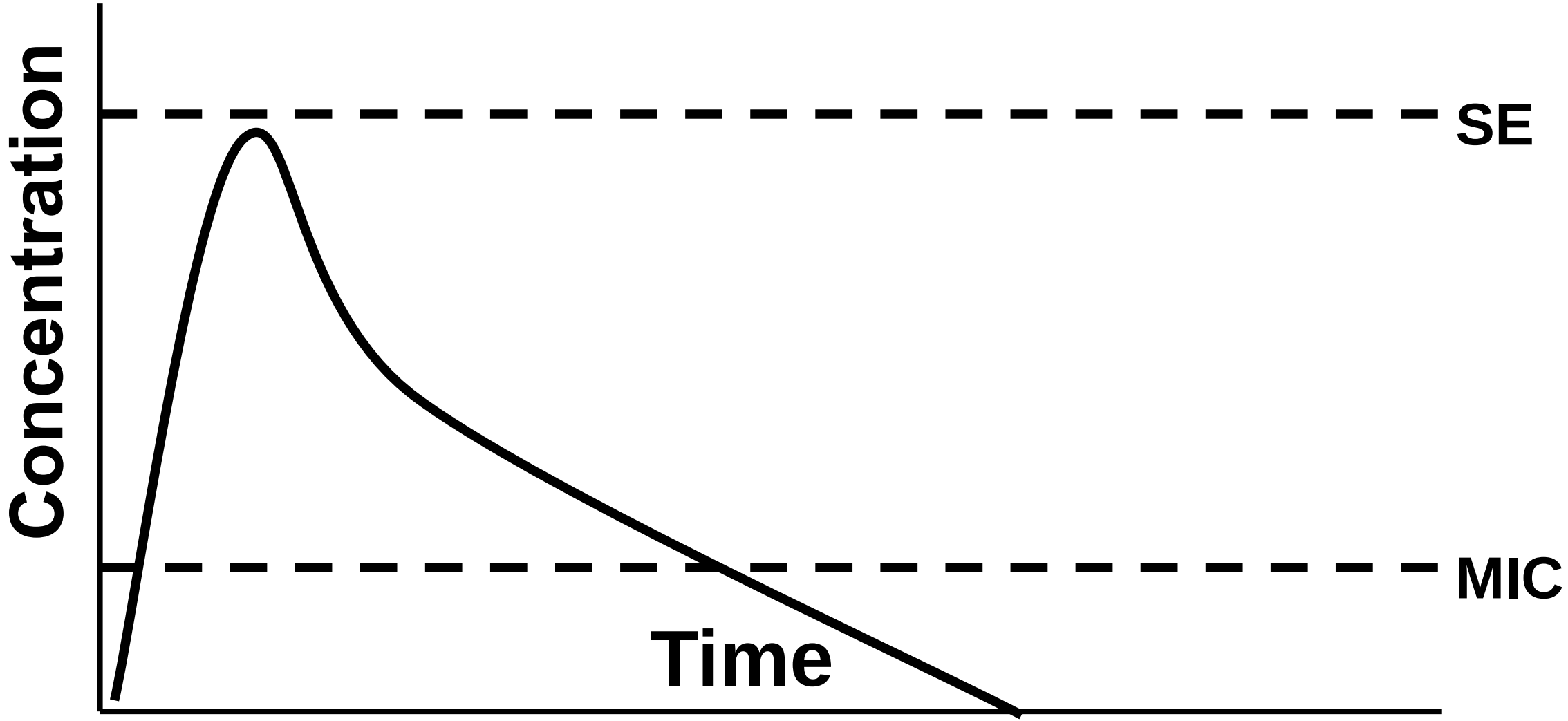
Krammer, F. *Nature* **586**, 516–527 (2020).

Preclinical PK/PD Studies and Clinical Trials in Antibiotic Development

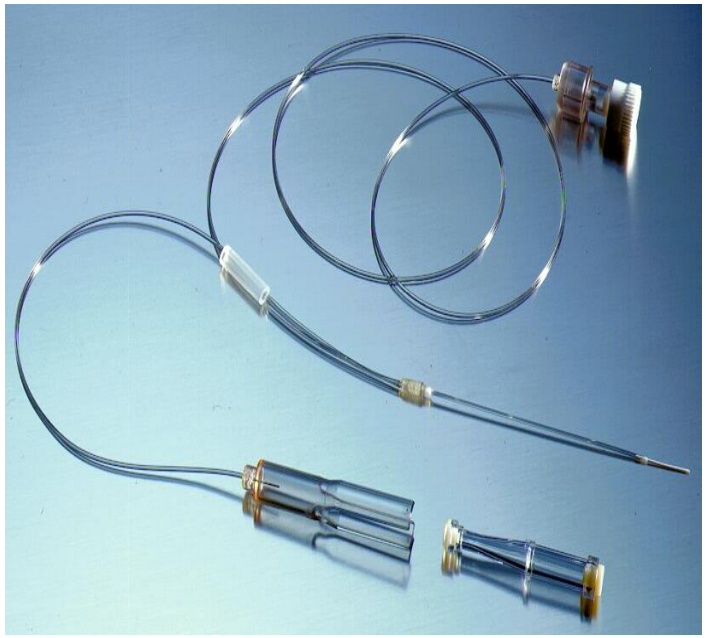


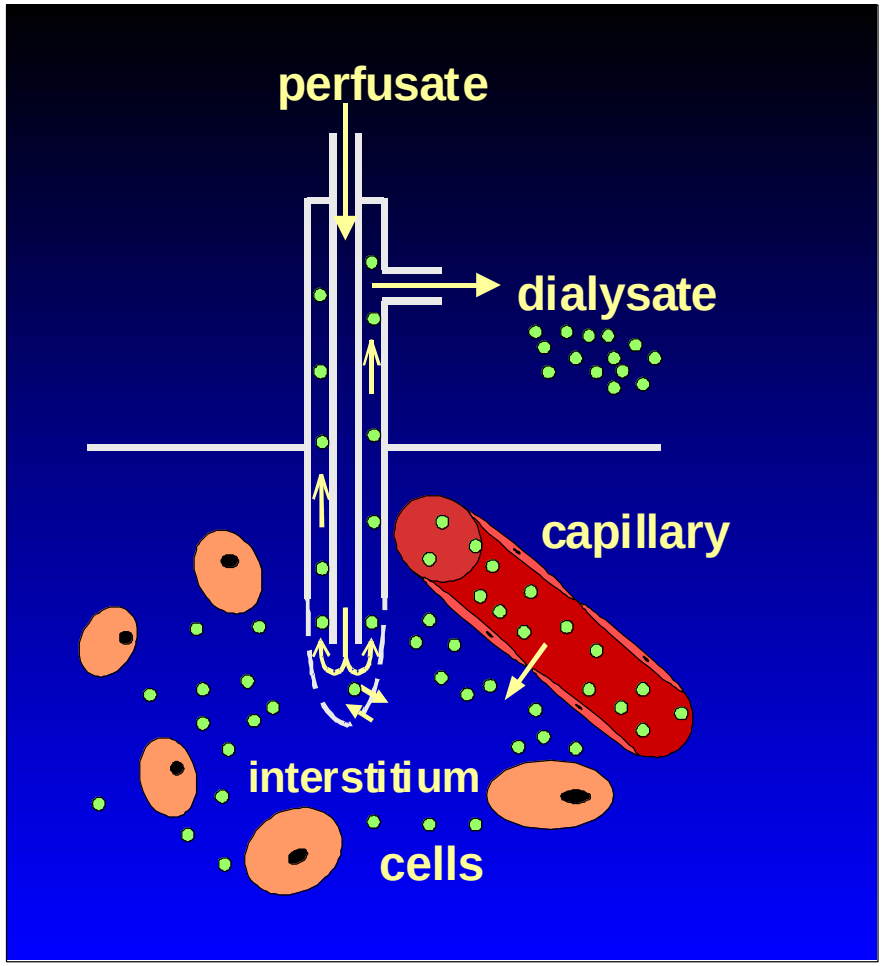
Jorda A, Zeitlinger M. Clin Pharmacokinet. 2020 Sep;59(9):1071-1084.

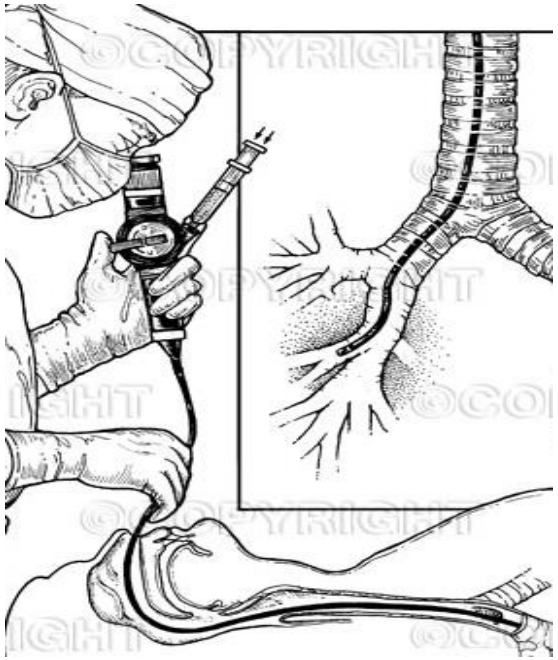
PK/PD



Tissue PK







Pleuromutilin (lefamulin)
Plasma, soft tissues and pulmonary epithelial lining fluid

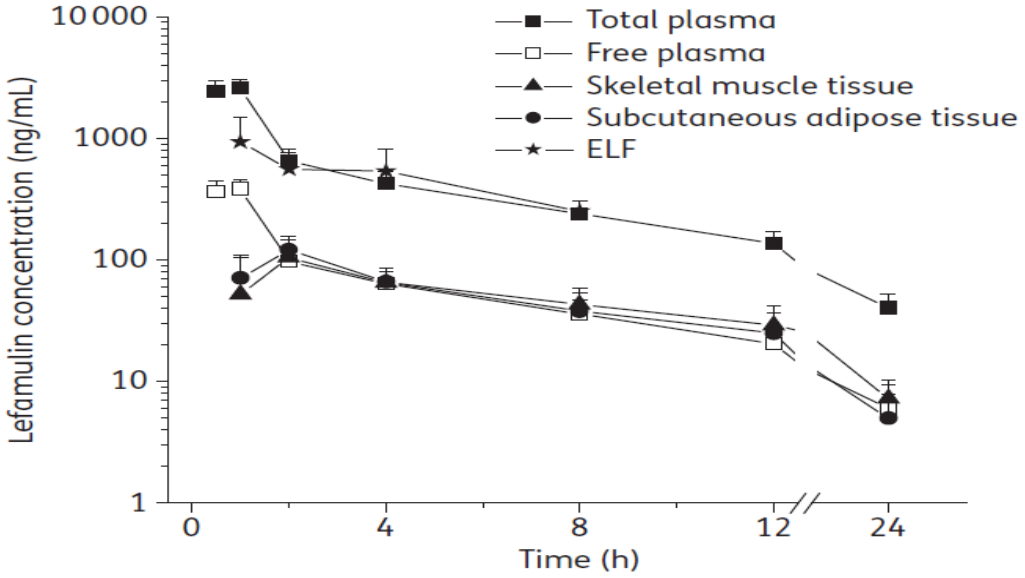


Figure 1. Mean ± standard deviation concentration–time curves of lefamulin in plasma ($n=12$), skeletal muscle tissue ($n=10$), subcutaneous adipose tissue ($n=8$) and ELF ($n=3$) after intravenous administration of 150 mg of lefamulin over 1 h. For free plasma concentrations, a protein-unbound fraction of 13% was estimated and used for calculations.

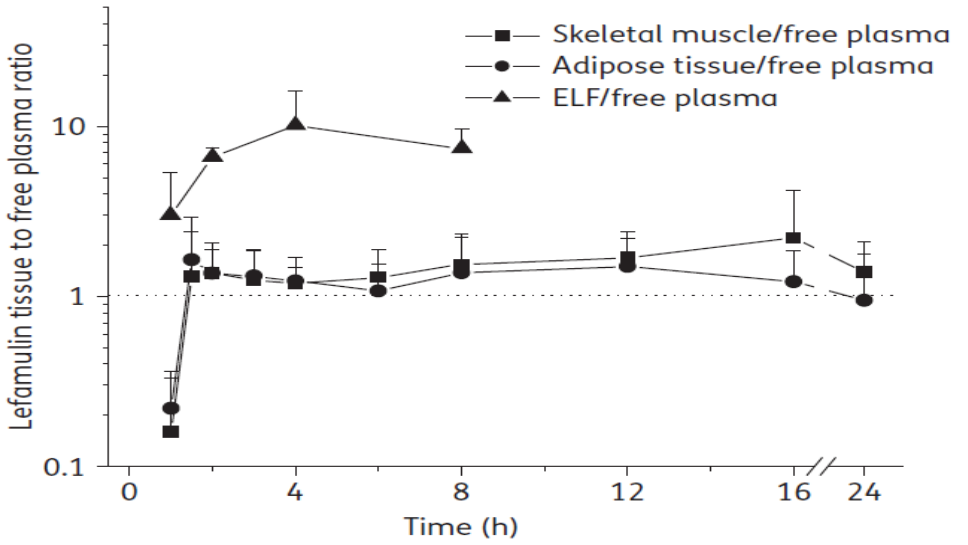


Figure 2. Ratios of lefamulin concentrations in skeletal muscle tissue, adipose tissue and ELF compared with free plasma concentrations over time. Values >1 describe concentrations exceeding free lefamulin concentrations achieved in plasma.

Zeitlinger M. J Antimicrob Chemother 2016

AMR ACCELERATOR – AB Direkt

Development of Gepotidacin for a niche indication

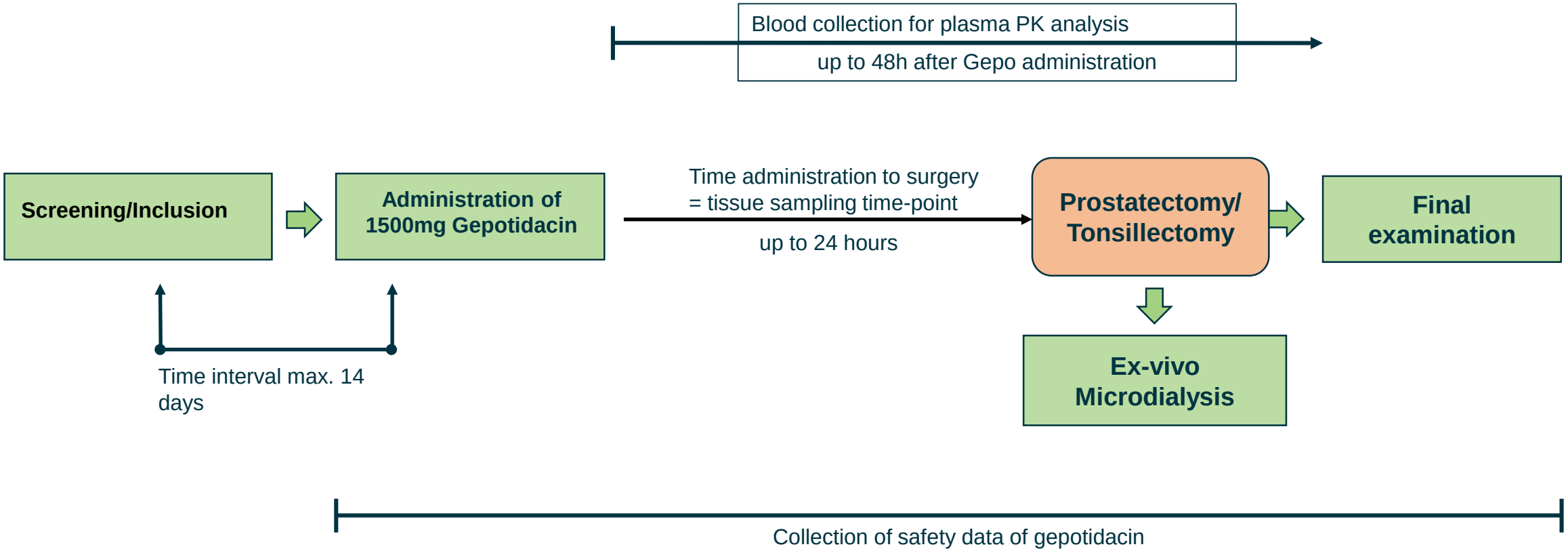
Primary Objectives

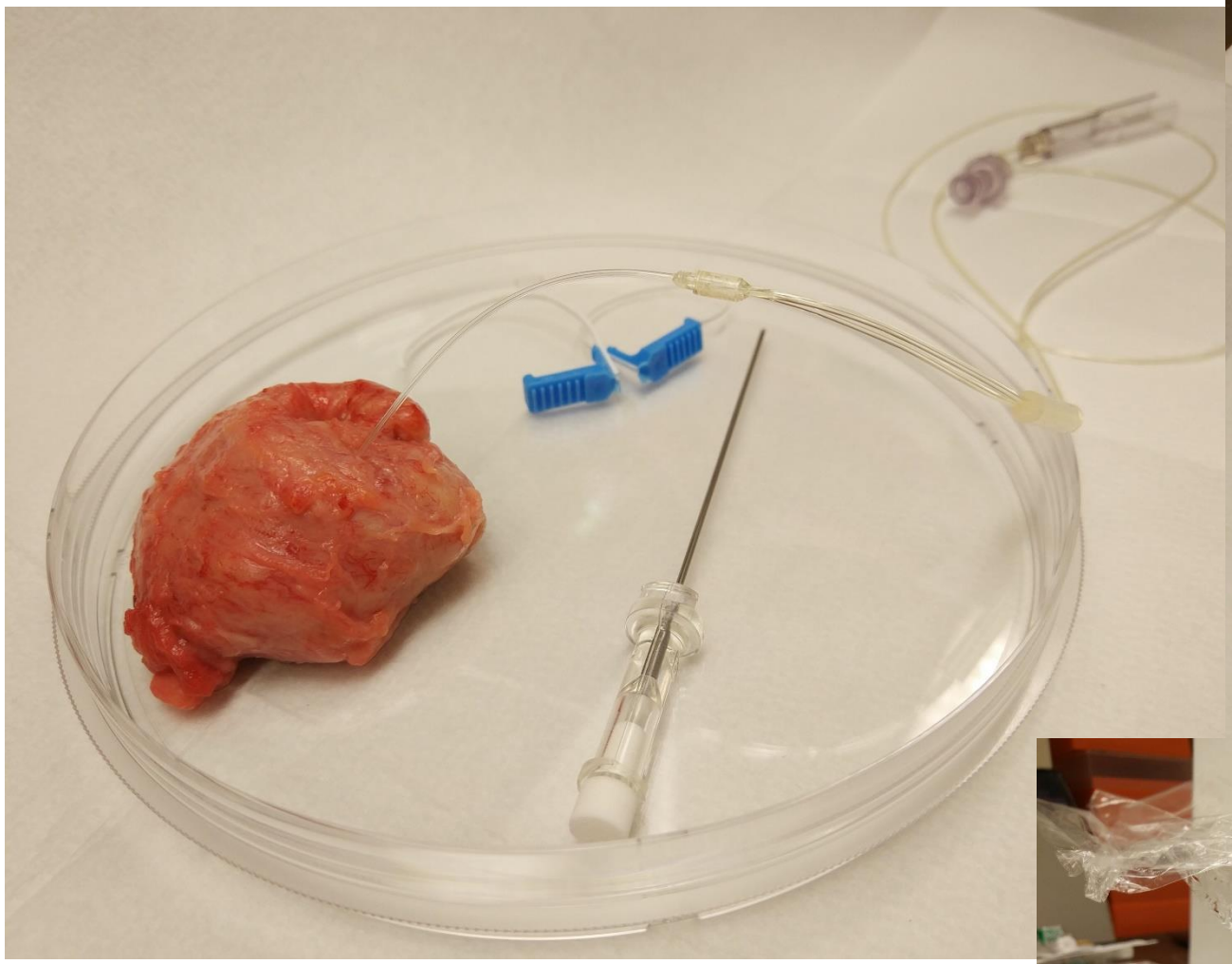
- determine the pharmacokinetic profile of gepotidacin
  - in plasma
  - tonsillar tissue
  - prostatic tissue

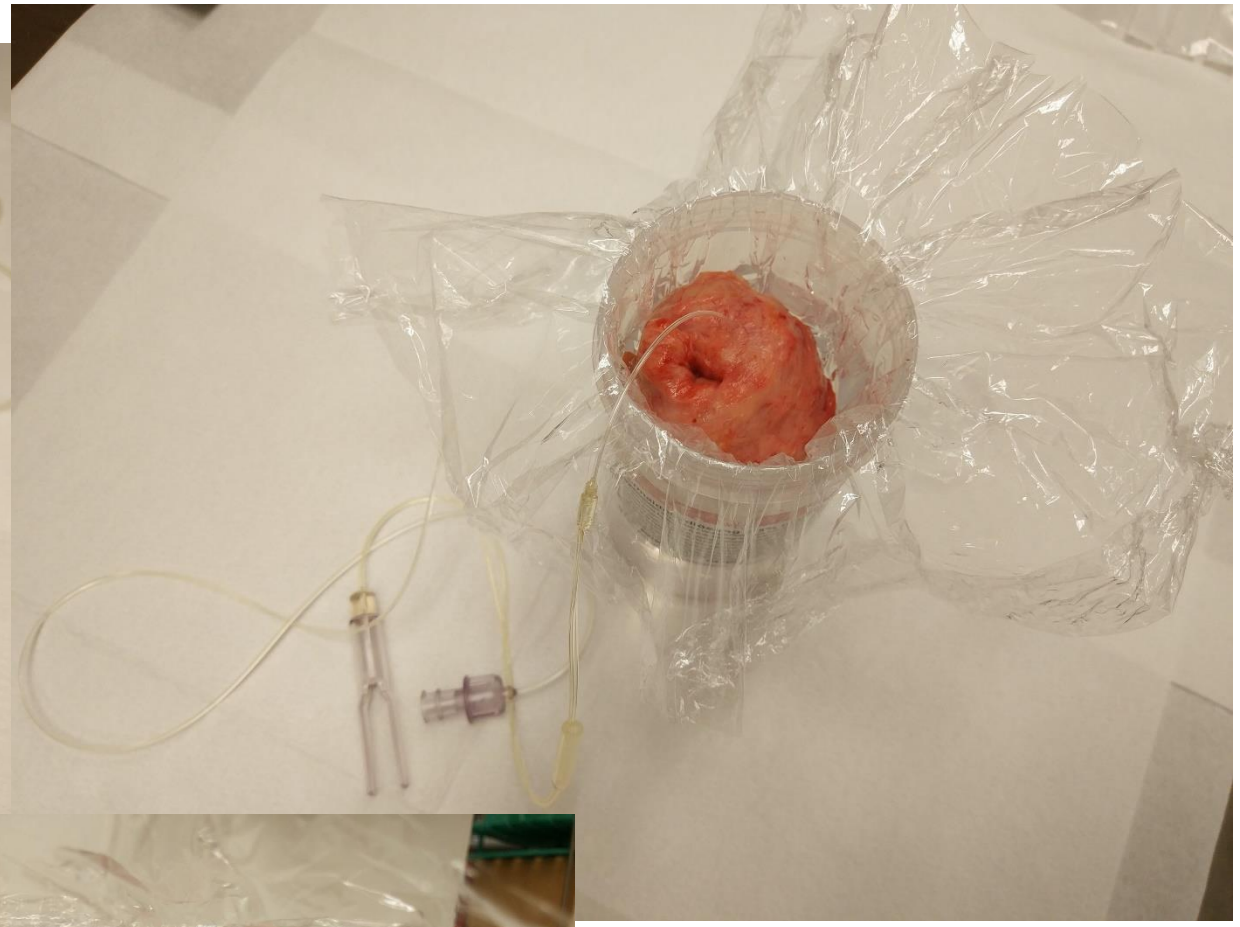
Secondary Objectives

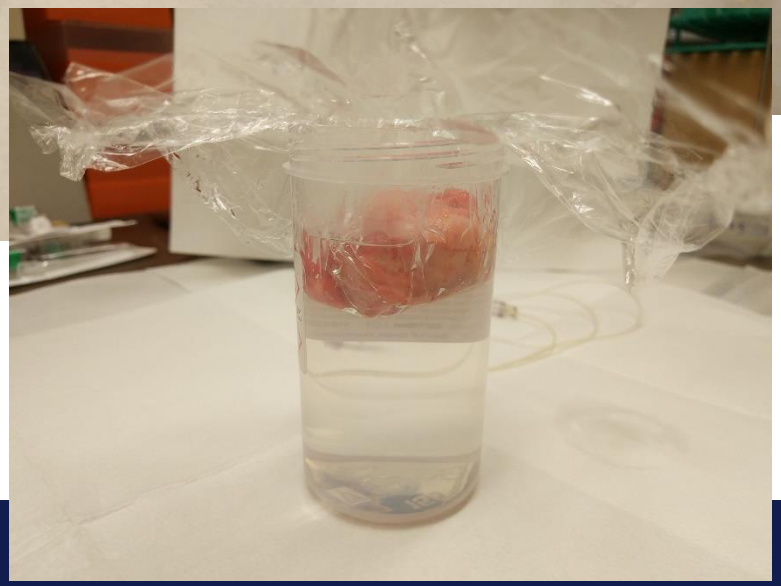
- Pharmacokinetic/pharmacodynamic (PK/PD) calculations in relation to common pathogens and possible breakpoints.

Study flow chart

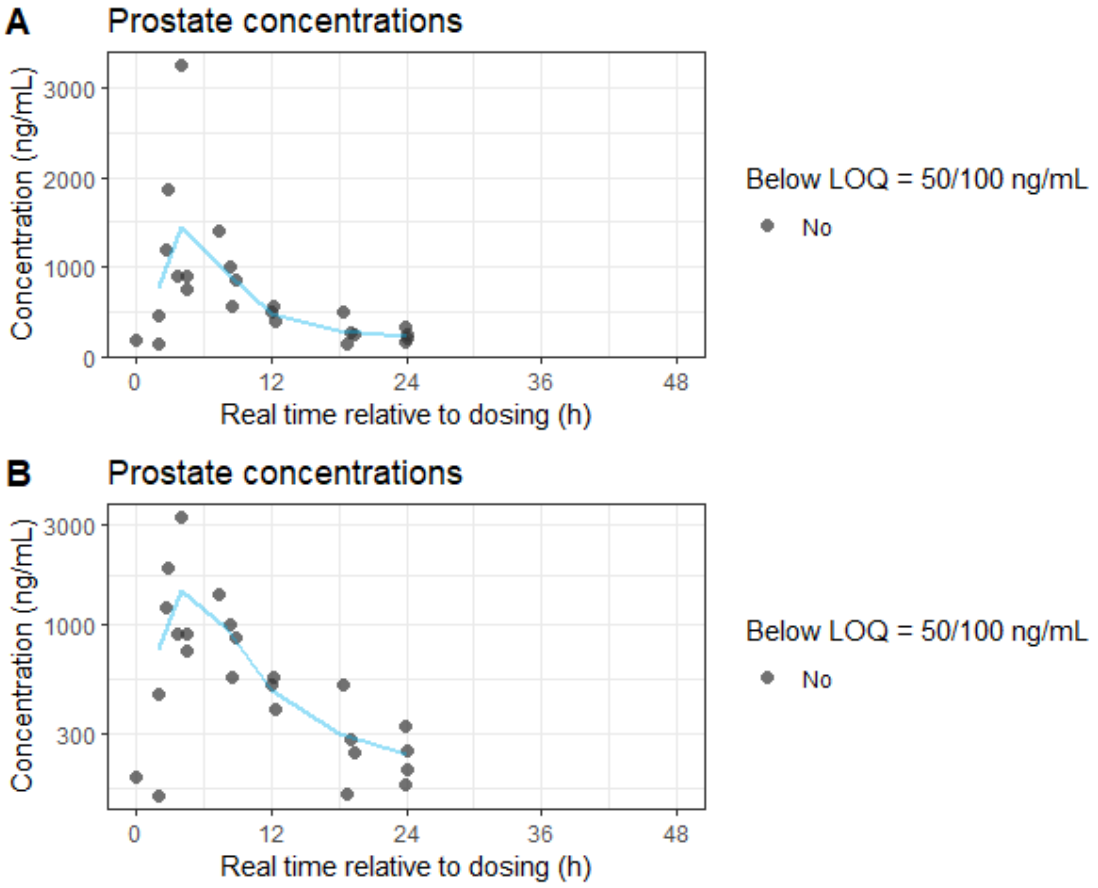


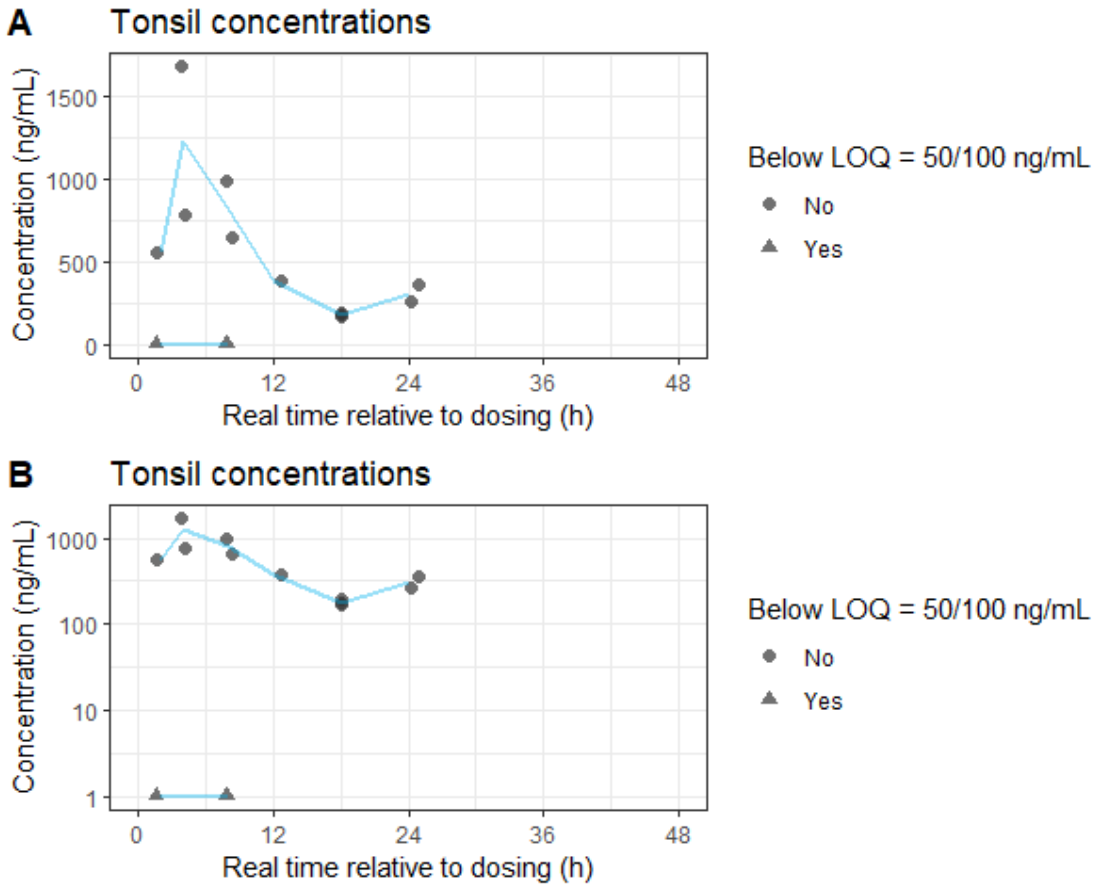






Pharmacokinetic data prostate





Mikrodosing

- ICH guideline M3(R2) on non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals

Table 3: Recommended Non-Clinical Studies to Support Exploratory Clinical Trials:

Clinical:		**Non clinical:**		
Dose to be Administered	**Start and Maximum Doses**	**Pharmacology**	**General Toxicity Studies[a]**	**Genotoxicity[b] / Other**
Approach 1: Total dose ≤ 100 µg (no inter-dose interval limitations) AND Total dose ≤ 1/100th NOAEL and ≤1/100th pharmacologically active dose (scaled on mg/kg for *i.v.* and mg/m^2 for oral)	Maximal and starting doses can be the same but not exceed a total accumulated dose of 100 µg	*In vitro* target/ receptor profiling should be conducted Appropriate characterization of primary pharmacology (mode of action and/or effects) in a pharmacodynamically relevant model should be available to support human dose selection.	Extended single dose toxicity study (see footnotes c and d) in one species, usually rodent, by intended route of administration with toxicokinetic data, or via the *i.v.* route. A maximum dose of 1000-fold the clinical dose on a mg/kg basis for *i.v.* and mg/m^2 for oral administration can be used.	Genotoxicity studies are not recommended, but any studies or SAR assessments conducted should be included in the clinical trial application. For highly radioactive agents (e.g. PET imaging agents), appropriate PK and dosimetry estimates should be submitted.

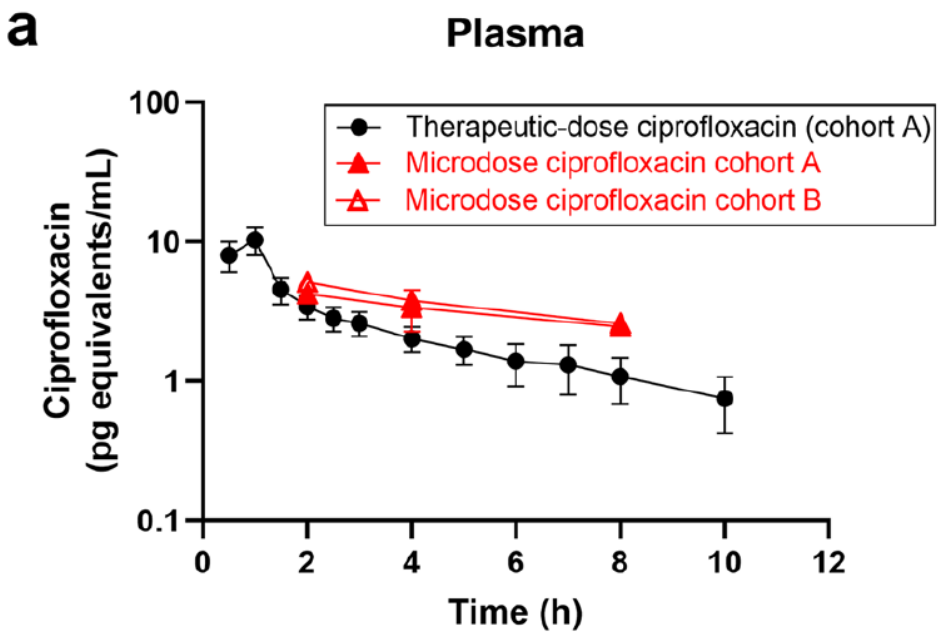
EMA/CPMP/ICH/286/1995

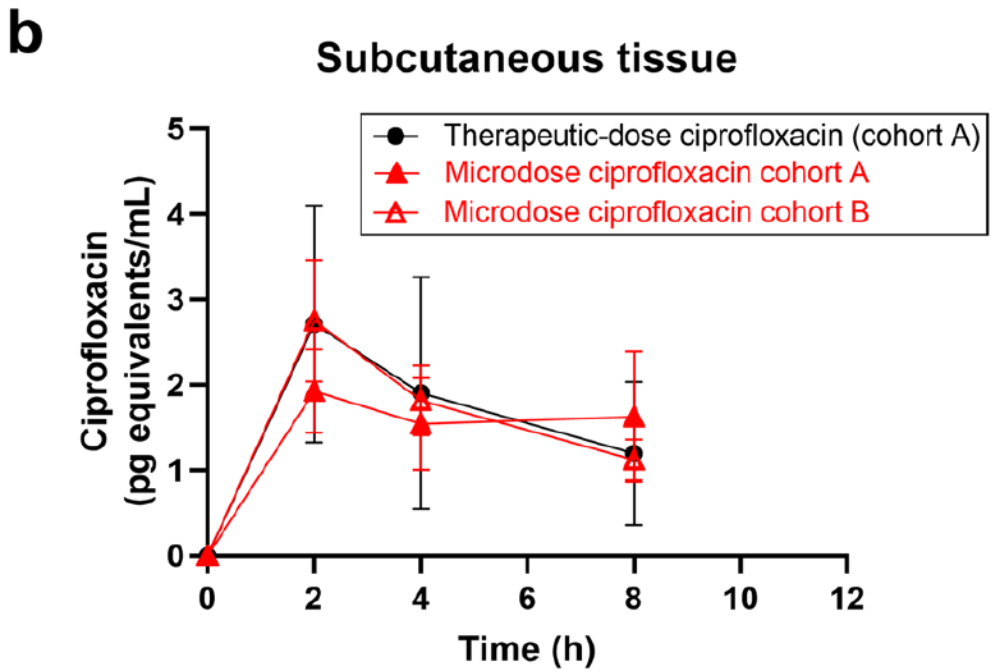
Clinical Pharmacokinetics (2022) 61:697–707
https://doi.org/10.1007/s40262-021-01091-1

ORIGINAL RESEARCH ARTICLE

Microdosing as a Potential Tool to Enhance Clinical Development of Novel Antibiotics: A Tissue and Plasma PK Feasibility Study with Ciprofloxacin

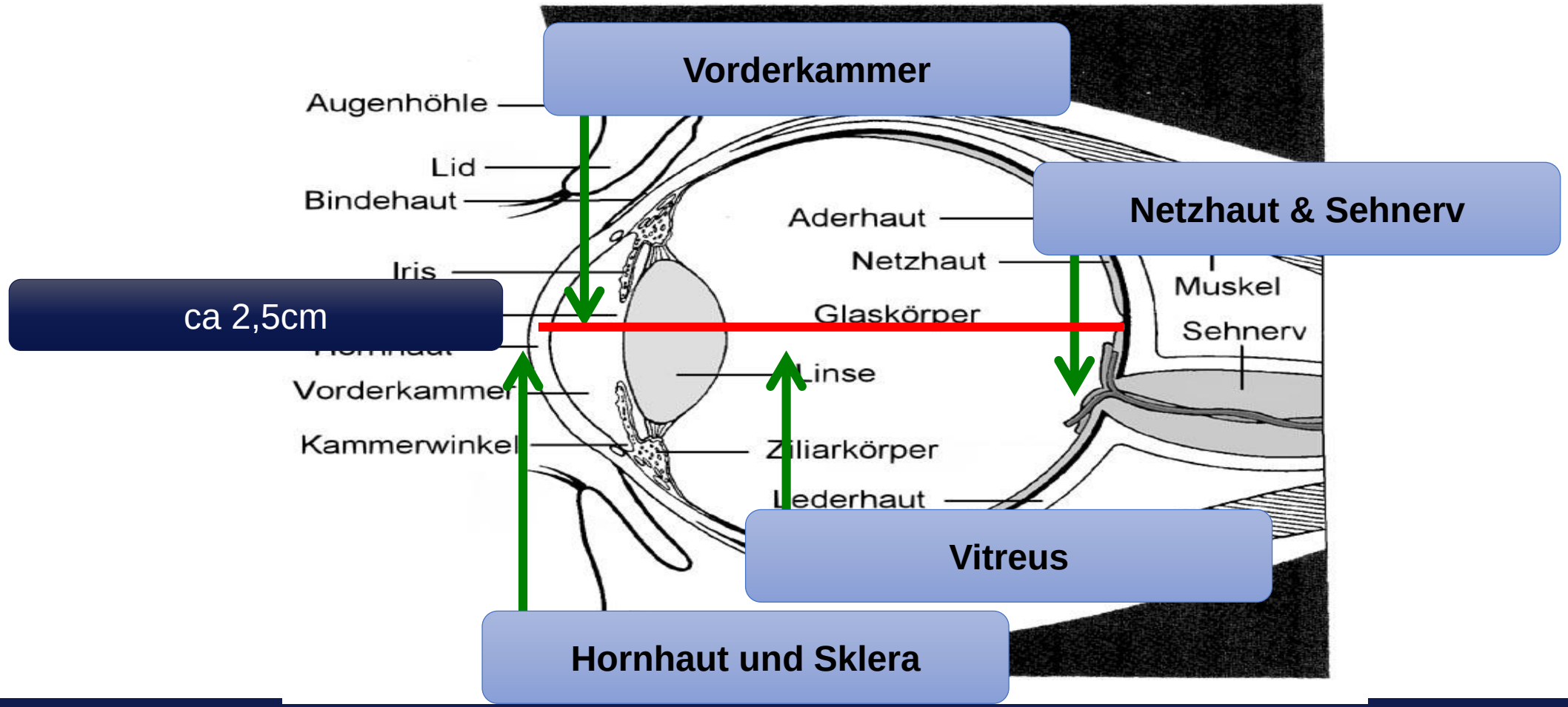
Zoe Oesterreicher[1,2] · Sabine Eberl[1] · Beatrix Wulkersdorfer[1] · Peter Matzneller[1] · Claudia Eder[1] · Esther van Duijn[3] · Wouter H. J. Vaes[3] · Birgit Reiter[4] · Thomas Stimpfl[4] · Walter Jäger[5] · Alina Nussbaumer-Proell[1] · Daniela Marhofer[6] · Peter Marhofer[6,7] · Oliver Langer[1] · Markus Zeitlinger[1]





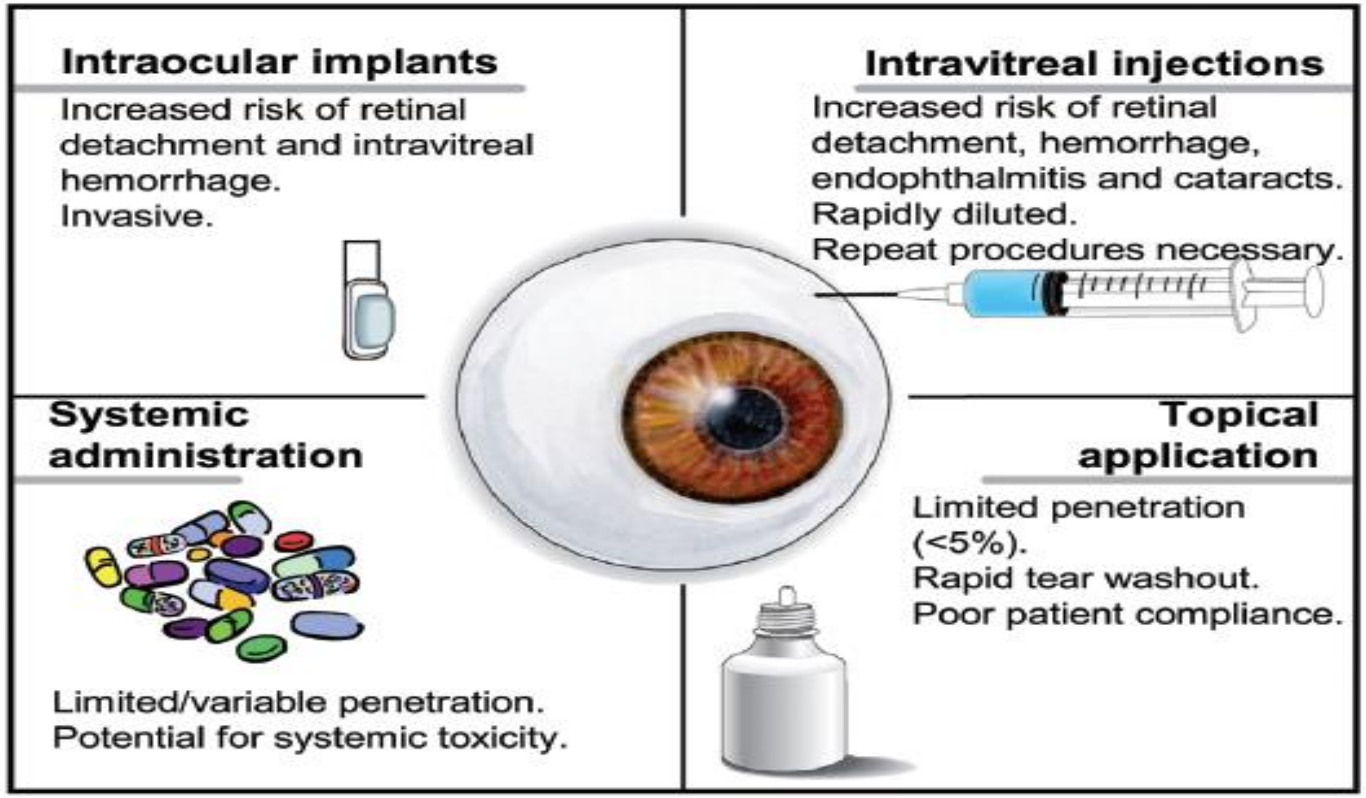
Topische Phase 1 Studien

Augenheilkunde: Pharmakologische Interventionsmöglichkeiten



Arzneimitteltherapie in der Ophthalmologie

- 90 % topische Verabreichung (Bourlais CL et al 1998)

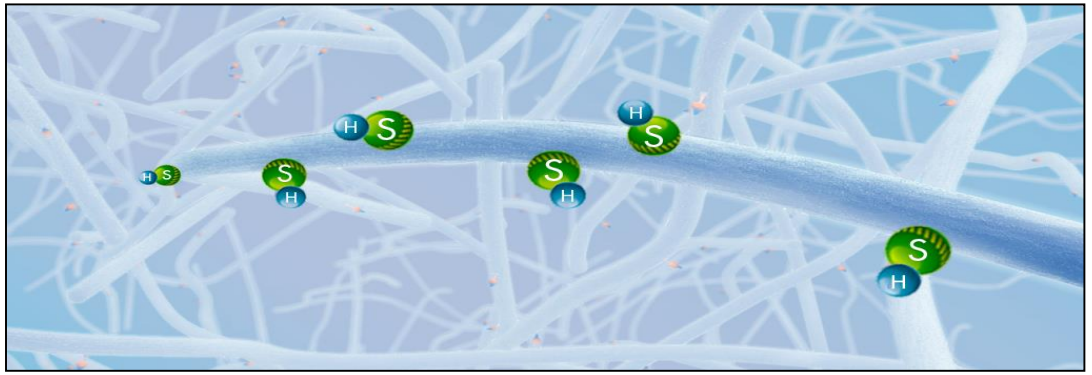


Herausforderungen der topischen Arzneimitteltherapie am Auge

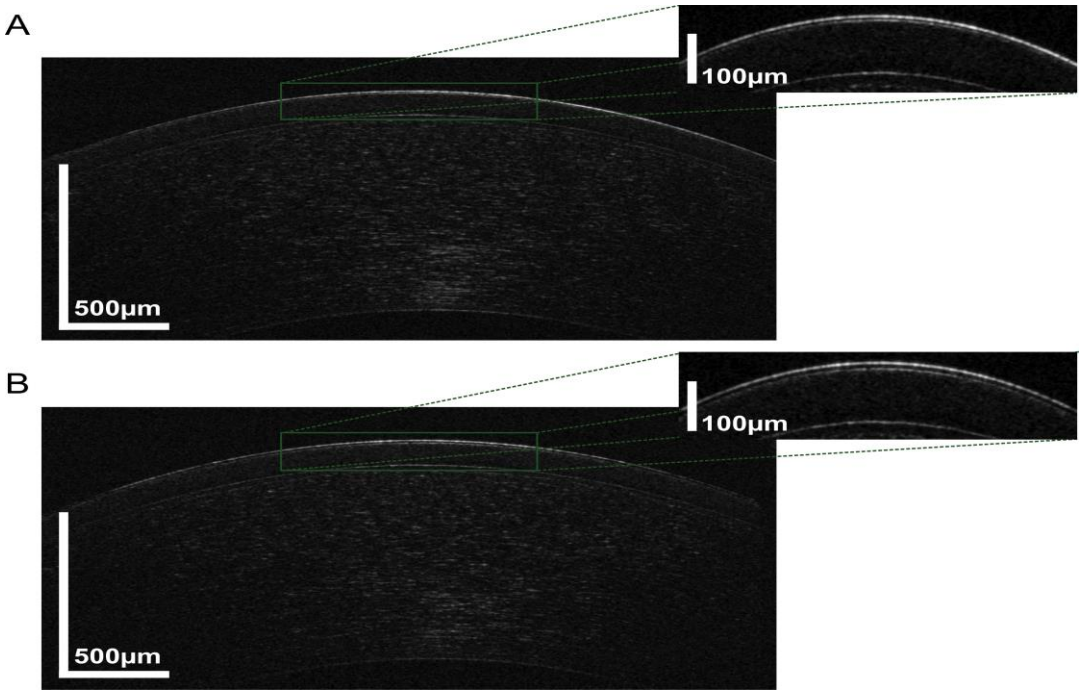
- Kurze Verweilzeiten der Pharmaka an der Augenoberfläche
- Schlechte Penetration durch die Augenoberfläche
- Toxizität von Konservierungsmitteln
- Schwer erfassbare Pharmakokinetik im Menschen

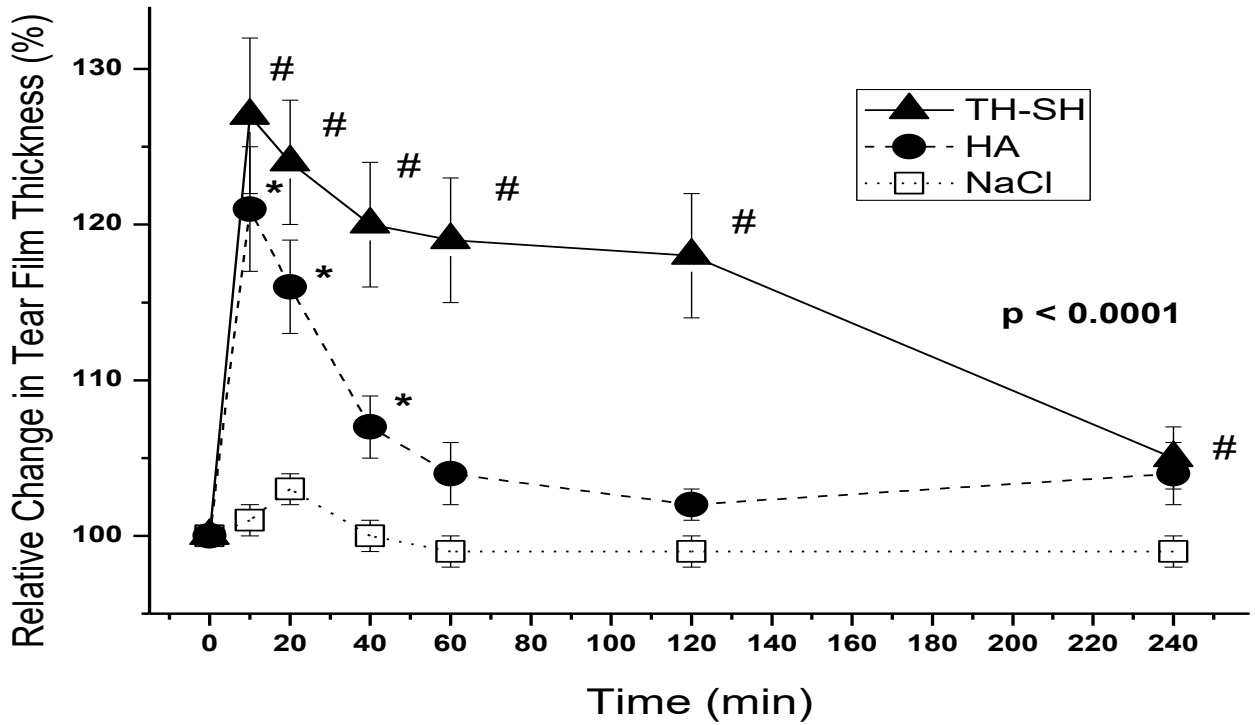
Erhöhung der Verweilzeit an der Augenoberfläche

- Erhöhung der Viskosität, Verwendung von Salben
- Kopplung an hochmolekulare Biopolymere
  - Hyaluronsäuren
  - Polyacrylsäuren
  - Chitosan-N-Acetylcystein
- Thiomer Technologie



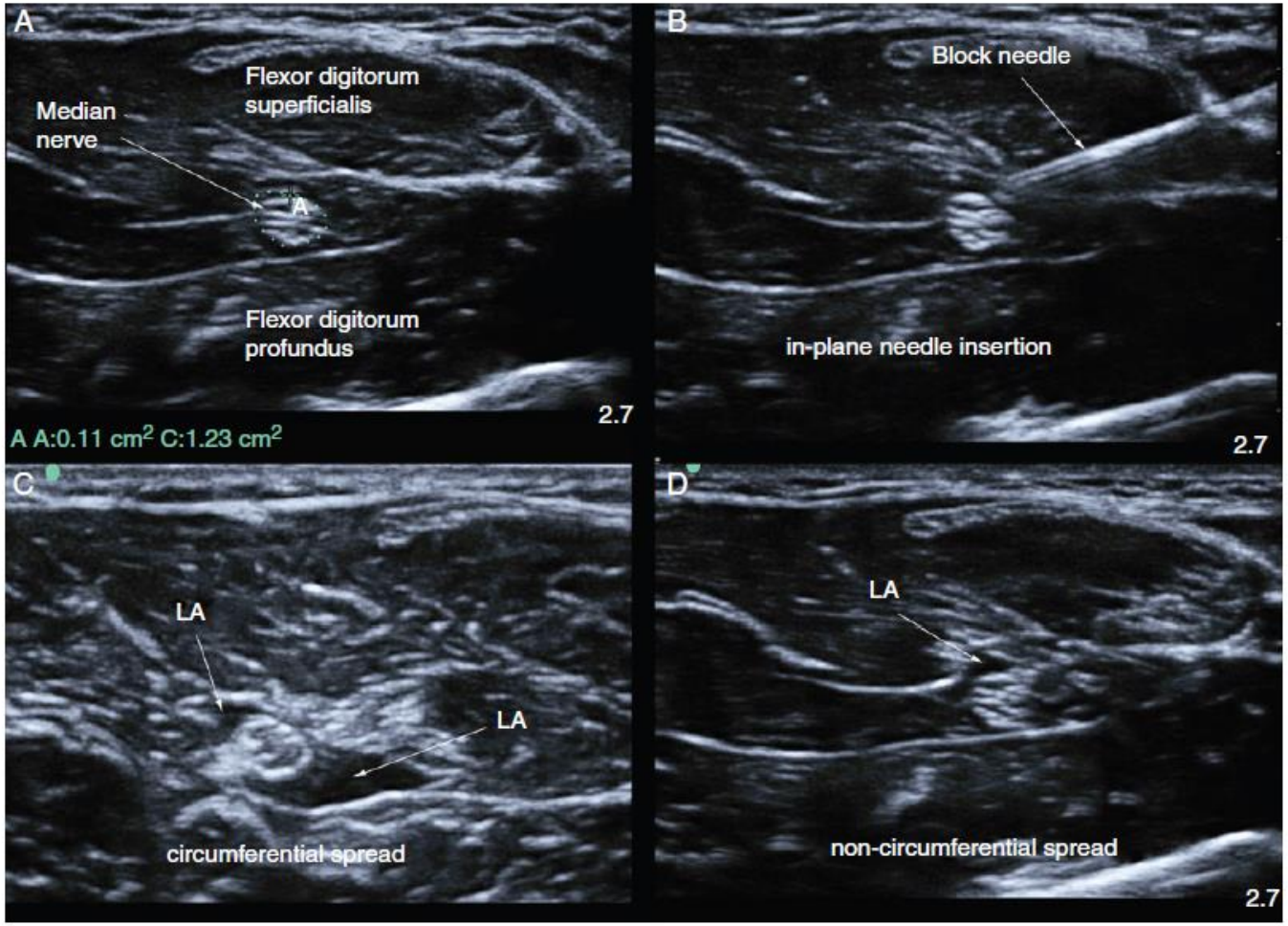
Verlängerte Haftungsdauer von hochmolekularen Trägersubstanzen an der Augenoberfläche





Schmidl et al. Cornea. 2015 Apr;34(4):421-6

Nervenleitblöcke



Marhofer D. Br J Anaesth. 2014 Jul;113(1):177-85.

Dexmedetomidine as an adjuvant to ropivacaine prolongs peripheral nerve block: a volunteer study

D. Marhofer[1], S. C. Kettner[1*], P. Marhofer[1], S. Pils[2], M. Weber[2] and M. Zeitlinger[2]

36 volunteers

- 3 ml ropivacaine 0.75%
- 3 ml ropivacaine 0.75% plus 20 μg dexmedetomidine (RpD)
- 3 ml ropivacaine 0.75% plus systemic 20 μg dexmedetomidine (RsD).

Table 2 Block characteristics; values are mean (SD). [1]$P<0.01$ *vs* Group R, [2]$P<0.01$ *vs* Group RpS, [3]$P<0.05$ *vs* Group R, [4]$P<0.01$ *vs* Group R, [5]$P<0.01$ *vs* Group RpS, [6]$P<0.05$ *vs* Group R, [7]$P<0.05$ *vs* Group R, [8]$P<0.05$ *vs* Group R, [9]$P<0.05$ *vs* Group RpS, [10]$P<0.05$ *vs* Group R

	R	RpD	RpS
Sensory onset time (min)	19 (14)	13 (18)	16 (18)
Duration of sensory block (min)	350 (54)	555 (118)[1,2]	395 (40)[3]
Time until pinprick testing 100%	455 (70)	743 (152)[4,5]	518 (59)[6]
Motor onset time (min)	47 (36)	21 (15)[7]	43 (25)
Duration of motor block (min)	348 (74)	590 (92)[8,9]	438 (54)[10]

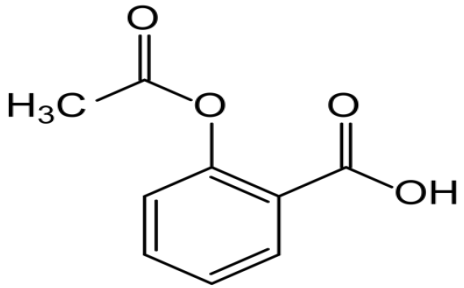
British Journal of Anaesthesia 110 (3): 438–42 (2013)

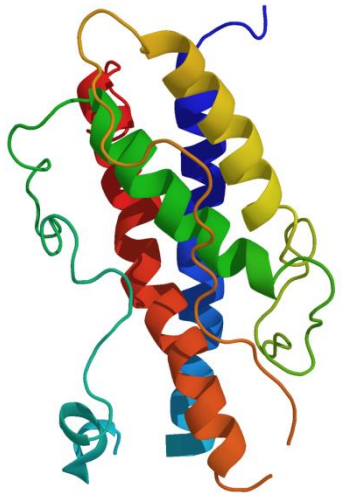
Bioequivalenz spezial

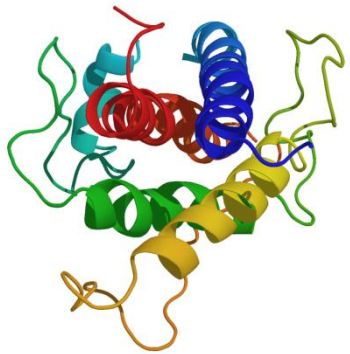
Definition von Nachbaupräperaten?

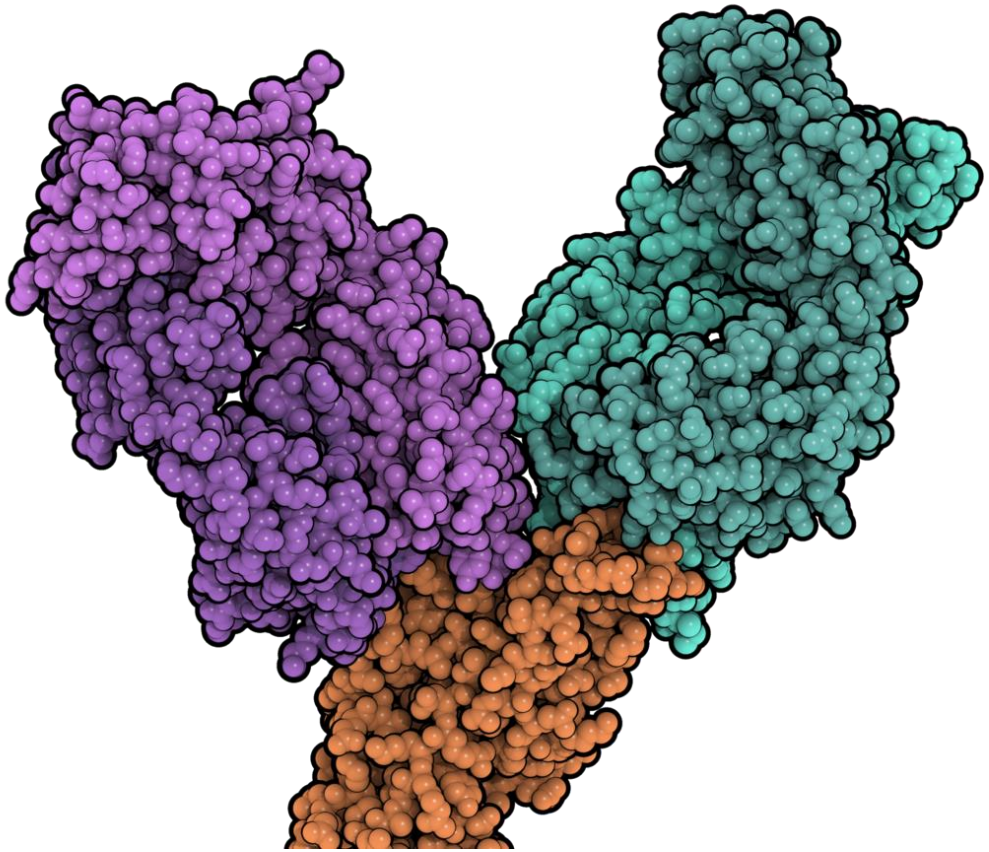
- ***Generika***
- ***Biosimilar***

Biologika und Antikörper vs. konventionelles Pharmakon









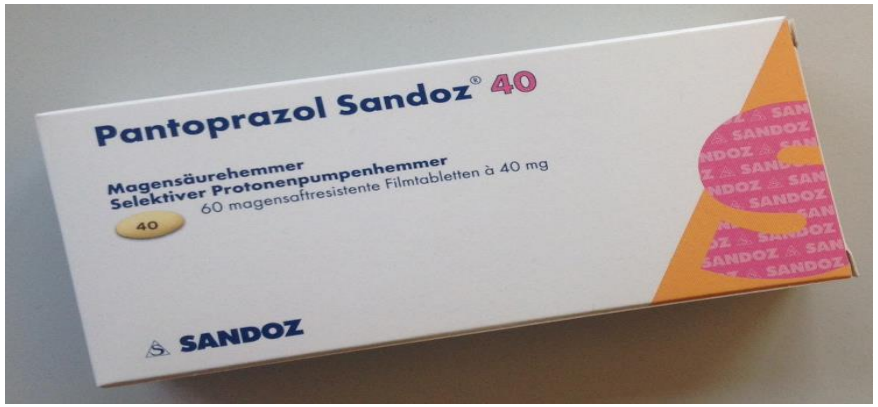
Aspirin: 180 D

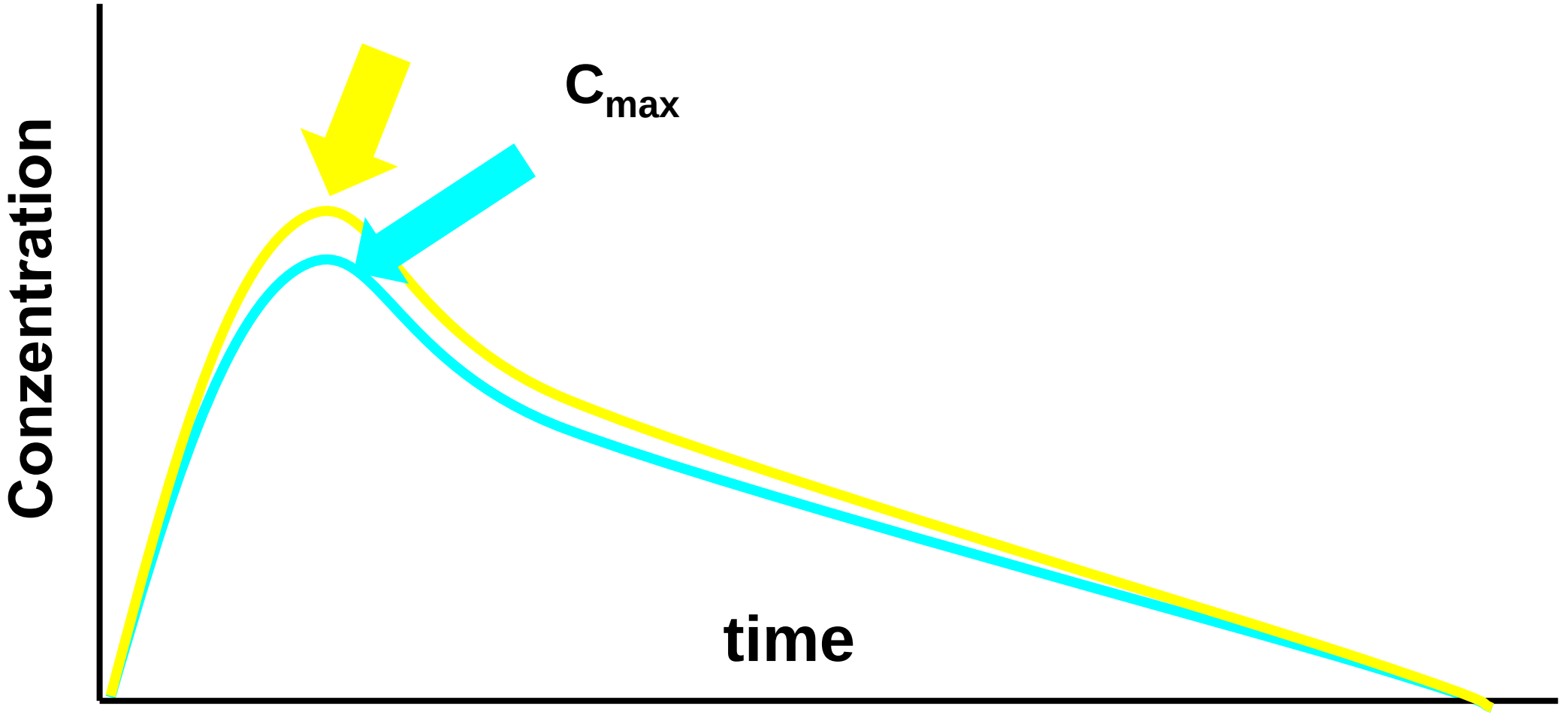
Somatotropin: 22 kD

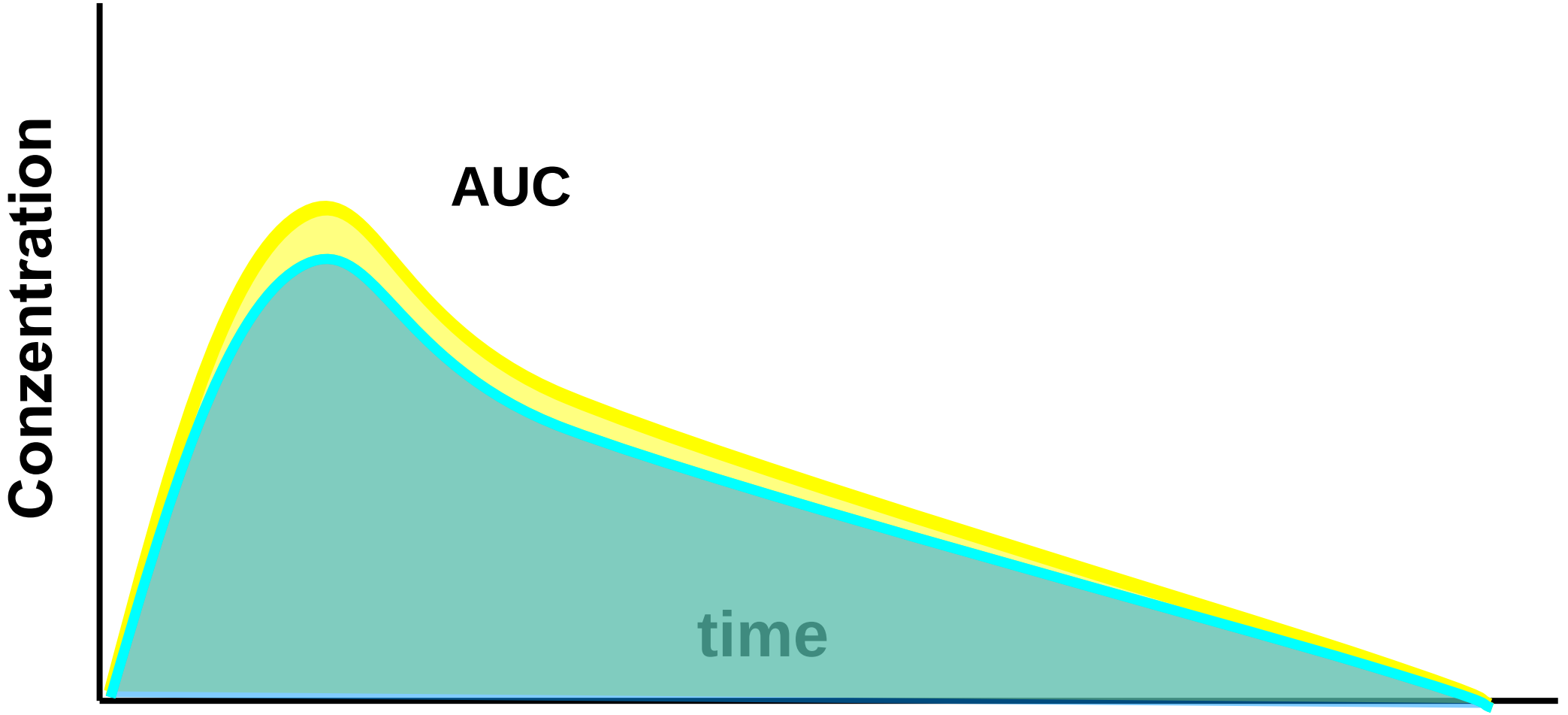
Tixagevimab: 149 kD
Cilgavimab: 152 kD

Generika

- Ist entwickelt um das gleiche Produkt wie ein bereits zugelassenes zu sein.
- Gleiche qualitative und quantitative Zusammensetzung hinsichtlich der aktiven Substanz(en) wie das Referenz Produkt
- Gleiche pharmazeutische Form
- Bioequivalenz wurde in einer entsprechenden Studie gezeigt




Conzentration
C_{max}
time


Conzentration
AUC
time

BE* for conventional drugs ANOVA*

Bioequivalence and interchangeability

- AUC* or C_{max} of test substance between 80-125% of comperator

- 90% Confidence Interval (CI) of the ratio test/comperator between 0.80 und 1.25

*BE – Bioequivalence, AUC – area under the curve, ANOVA – analysis of variance

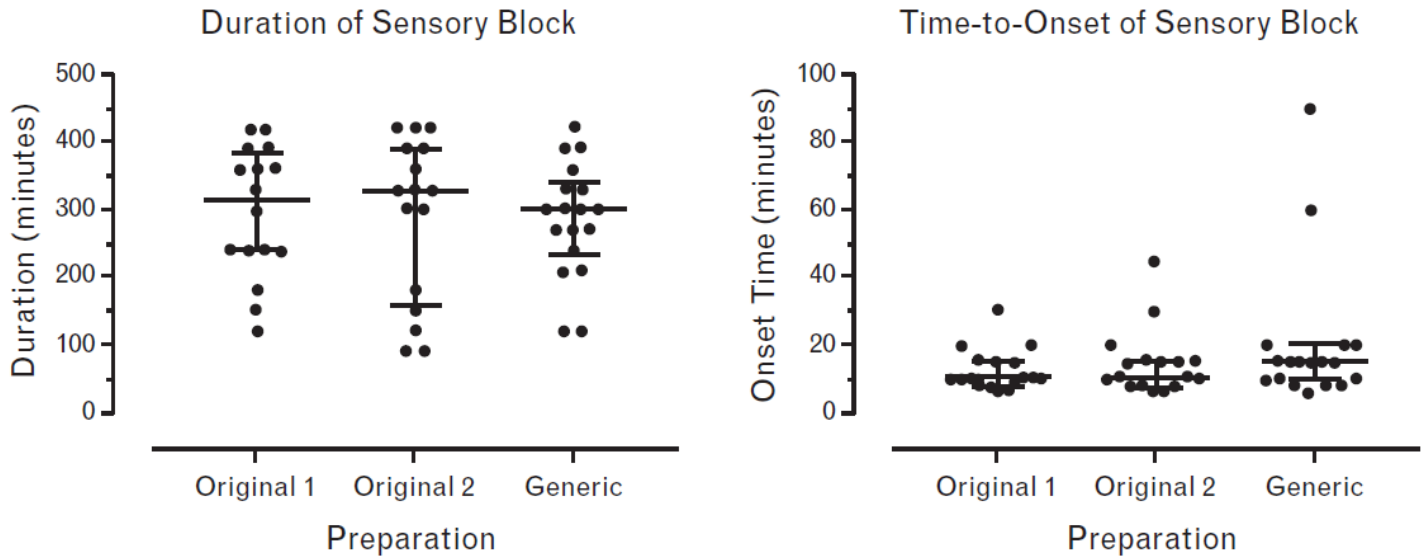
Generisches ropivacaine

Generic versus reference listed ropivacaine for peripheral nerve blockade

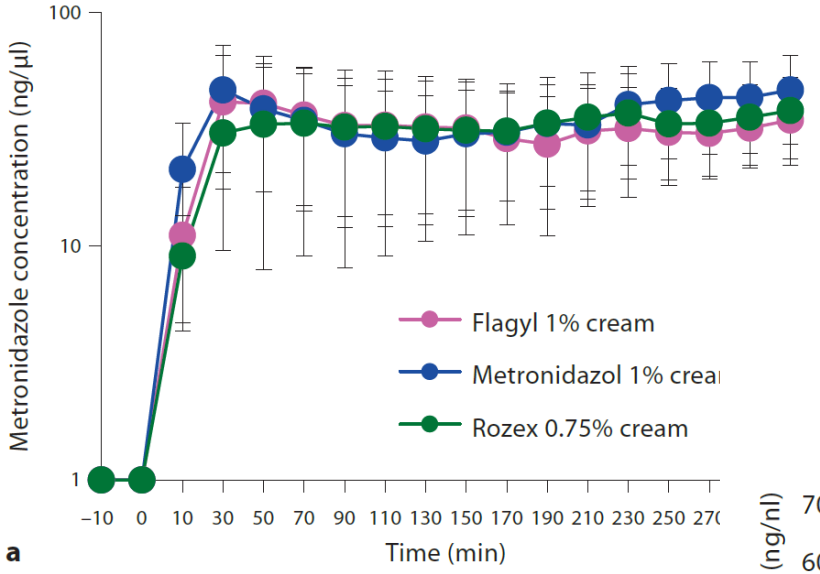
A randomised, triple-blinded, crossover, equivalence study in volunteers

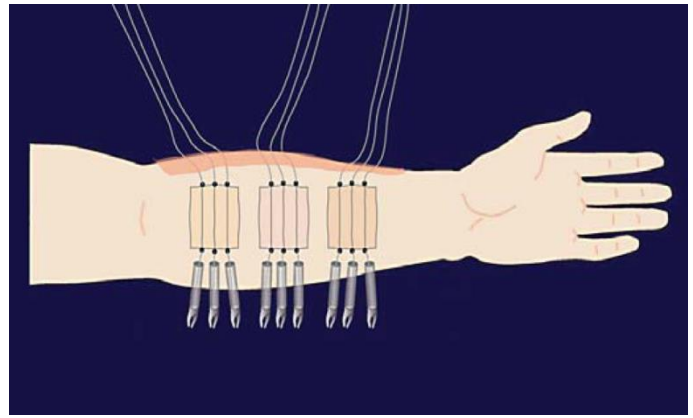
Philipp Opfermann, Peter Marhofer, Philip M. Hopkins, Malachy O. Columb, Markus Zadrazil, Thomas Stimpfl, Melanie Marhofer and Markus Zeitlinger

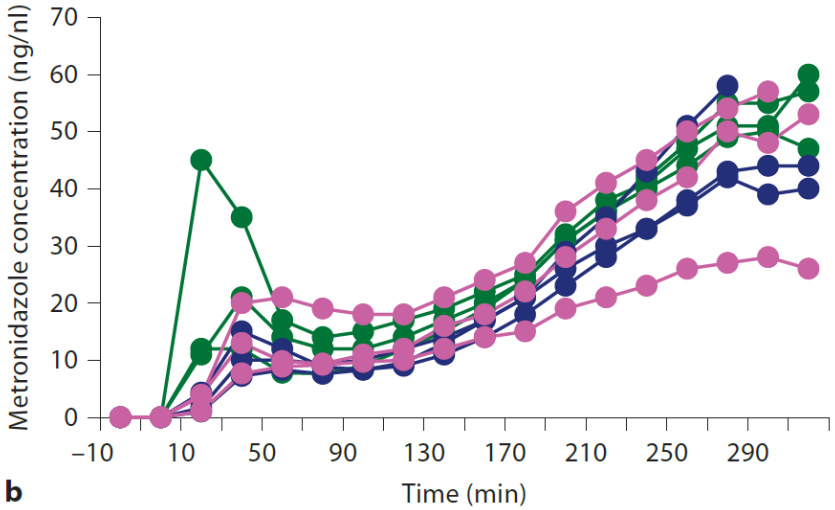
Fig. 2 Pharmacodynamic results for duration of sensory block (primary outcome) and time-to-onset of sensory block

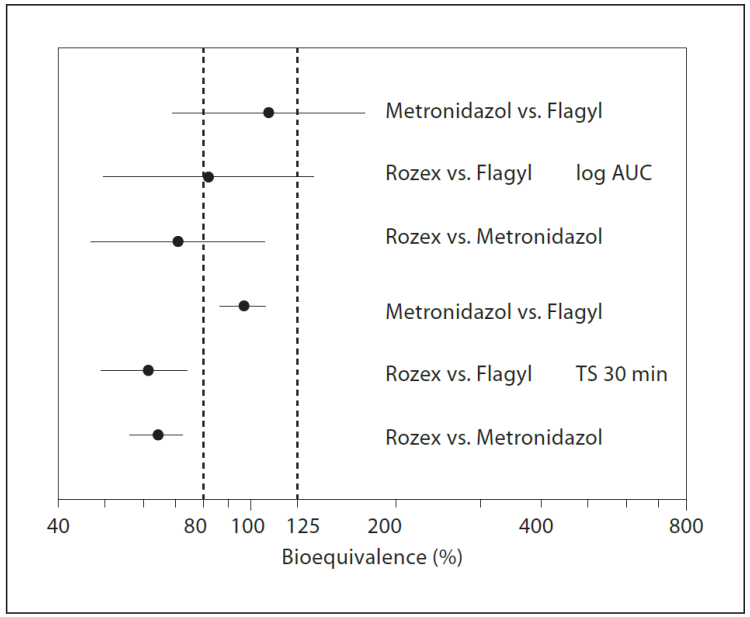


Marketed Topical Metronidazole Creams







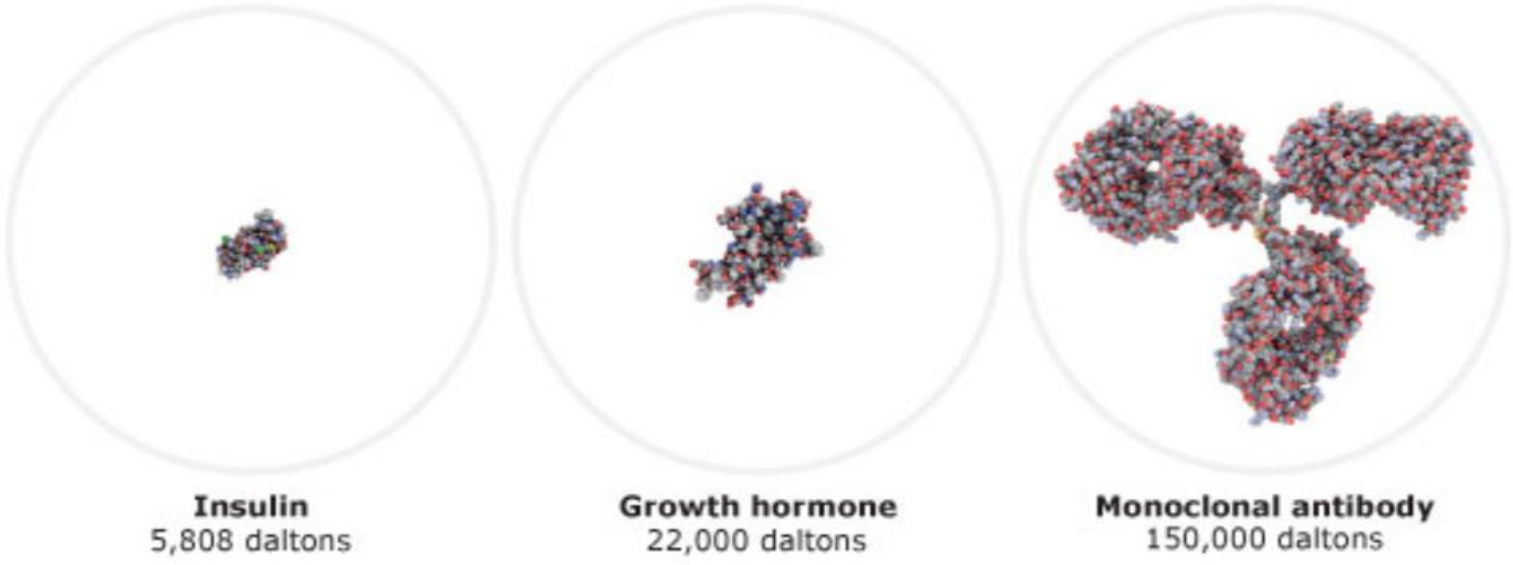


García Ortiz. Skin Pharmacol Physiol 2011;24:44–53

Biosimilar

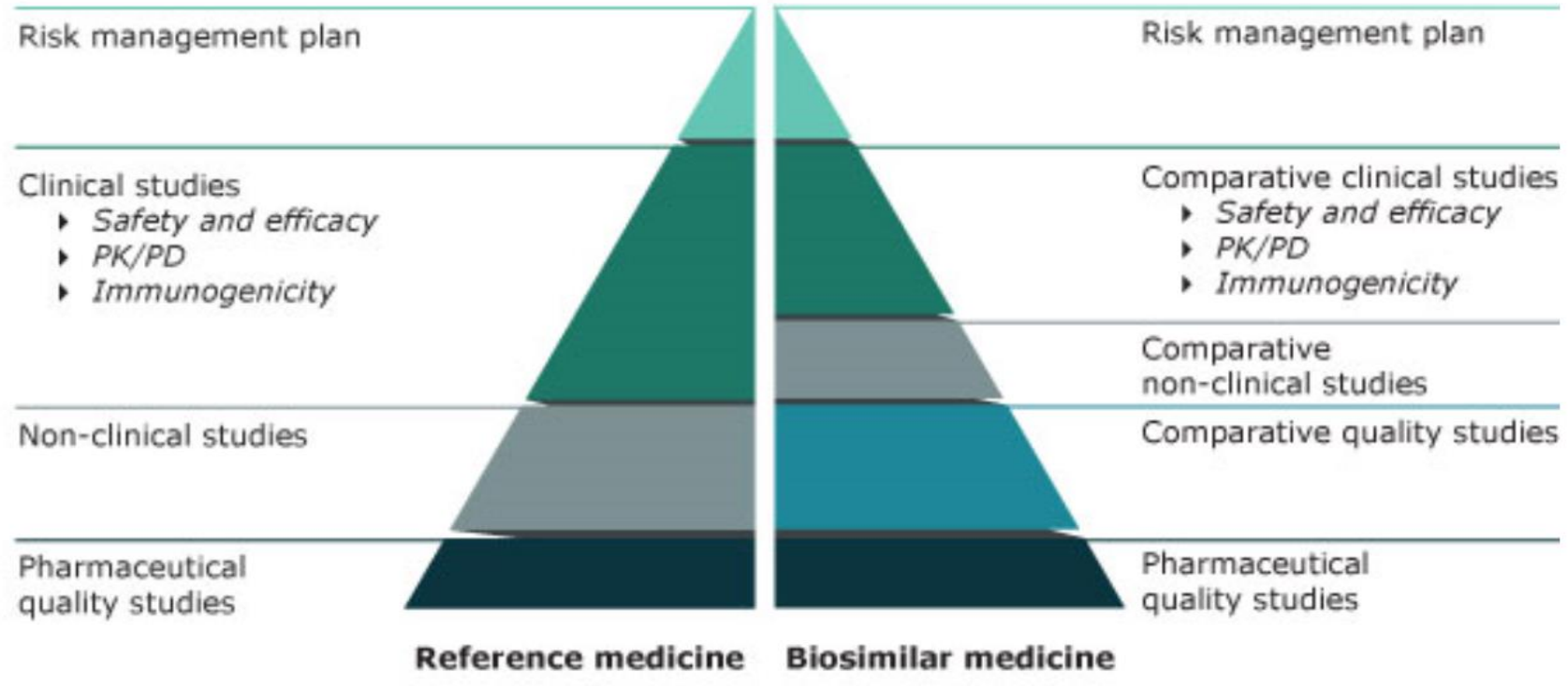
- Ein Biosimilar ist ein Biologika das “highly similar” zu einem anderen Biologika ist, das bereits in der EU zugelassen ist
- In Hinsicht auf Struktur, biologischer Aktivität, Effektivität, Sicherheit und Immunologischem Profil

“notwithstanding natural variability inherent to all biological medicines”



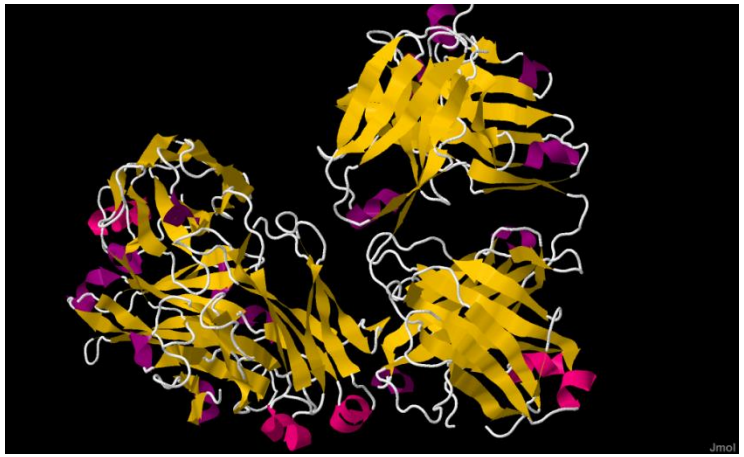
Comparability with the reference product ensured on all levels

Comparison of data requirements for approval of a biosimilar versus the reference medicine



Single, very low rituximab doses in healthy volunteers - a pilot and a randomized trial: implications for dosing and biosimilarity testing

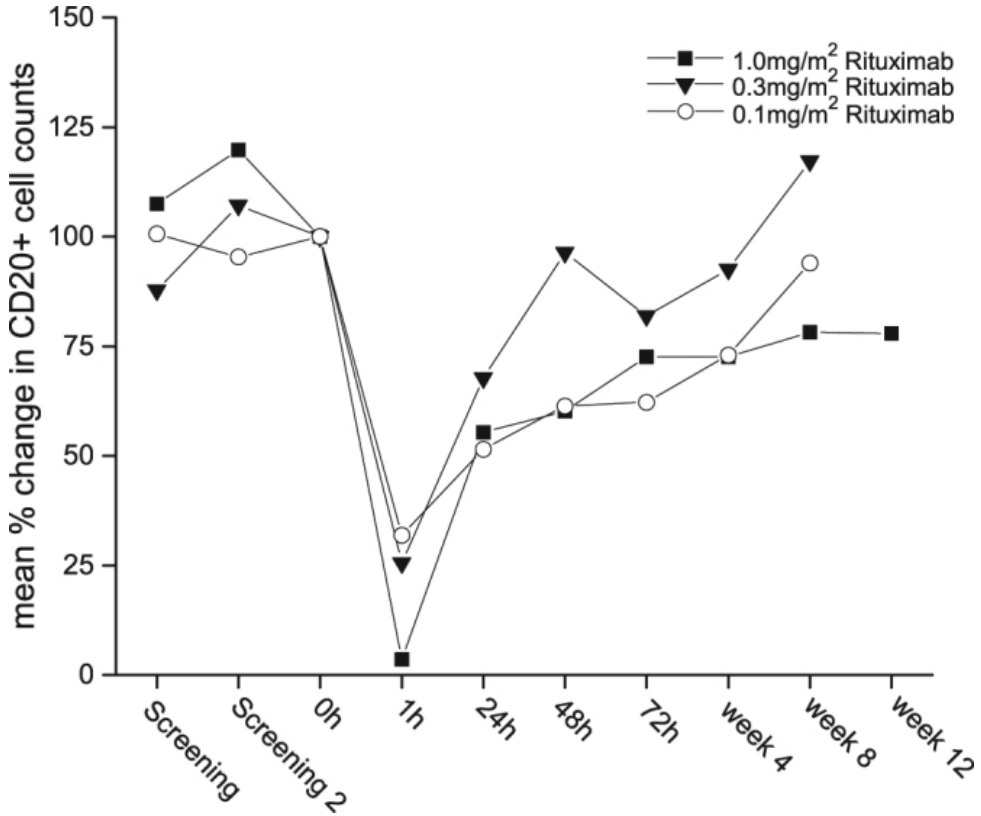
- hypothesized that currently used doses (≥375 mg/m2) exceed several hundred-fold the half-maximal effective dose
- most sensitive for detecting putative differences between biosimilars and important for dose finding



Schörgenhofer C. Scientific Reports. (2018) 8:124

Single, very low rituximab doses in healthy volunteers - a pilot and a randomized trial: implications for dosing and biosimilarity testing

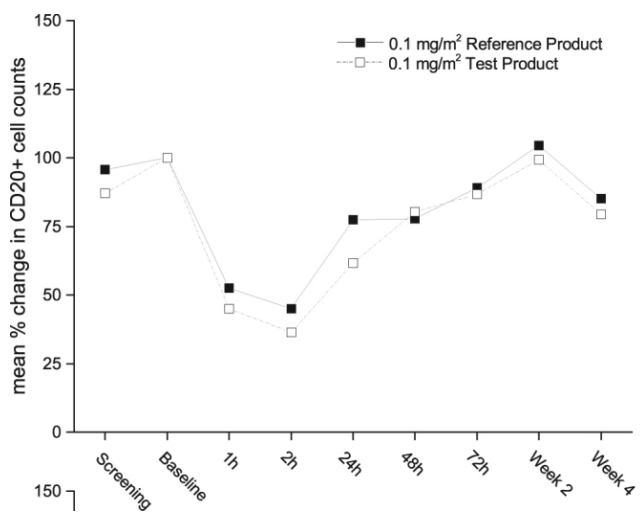
- In an open label, exploratory trial healthy volunteers received single infusions of rituximab at doses of 0.1, 0.3 or 1.0 mg/m2.

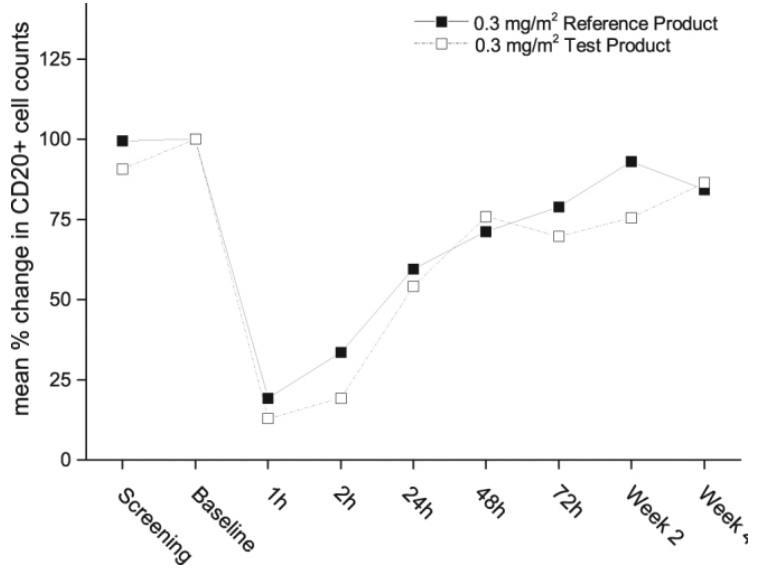


Schörgenhofer C. Scientific Reports. (2018) 8:124

Single, very low rituximab doses in healthy volunteers - a pilot and a randomized trial: implications for dosing and biosimilarity testing

- in a double-blind, randomized trial healthy volunteers received single infusions



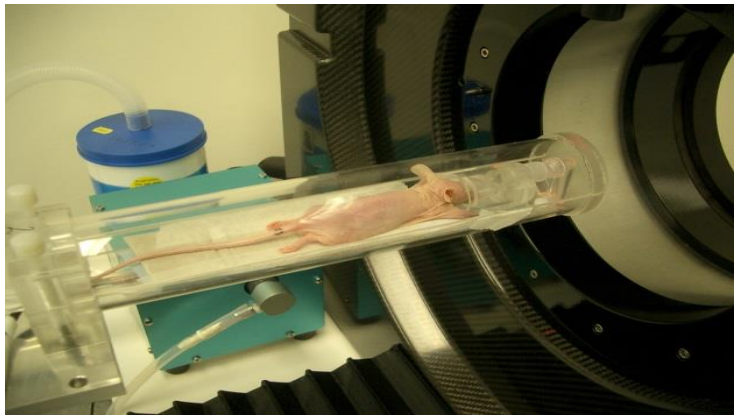


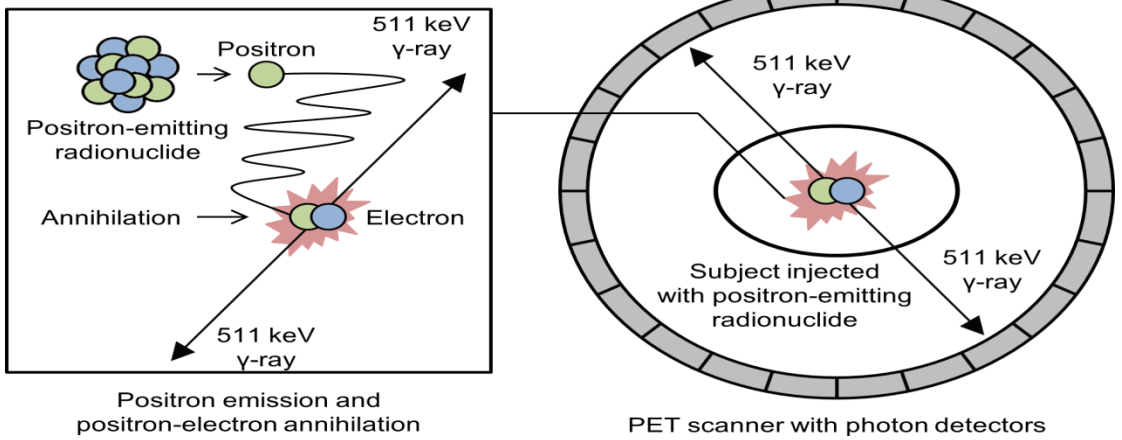
- in healthy volunteers <1% of the authorized rituximab doses depletes almost all circulating B lymphocytes.

Schörgenhofer C. Scientific Reports. (2018) 8:124

Bildgebung

Positron Emission Tomography (PET)

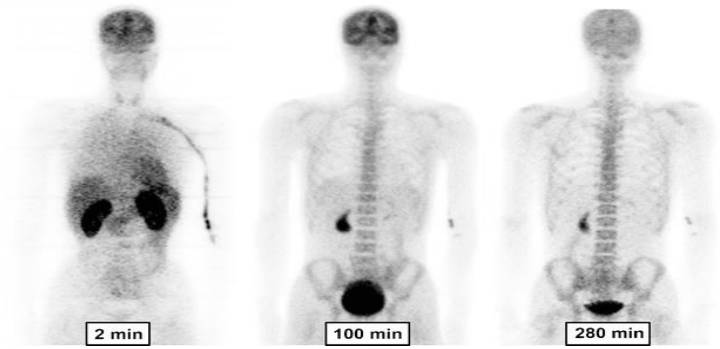




Positron emission and positron-electron annihilation

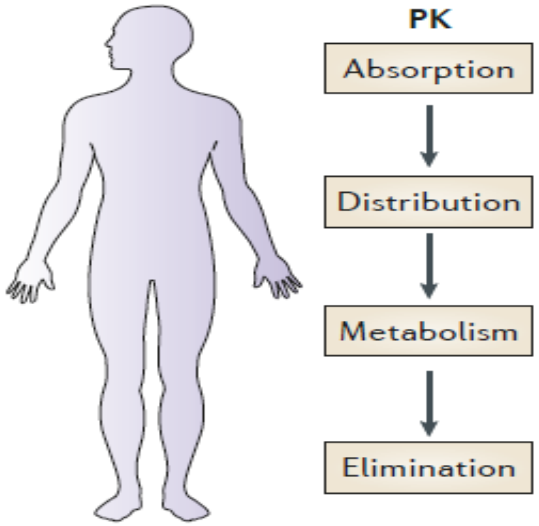
PET scanner with photon detectors

Radiolabeled drug



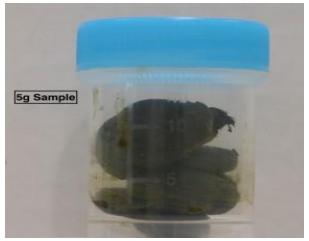
Beschreibung der PK im ganzen Körper

Traditional PK analysis



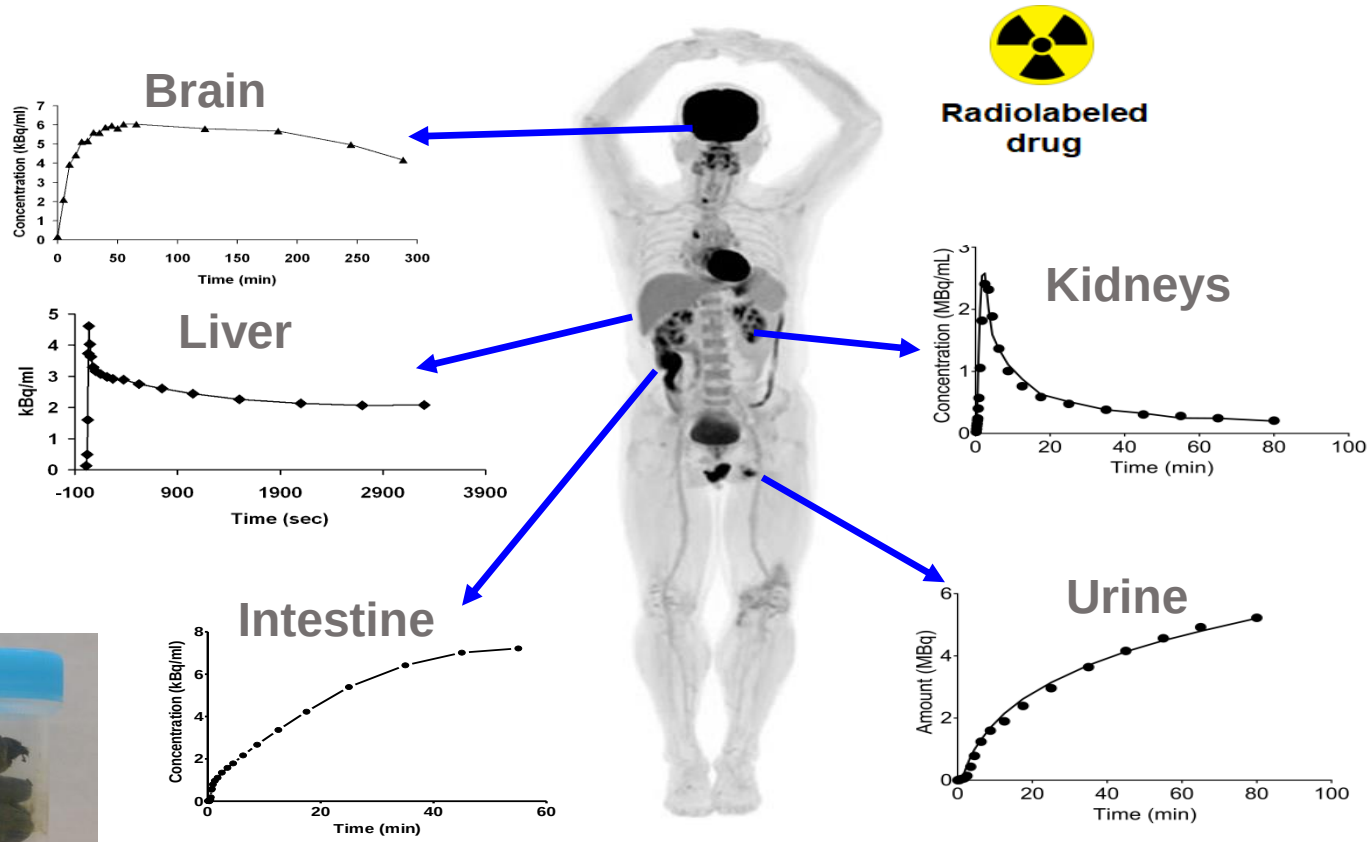
Blood/plasma

Urine

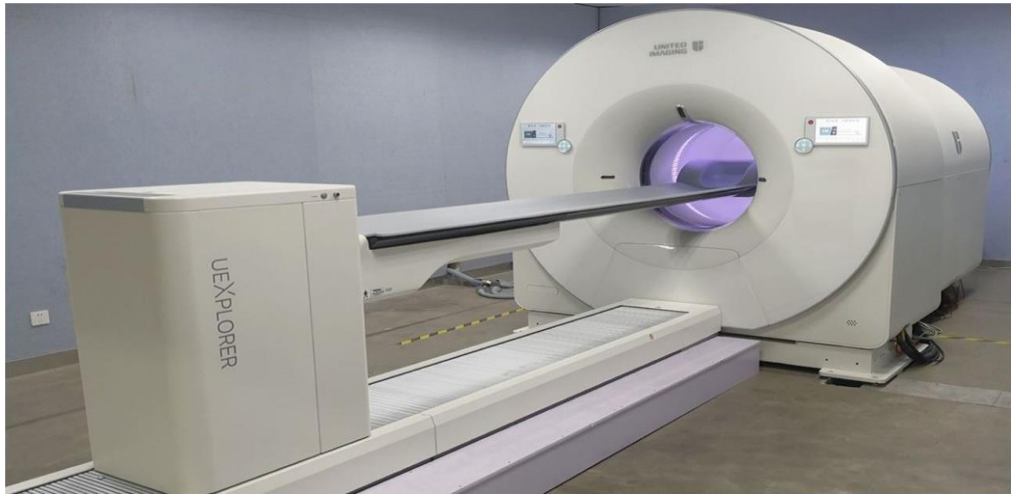


Feces

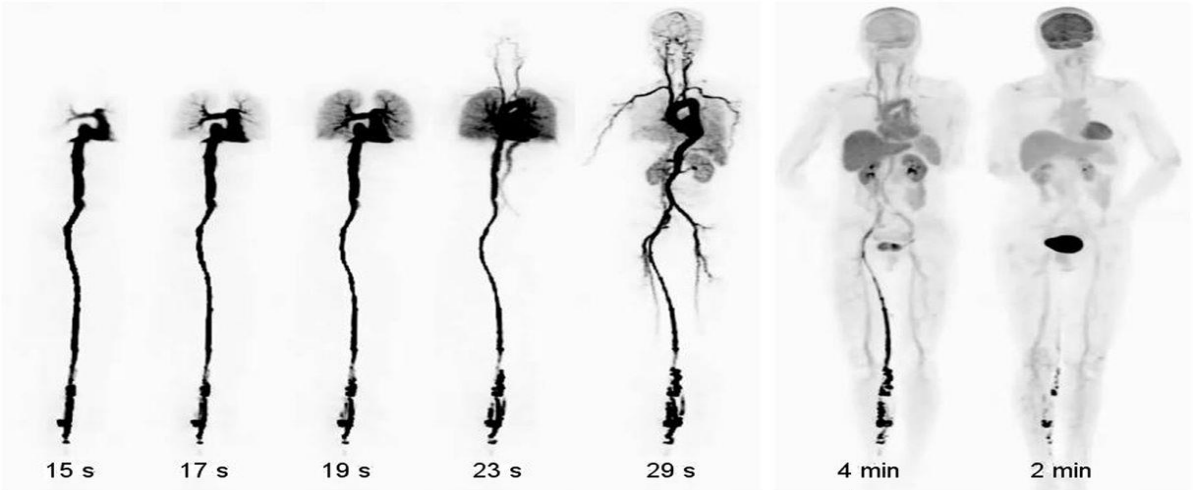
Imaging-based PK analysis



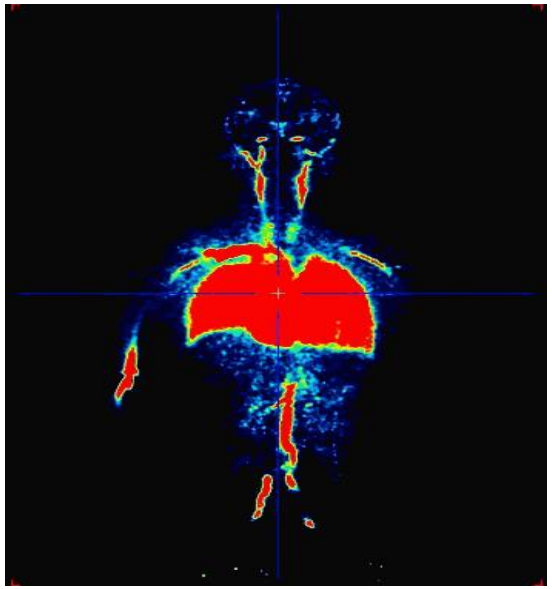
Long axial field of view PET systems



uEXPLORER® total-body PET/CT scanner
(axial field of view: 194 cm)



RD Badawi et al J Nucl Med 2019;60:299-303

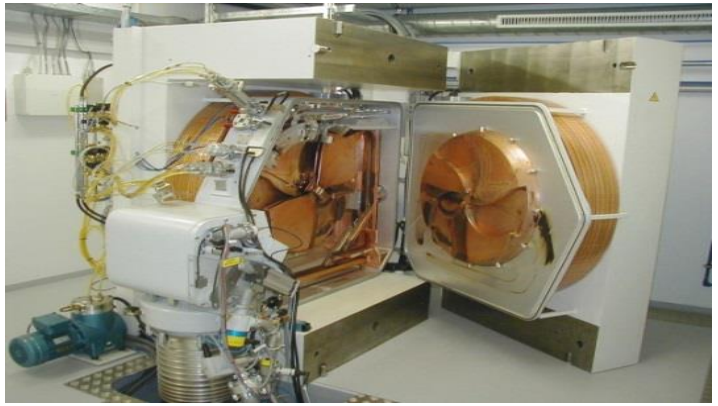


Biograph Vision Quadra PET/CT scanner
(axial field of view: 106 cm)

Wichtigste Radionukleotide

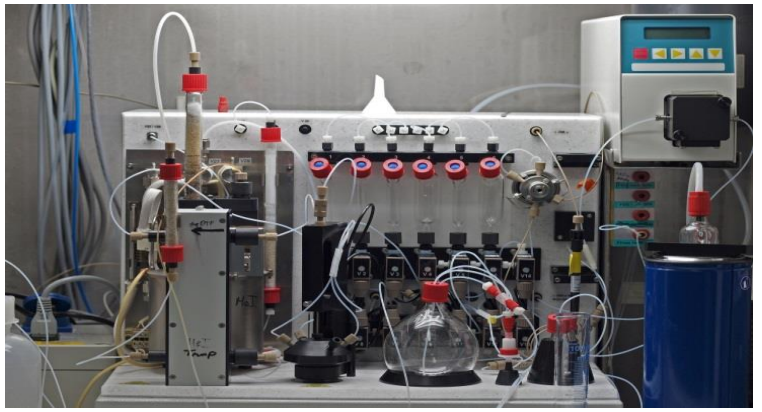
Radionuclide	$T_{1/2}$	Max.β^+ energy (MeV)	Production
^{15}O	2.07 min	1.7	$^{14}N(d,n)^{15}O$
^{13}N	9.96 min	1.2	$^{16}O(p,\alpha)^{13}N$
^{11}C	20.4 min	0.96	$^{14}N(p,\alpha)^{11}C$
^{68}Ga	67.6 min	1.90	$^{68}Ge/^{68}Ga$ generator
^{18}F	109.8 min	0.64	$^{18}O(p,n)^{18}F$
^{64}Cu	12.7 h	0.653	$^{64}Ni(p,n)^{64}Cu$
^{89}Zr	3.3 days	0.897	$^{89}Y(p,n)^{89}Zr$
^{124}I	4.18 days	1.53; 2.13	$^{124}Te(p,n)^{124}I$

Infrastruktur



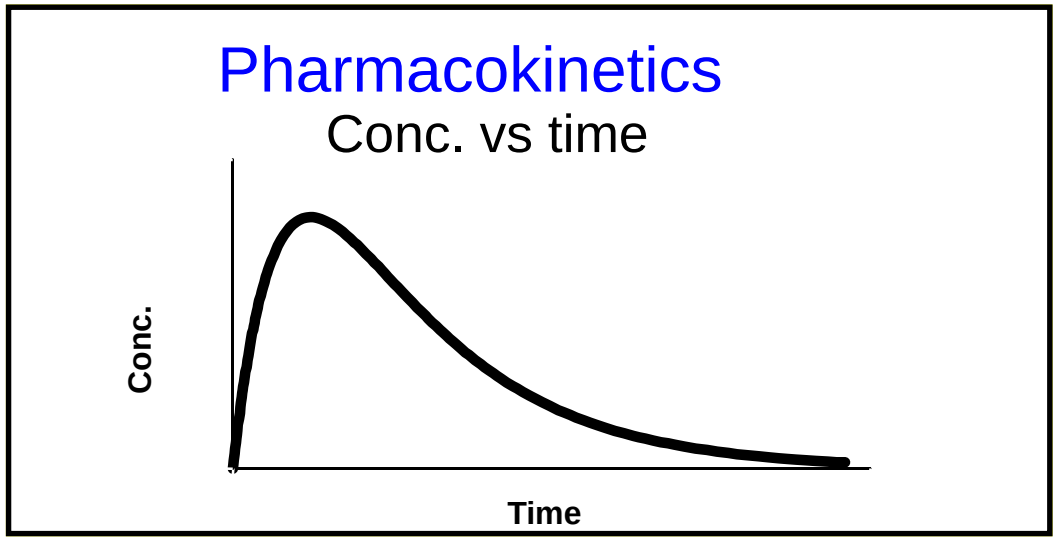
Cyclotron

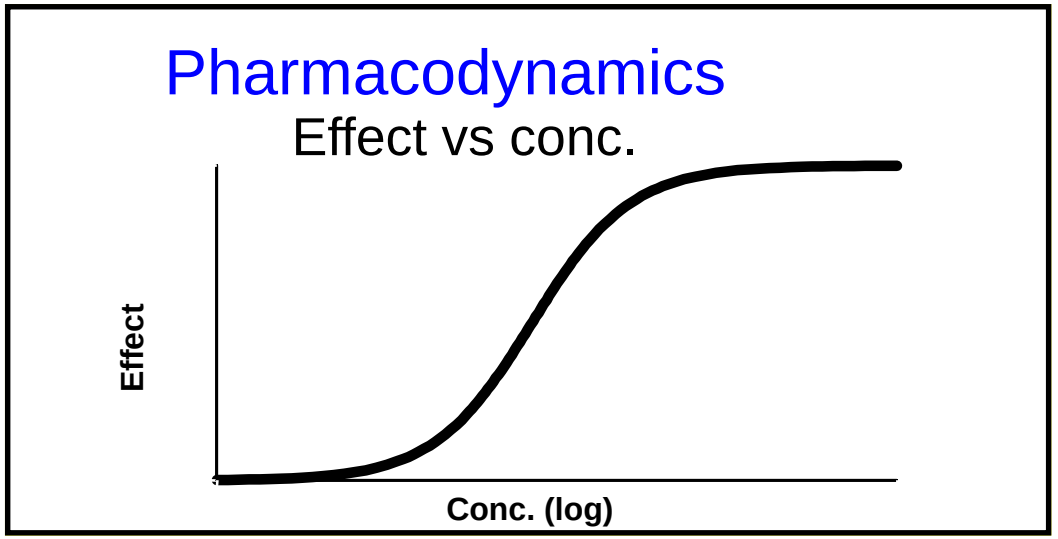
Radiochemistry lab



Radiosynthesis modules

PET in drug development

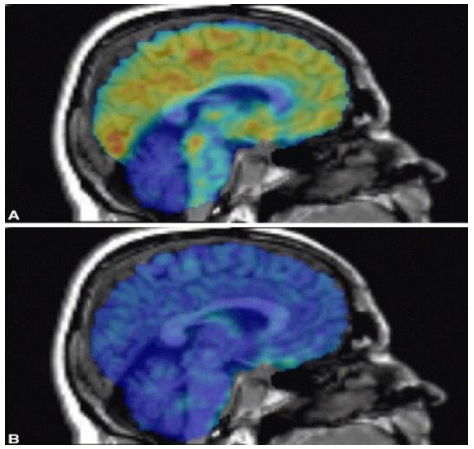


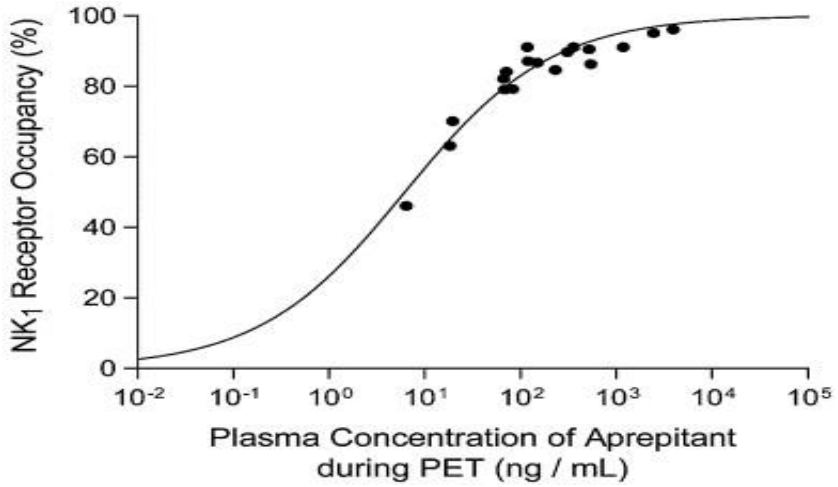


Direct radiolabeling of drug molecules ("PET-microdosing", "pharmacokinetic imaging")

Quantification of drug effects with appropriate PET tracers ("target engagement studies")

Target engagement / receptor occupancy studies - Aprepitant





M Bergström et al Biol Psychiatry 2004;55:1007-12; M Bergström et al Biol Psychiatry 2006;59:216-23

- Establishing a relationship between the plasma concentration of the (unlabeled) drug and the percent occupancy of the target receptor → guidance for dose selection
- Evidence whether the drug reaches its therapeutic target tissue
- This approach can only be applied if the molecular target of the drug can be quantified with a PET tracer (typically CNS-targeted drugs)

PET-microdosing

INNOVATION

Big physics, small doses: the use of AMS and PET in human microdosing of development drugs

Graham Lappin and R. Colin Garner

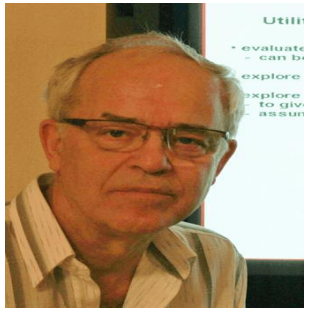
G Lappin et al Nat Rev Drug Discov 2003;2(3):233-40

Eur J Clin Pharmacol (2003) 59: 357–366
DOI 10.1007/s00228-003-0643-x

REVIEW ARTICLE

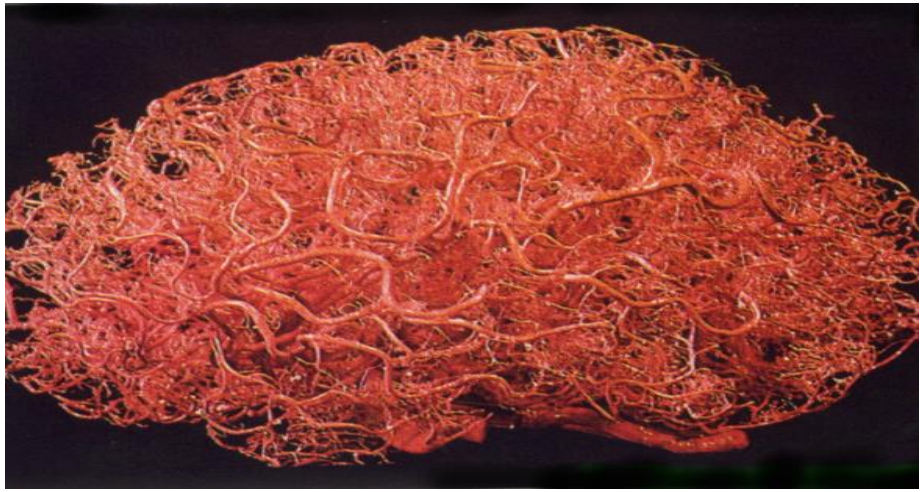
Mats Bergström · Anders Grahnén · Bengt Långström

Positron emission tomography microdosing: a new concept with application in tracer and early clinical drug development

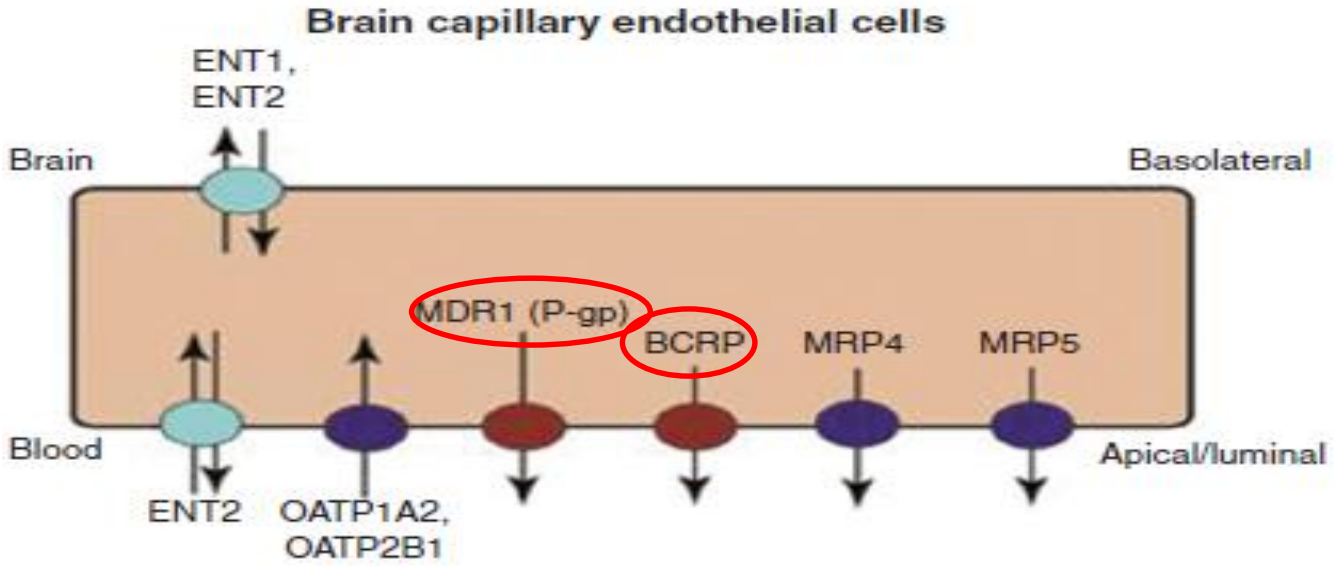


M Bergström et al Eur J Clin Pharmacol 2003;59:357-66

Beispiel 1: Assessment of the brain distribution of drugs



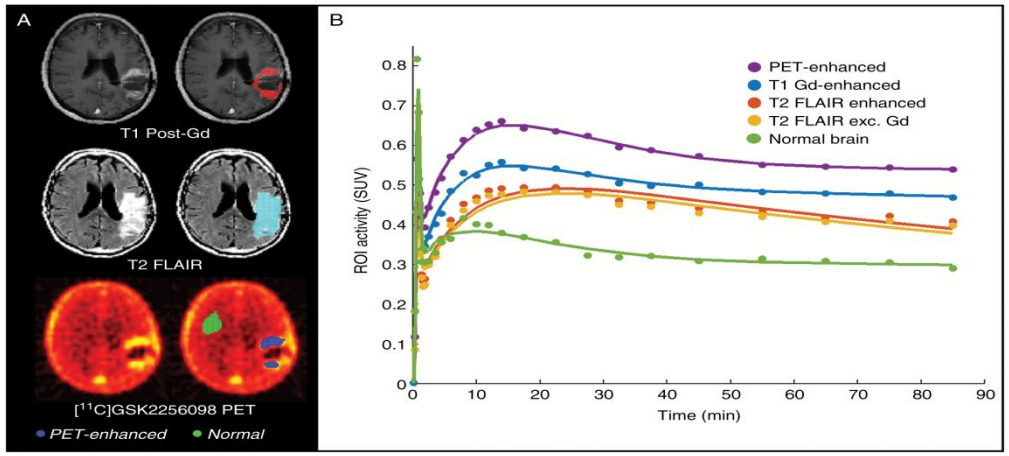
BV Zlokovic et al Neurosurgery 1998;43:877-8



- Many drugs (e.g. molecularly targeted anticancer drugs) are dual P-gp/BCRP substrates leading to very low brain distribution
- The BBB is often regionally disrupted in brain tumors → large heterogeneity in penetration of drugs into brain tumors
- PET can be used to measure concentrations of drugs in healthy brain tissue and in brain tumors

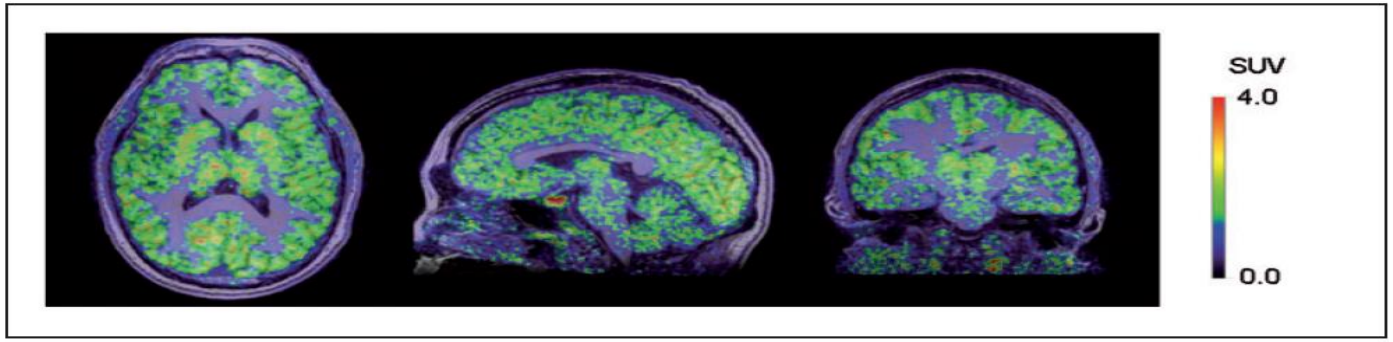
Brain distribution of molecularly targeted anticancer drugs measured with PET in healthy volunteers and tumor patients

[^{11}C]GSK2256098



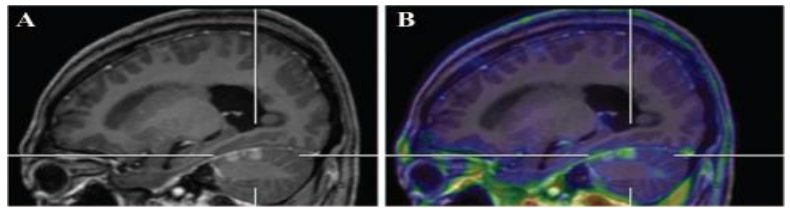
NF Brown et al Neuro Oncol 2018;20:1634-42

[^{11}C]Osimertinib



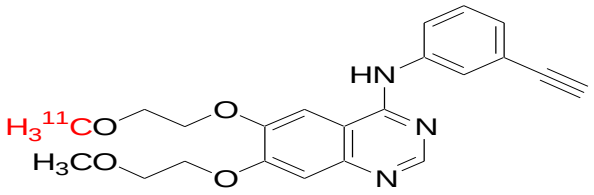
A Varrone et al JCBFM 2020;40(4):799-807

[^{11}C]Erlotinib



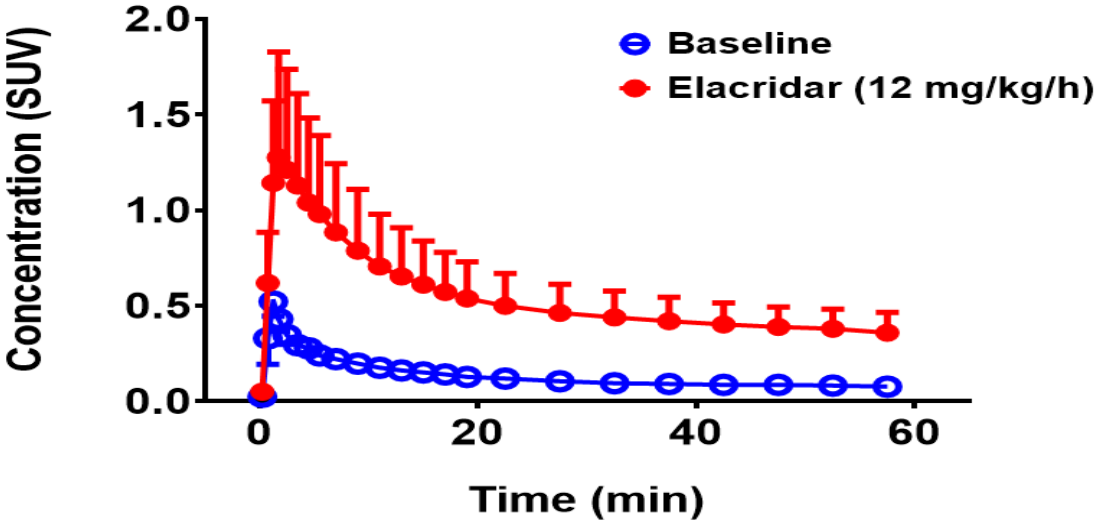
B Weber et al J Thorac Oncol 2011;6:1287-9

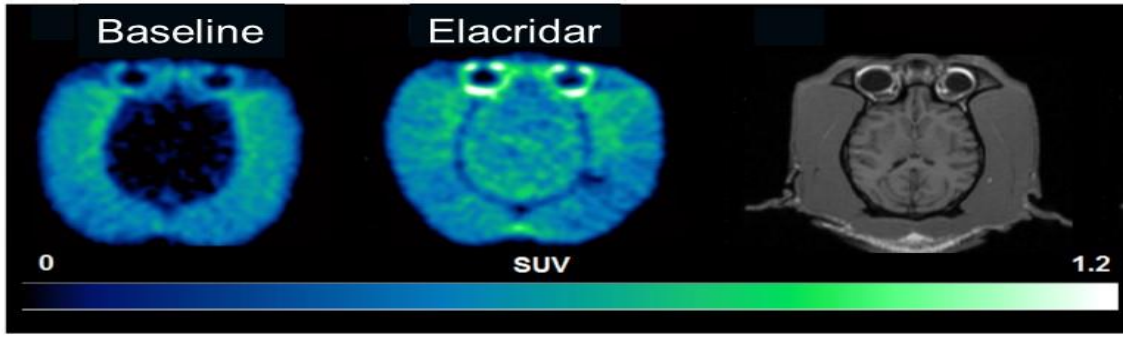
PET as a tool to assess drug delivery strategies to the brain

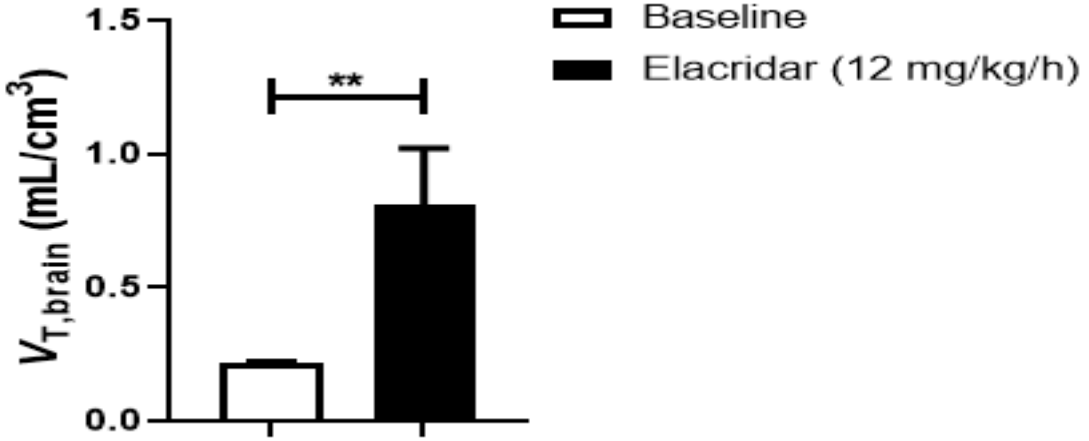


[^{11}C]Erlotinib

- The EGFR-targeted tyrosine kinase inhibitor erlotinib is excluded from the brain by P-gp/BCRP-mediated efflux transport and lacks therefore efficacy to treat CNS metastases of NSCLC
- Pharmacological inhibition of efflux transporters as a possible strategy to enhance the brain distribution of CNS-targeted P-gp/BCRP substrate drugs



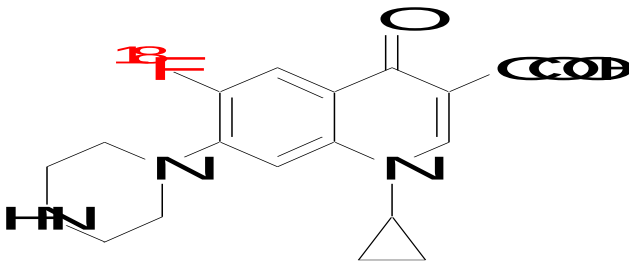




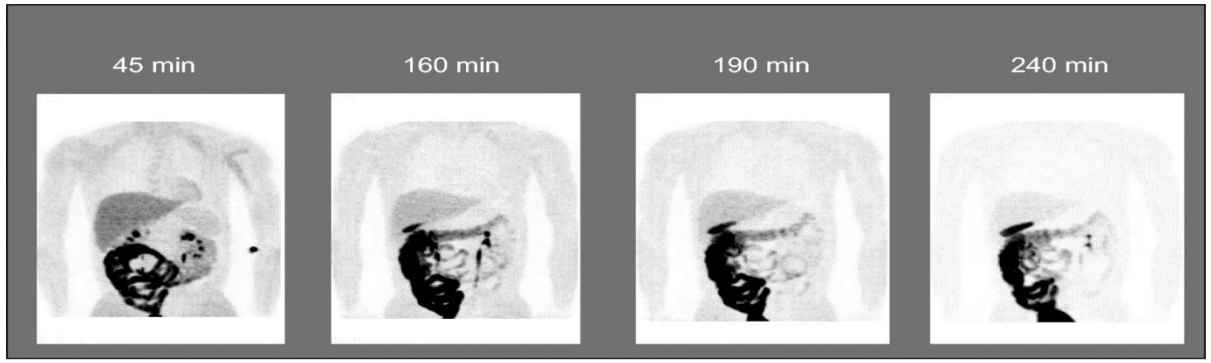
N Tournier et al J Nucl Med 2017;58:117–122

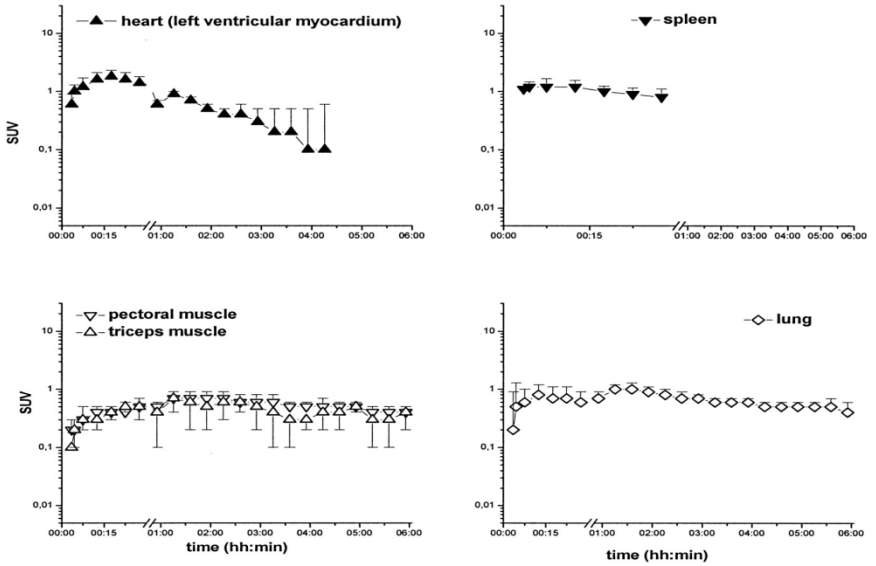
Beispiel 2: PET to assess the tissue distribution of antimicrobial drugs

- For antimicrobial drugs, efficacy is often directly related to the extent of drug tissue exposure (C_{max}, AUC)



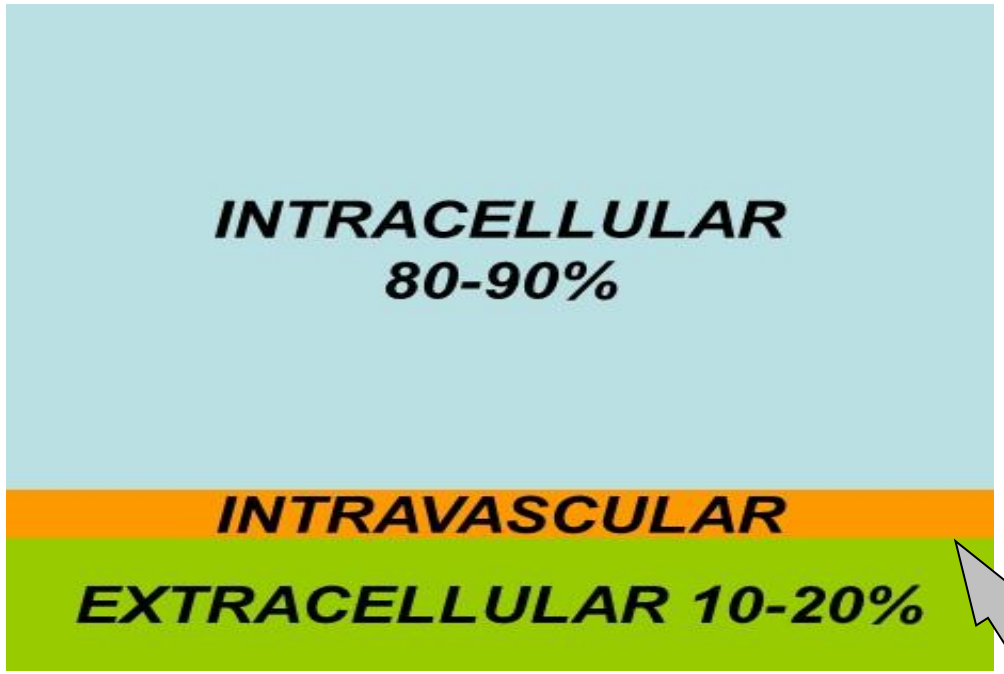
[^{18}F]Ciprofloxacin





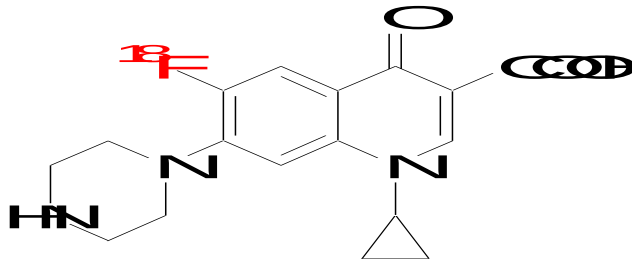
M Brunner et al Antimicrob Agents Chemother 2004;48:3850-7

Combination of PET and microdialysis to assess intracellular PK of ciprofloxacin in humans

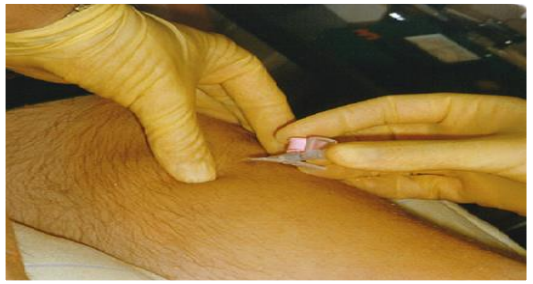


Muscle tissue

PET



[^{18}F]Ciprofloxacin



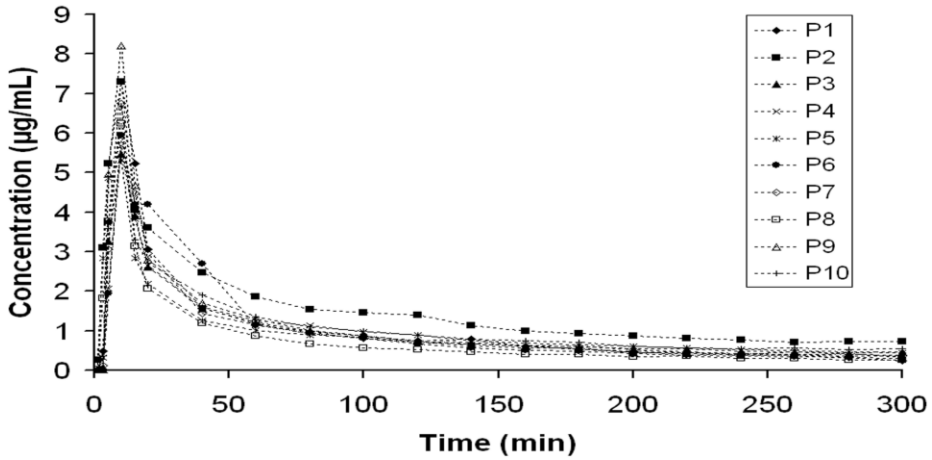
MICRODIALYSIS

HPLC

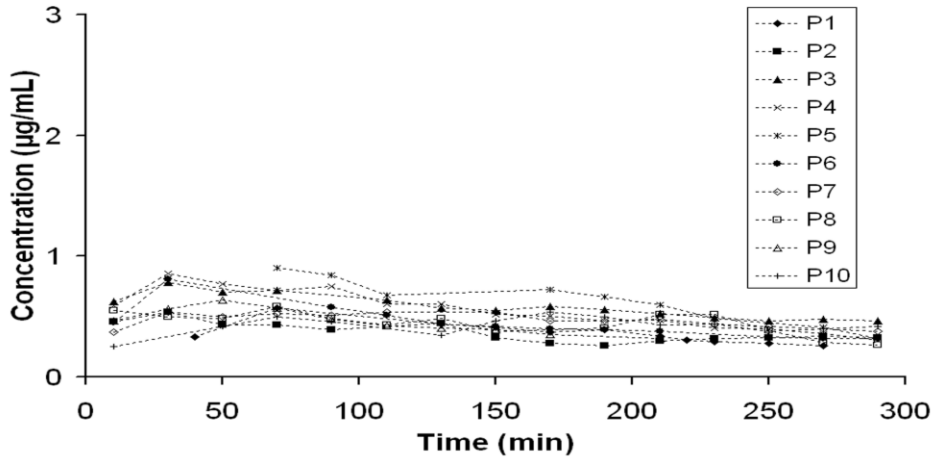
O Langer et al J Nucl Med 2005;46:1835-41

PET/MD combination

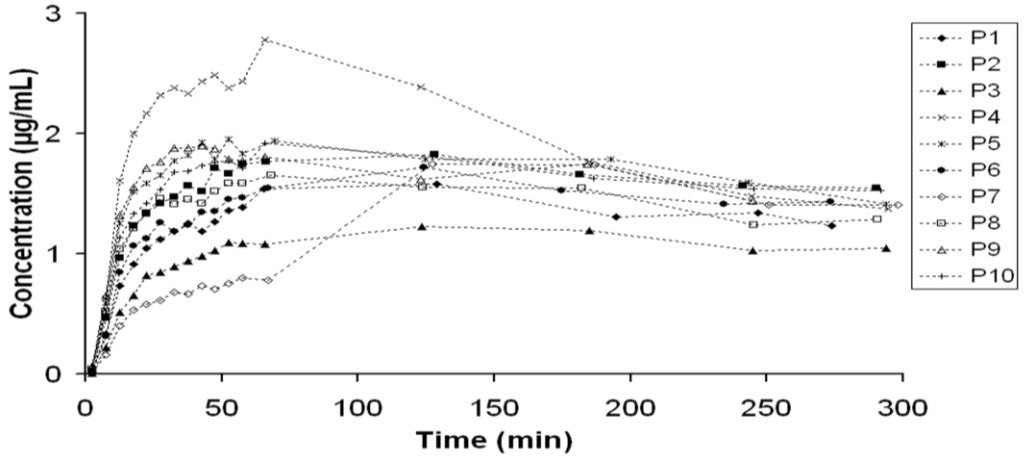
Venous plasma



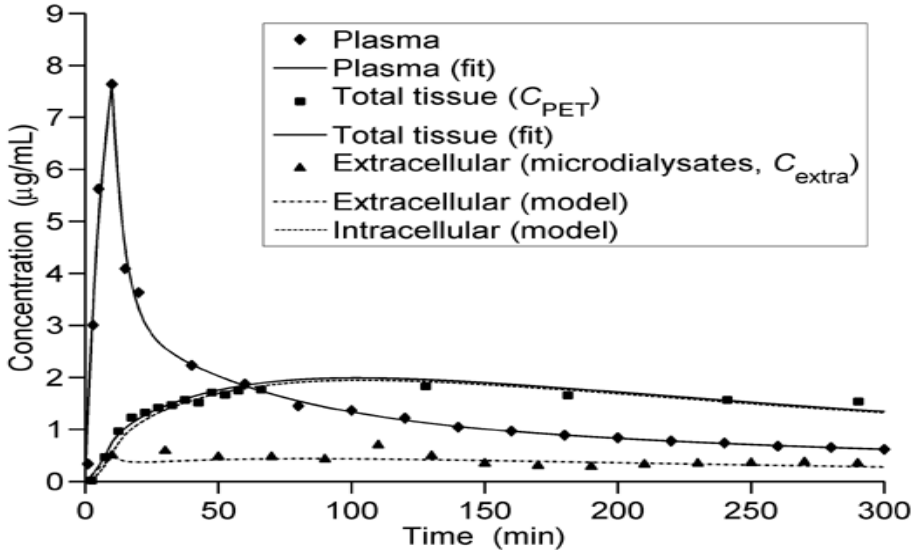
Extracellular PK in muscle tissue (MD)



Total tissue PK (PET)

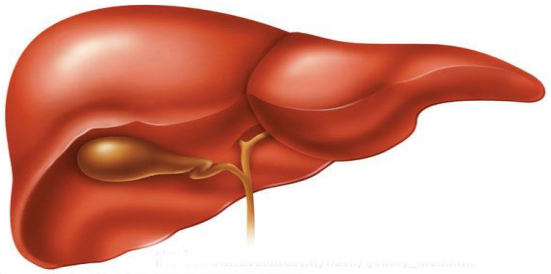


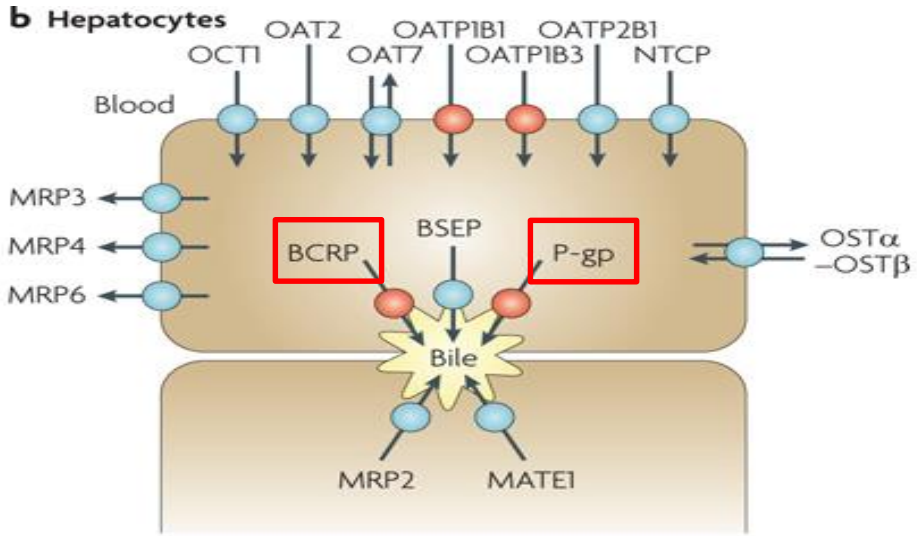
Modeled curves

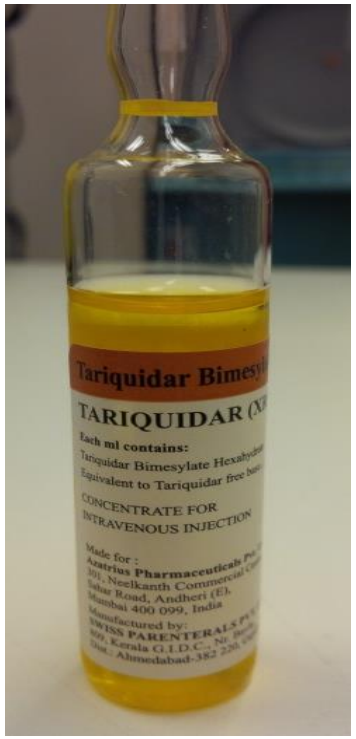


O Langer et al J Nucl Med 2005;46:1835-41

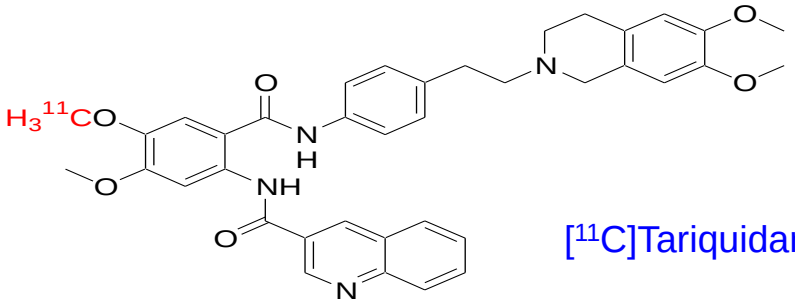
Beispiel 3: PET to assess drug excretion pathways





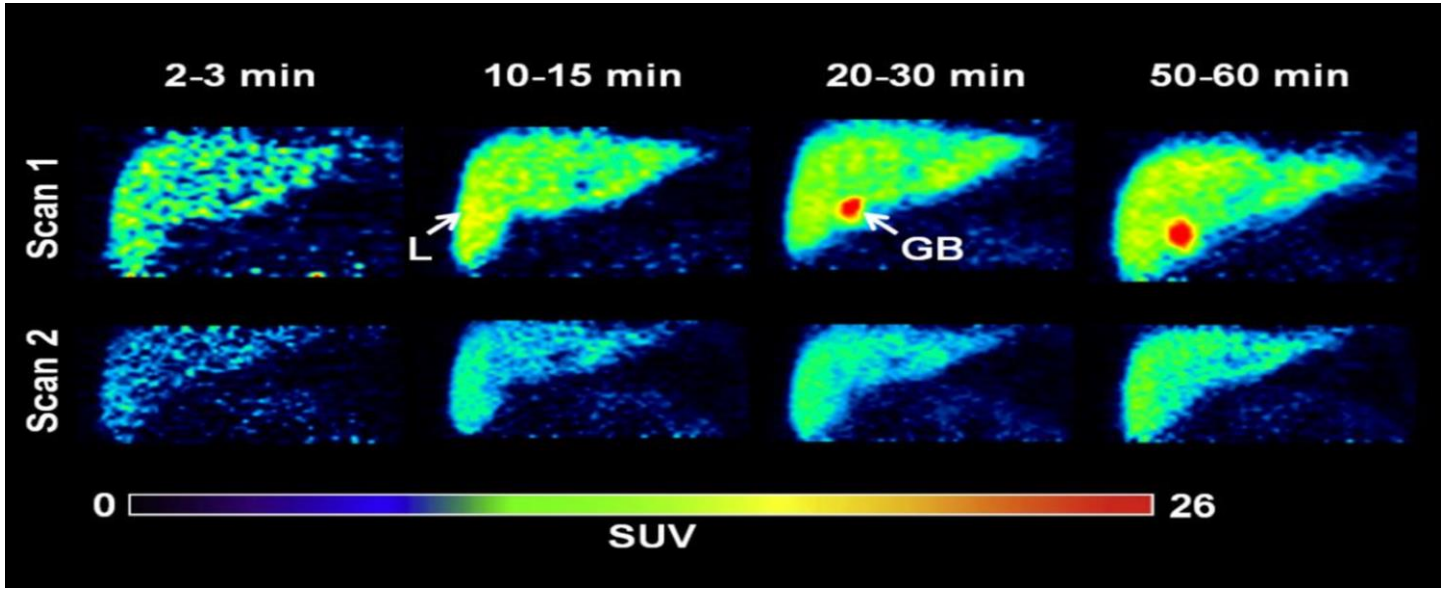


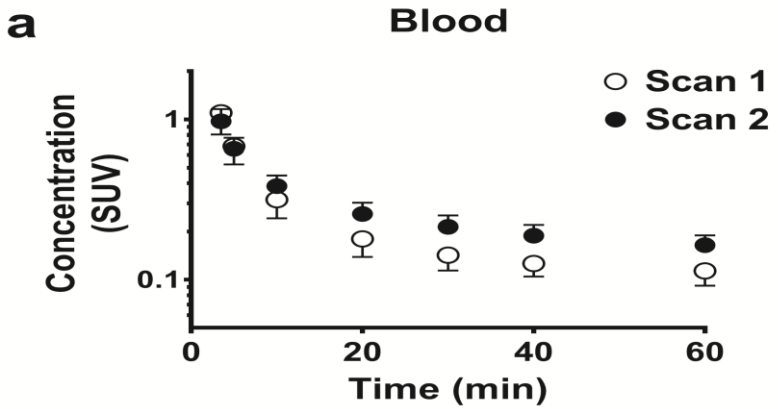
PET with [^{11}C]tariquidar in humans

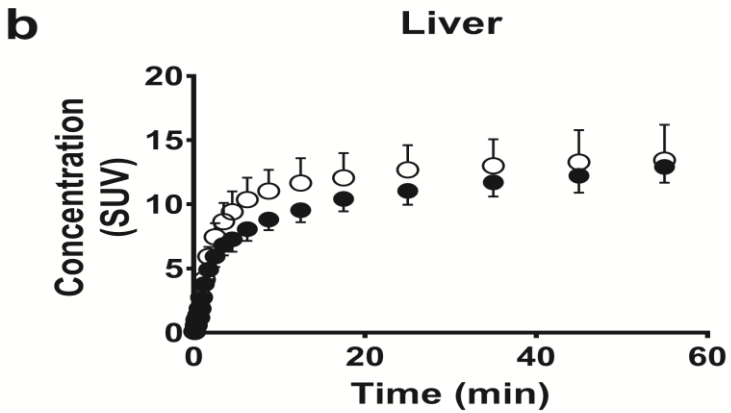


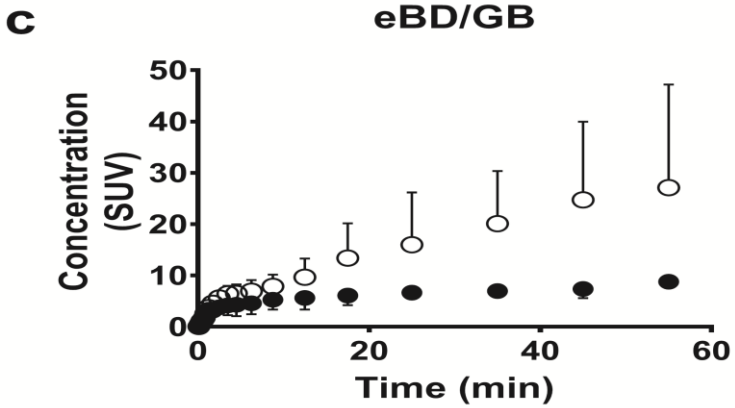
[^{11}C]Tariquidar

Scan 1: [^{11}C]tariquidar microdose (< 10 µg)
Scan 2: [^{11}C]tariquidar microdose + co-infusion of tariquidar



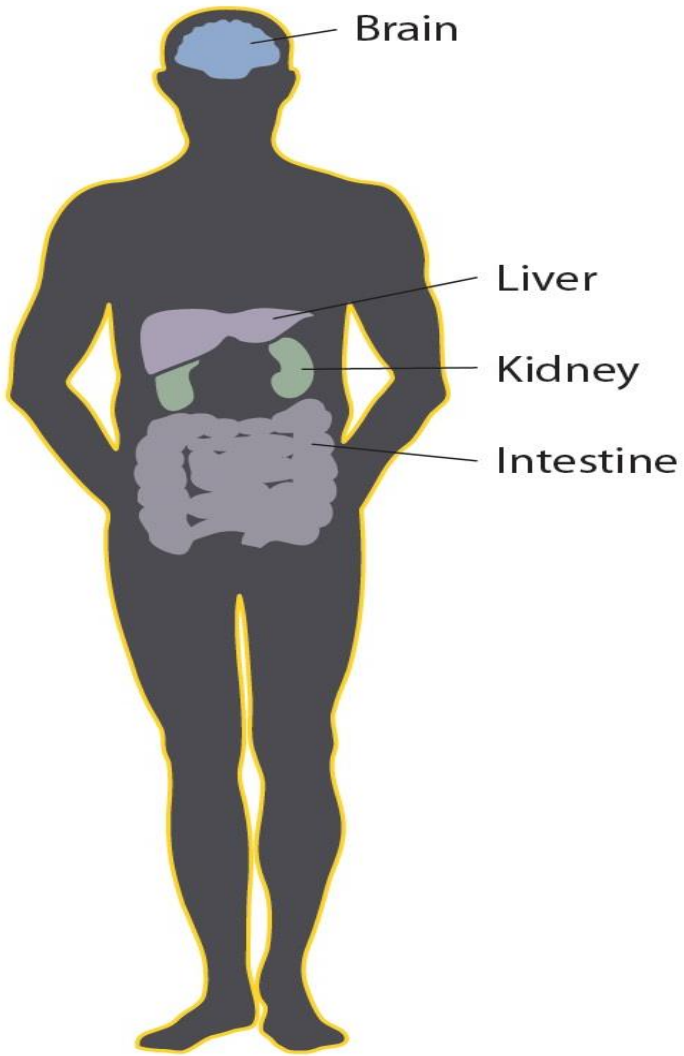


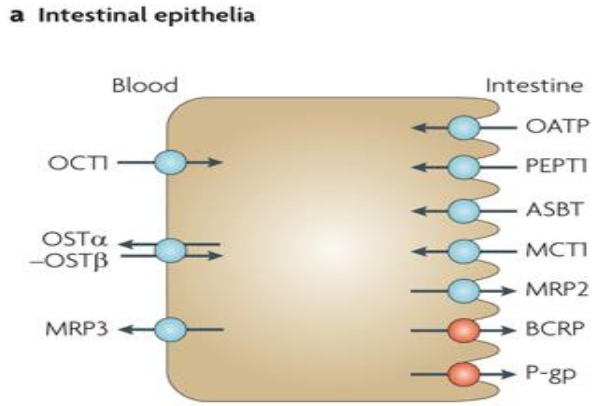


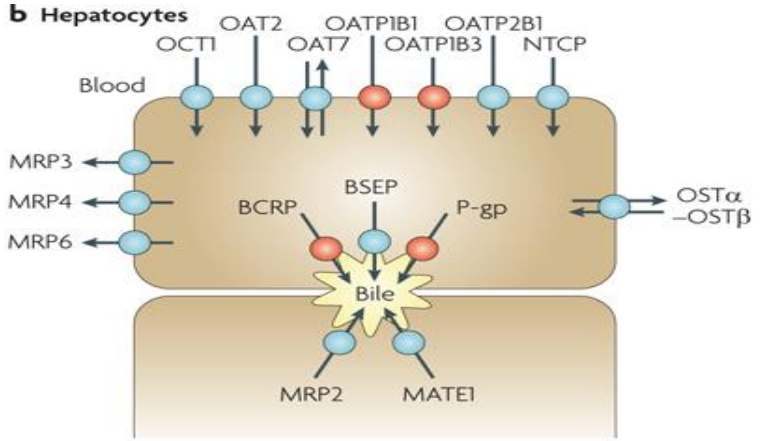


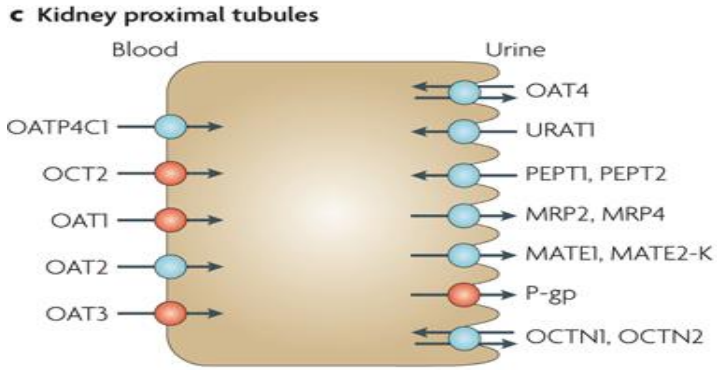
I Hernández Lozano et al Mol Pharm 2020;17:316-26

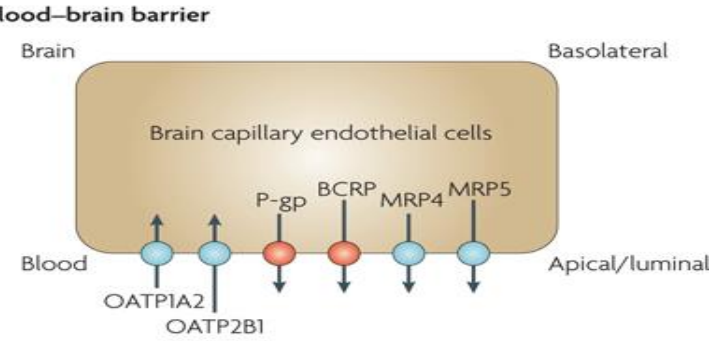
Beispiel 4: Assessment of transporter-mediated drug-drug interactions in tissue(s)









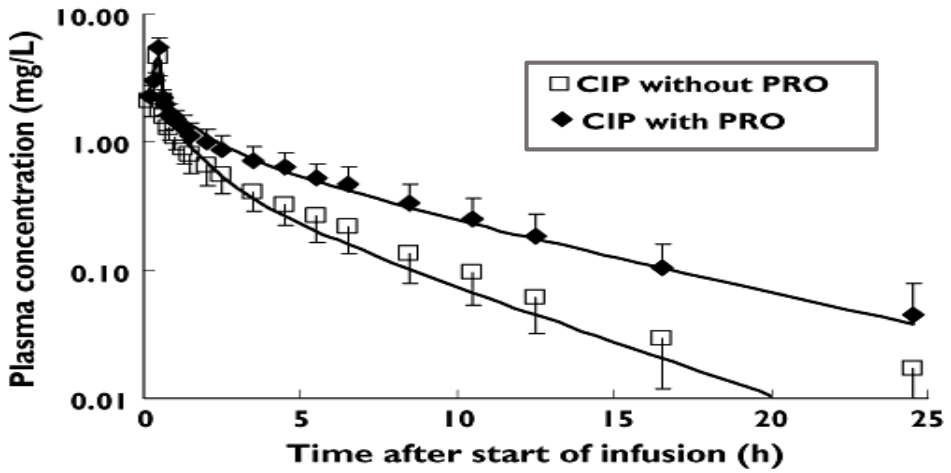


- Concomitant intake of two drugs which interact with the same transporter(s) → regulatory authorities require assessment of DDI risk for new drug candidates

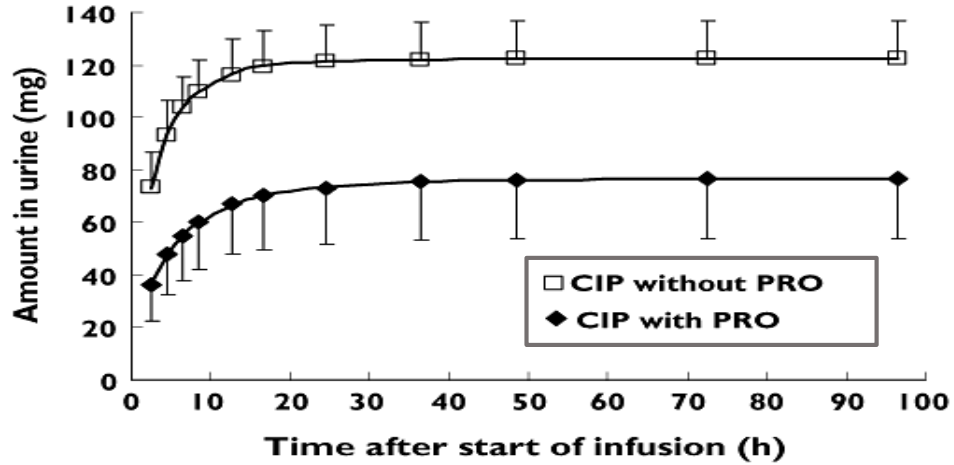
K Giacomini et al Nat Rev Drug Discov 2010;9:215-36

DDI between probenecid and ciprofloxacin in humans

Ciprofloxacin in plasma



Ciprofloxacin in urine

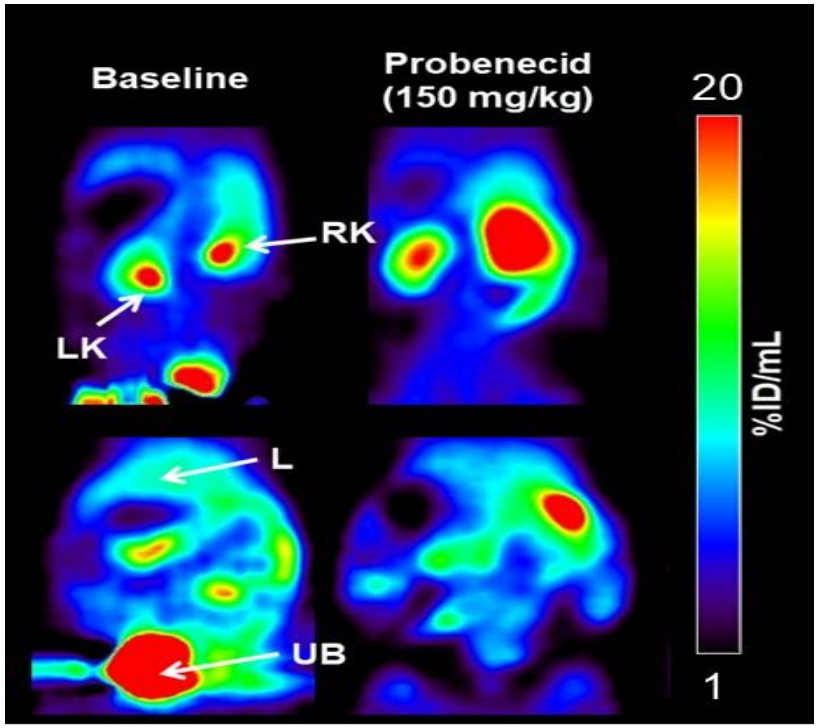


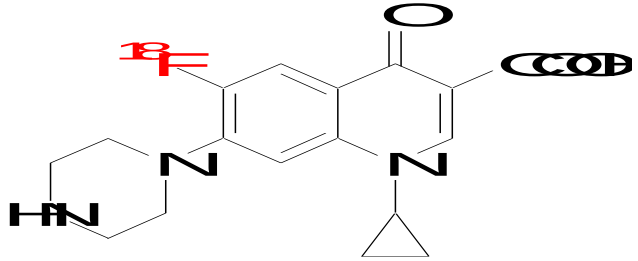
PK parameters

	Ciprofloxacin Average [95% CI] With PRO	Without PRO
CL_T (l h^{-1})	21.8 [17.9–25.6]	37.0 [31.8–42.2]
CL_R (l h^{-1})	8.12 [6.45–9.79]	22.5 [19.4–25.5]
CL_{NR} (l h^{-1})	13.6 [10.5–16.7]	14.5 [11.5–17.5]
AUC_{inf} (mg l^{-1} h)	9.90 [8.05–11.8]	5.68 [4.81–6.56]

U Jaehde et al Clin Pharmacol Ther 1995;58:532-41; C Landersdorfer et al Br J Clin Pharmacol 2010;69:167-78

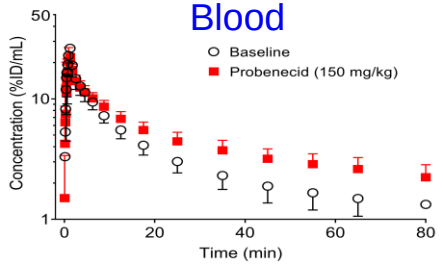
Probenecid/[^{18}F]ciprofloxacin DDI assessed with PET in mice



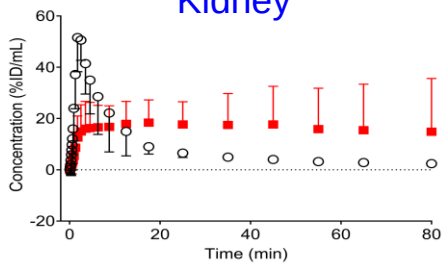


[^{18}F]Ciprofloxacin

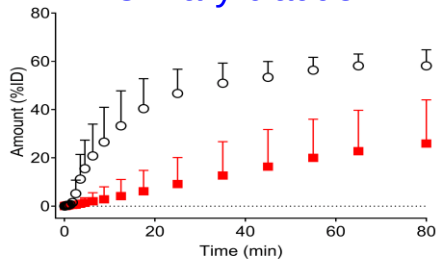
Blood



Kidney



Urinary bladder



I Hernández Lozano et al Antimicrob Agents Chemothern 2023; 67(3):e0149322

Strenghts and limitations of PET-microdosing

Strength	Limitation
Labeling of small drug molecules without structural modification (^{11}C, ^{18}F)	Radiolabeling required
Assessment of drug tissue distribution and tissue PK → long axial FOV PET permits dynamic whole-body imaging	Measures total tissue radioactivity → cannot distinguish radiolabeled parent drug from metabolites
Kinetic tissue data + arterial blood sampling → modeling	Limited spatial resolution → cannot distinguish different tissue compartments or cell types or intracellular from extracellular drug
Multiple PET scans per subject possible depending on radionuclide (radiation exposure) → scans without/with dosing of unlabeled drug (target engagement studies), longitudinal studies	Radiation exposure of subjects (depending on radionuclide)
Usually no toxicity concerns (microdosing)	Microdose may not always predict the tissue distribution of a therapeutic dose (lack of dose linearity due to saturable processes)
Regulatory framework for abbreviated toxicity studies (ICH guideline M3(R2))	Short half-life of ^{11}C (limited measurement time)

Zusammenfassung

- Phase 1 viel mehr als nur Sicherheit und Verträglichkeit in Gesunden
- Regulativ können Sie ganze (Sub) Indikationen unterstützen
- Müssen nicht auf eine eng definierte Population beschränkt sein
- PK und PD Studien sensitiver als Phase 3 und Endpunkt Studien
- Imaging ist ein Phase 1 Werkzeug das für PD und PK (ADME) eingesetzt werden kann.