

# Messung von Antibiotika im Gewebe

Markus Zeitlinger

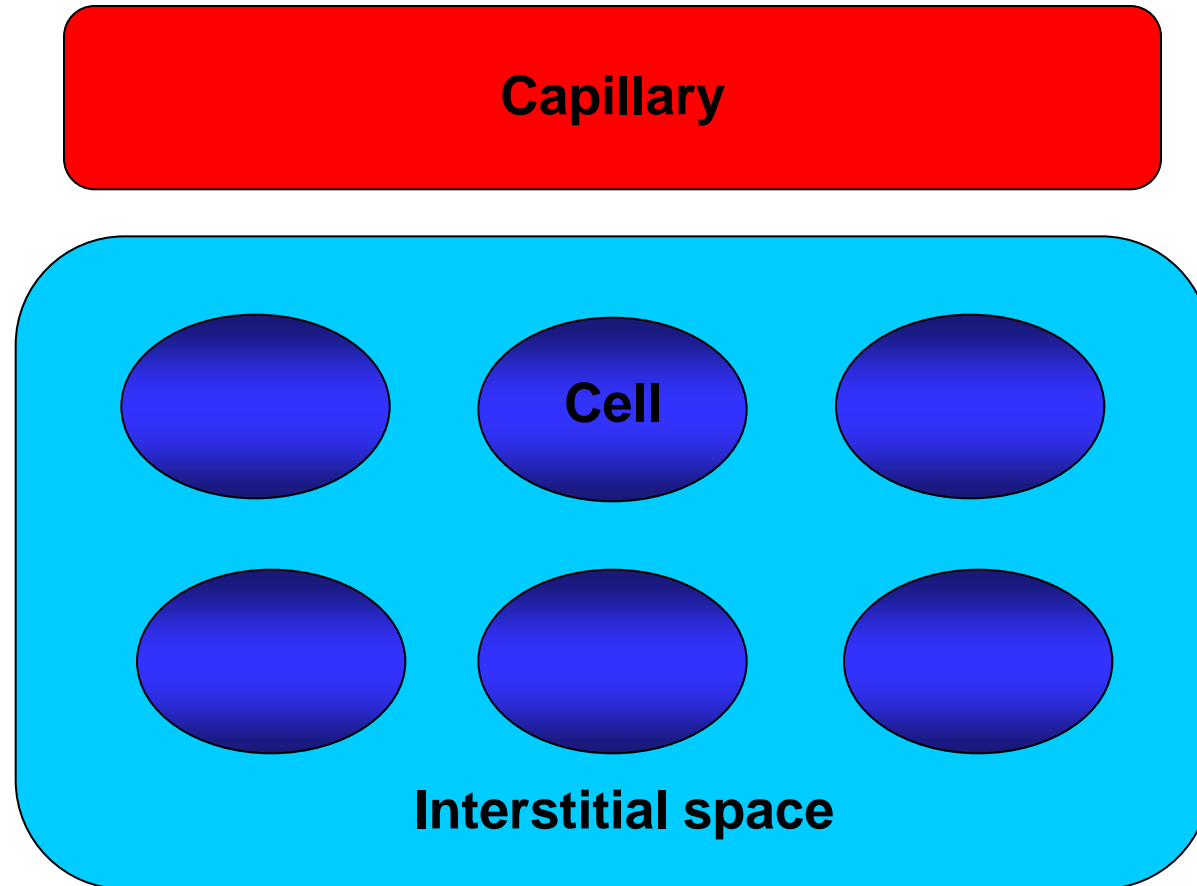
# Überblick

- 1) Wieso ist das Gewebe von Interesse, reicht Plasma nicht?
- 2) Welche Techniken stehen uns zur Verfügung?

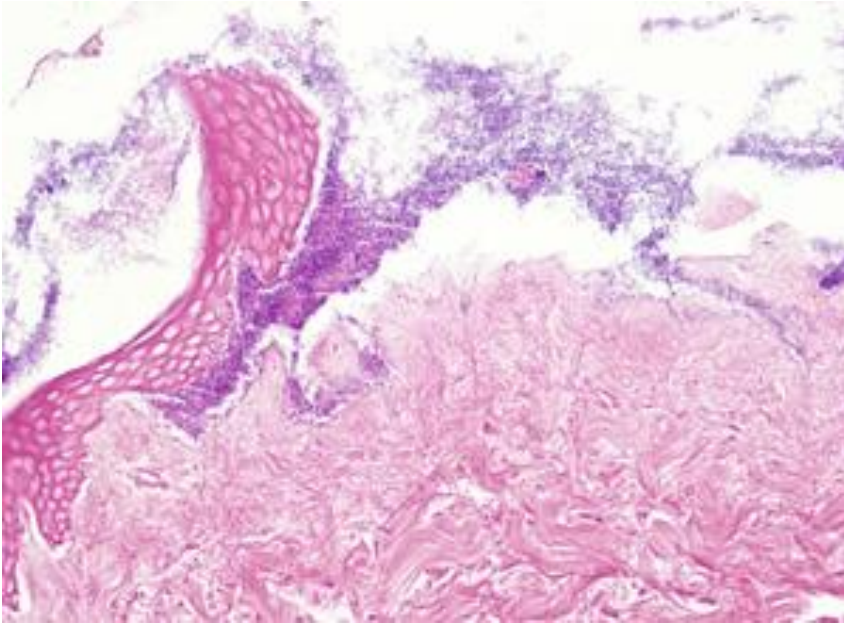
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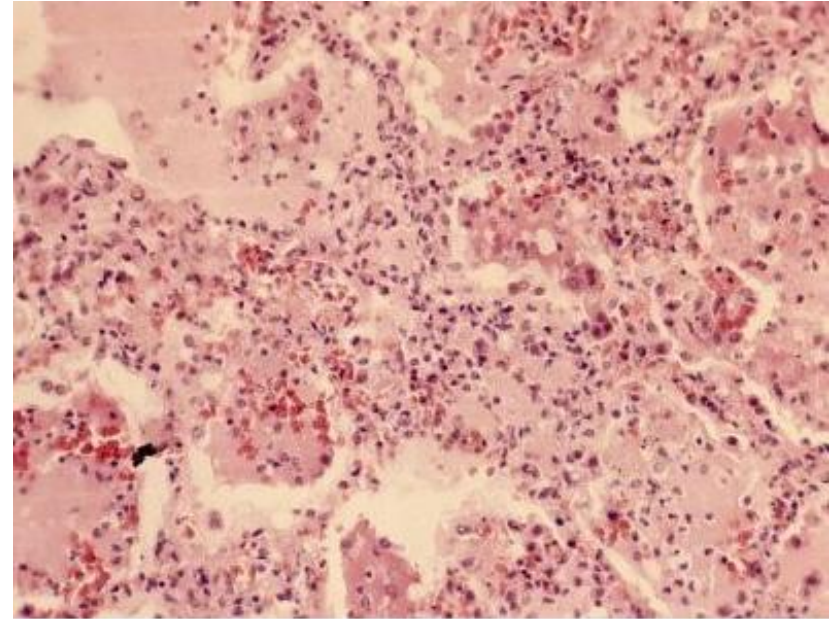
# I: Wo messen wir und wo befindet sich der Keim?



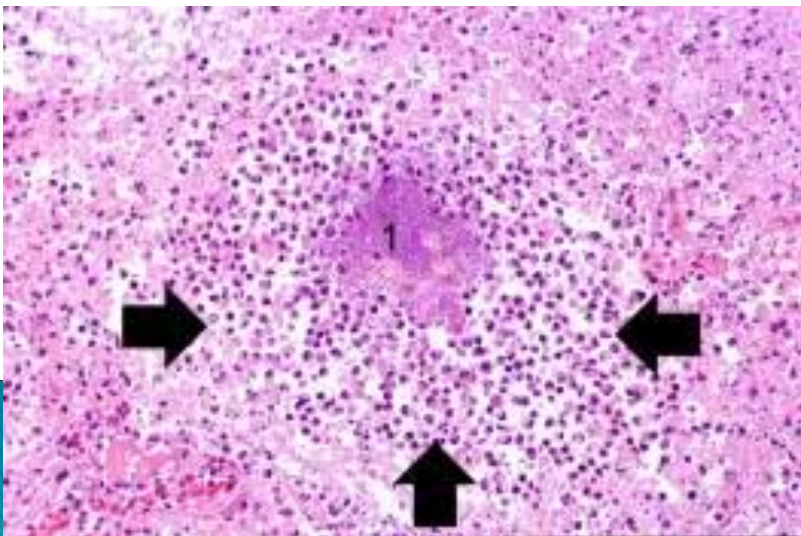
Wunde



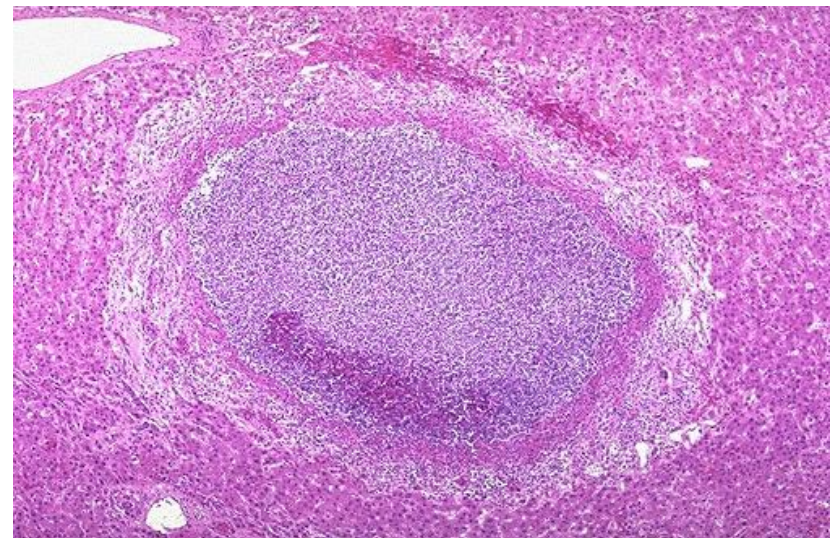
Pneumonie



Früher Abszess



Reifer Abszess



## II: Ist Blut/Gewebe Equilibrium immer garantiert?

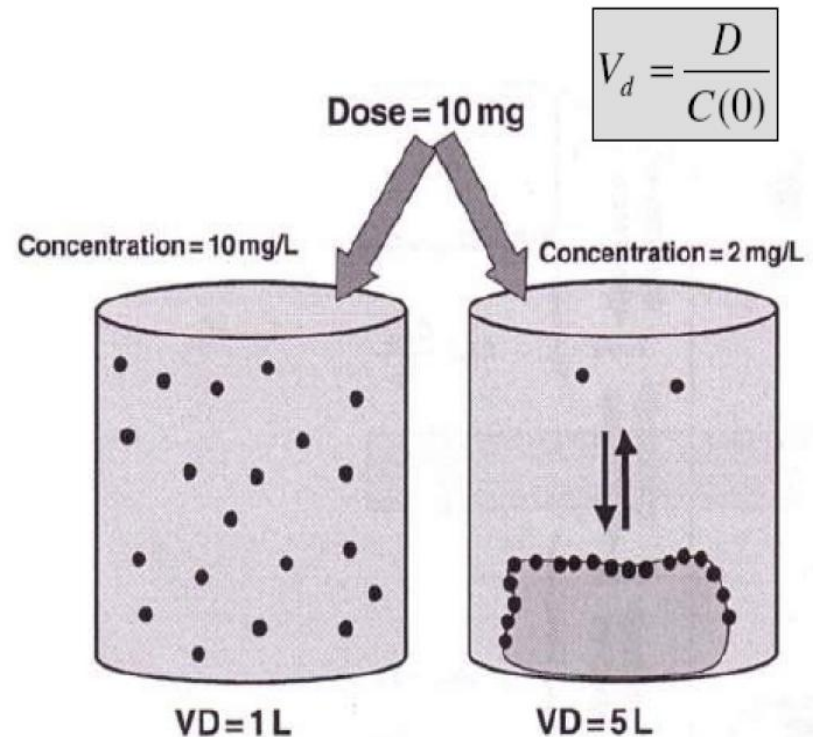


# Scheinbares Verteilungsvolumen

Amoxicillin 0.2 l/kg

Isoniazid 0.6 l/kg

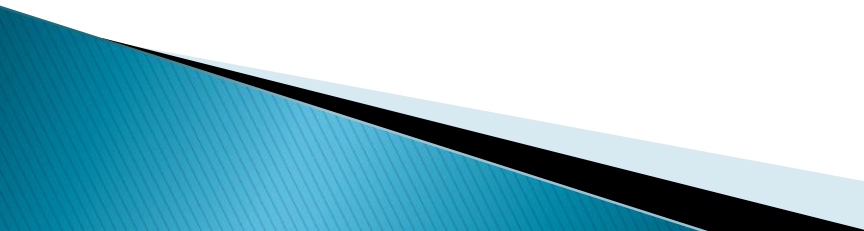
Azithromycin 30.0 l/kg



# Verteilung ist nicht nur durch spontane Diffusion bestimmt

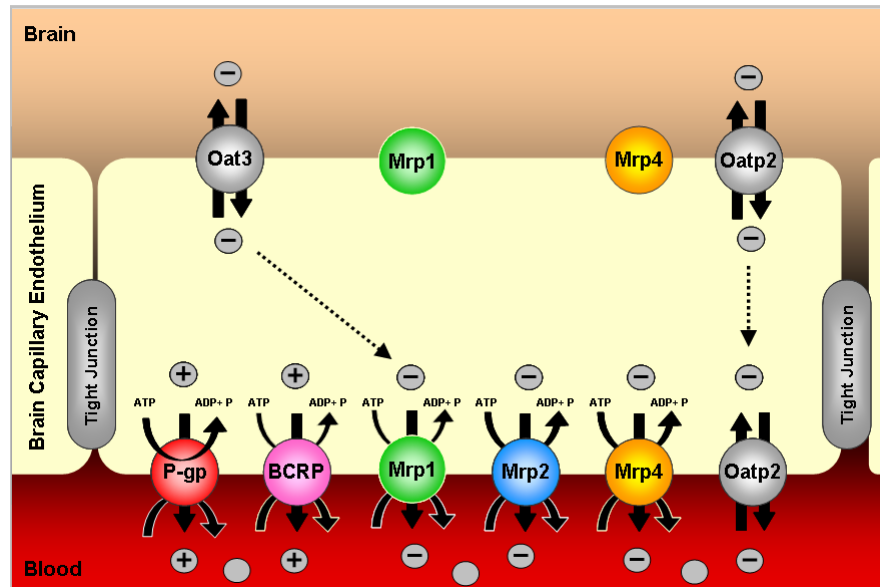
- ▶ Dichte der Kapillaren und Blutfluss

## Ungleichgewicht im Steady State

- ▶ Aktive Transporter
  - ▶ pH-Falle
  - ▶ Onkotischer Druck
  - ▶ Spontanmetabolismus
  - ▶ Abtransport durch Lymphgefäße
- 



# Verschiedene Barrieren im Körper



P-glycoprotein

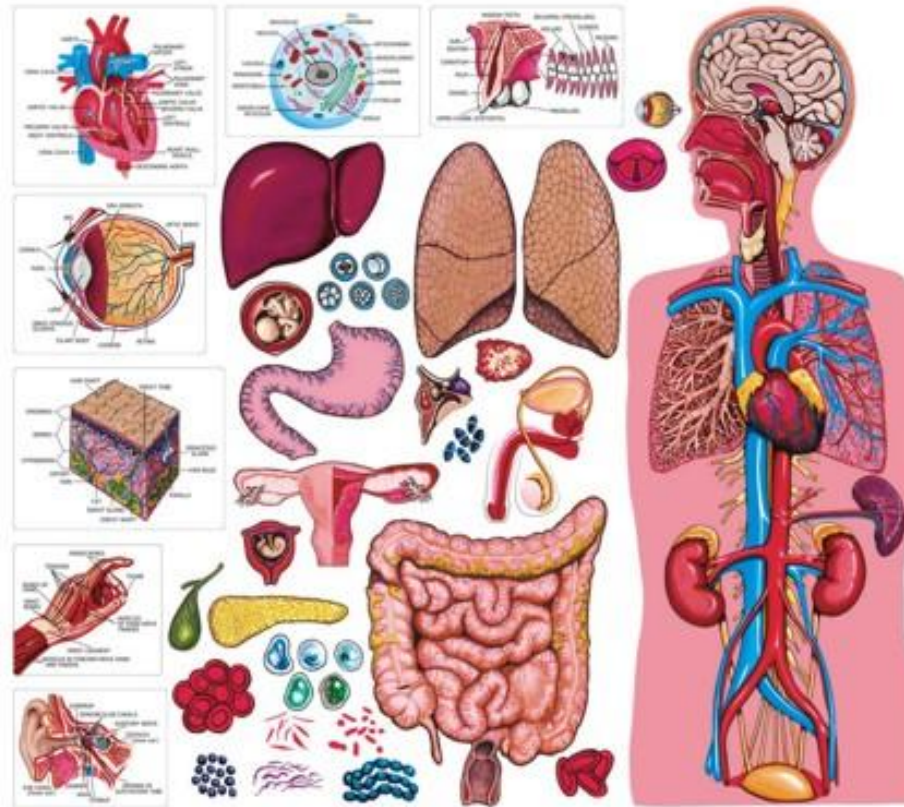
Multidrug resistance proteins

Breast cancer resistance protein

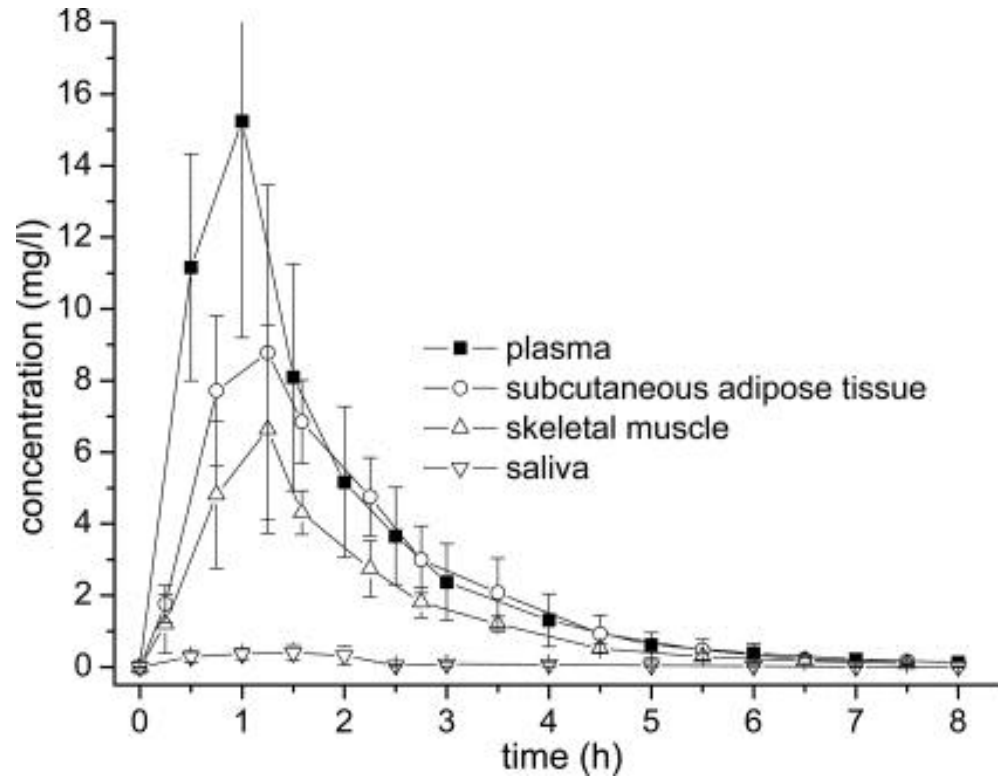
Organic anion transporting polypeptides

Organic anion transporter

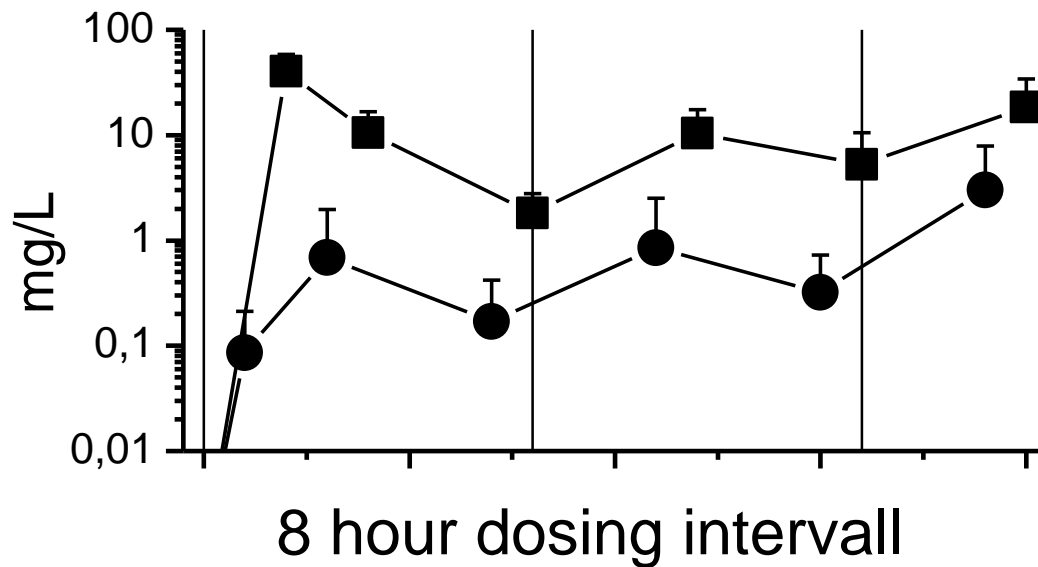
# III: Reicht ein Gewebe aus um die PK in anderen vorherzusagen?



# Doripenem PK I



# Doripenem PK II

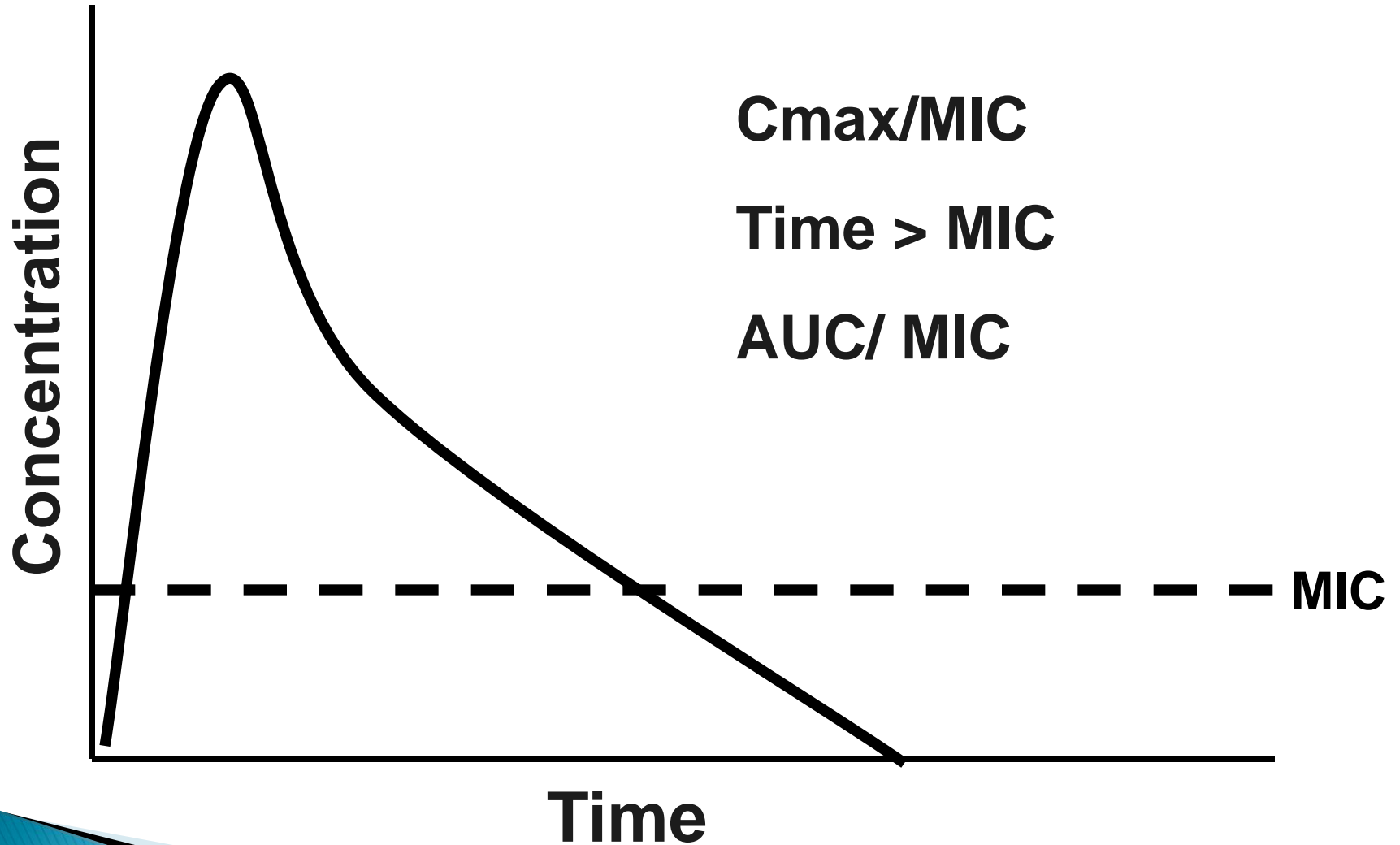


# Überblick

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# Optimal I:

## Volles Konzentrations - Zeit Profil



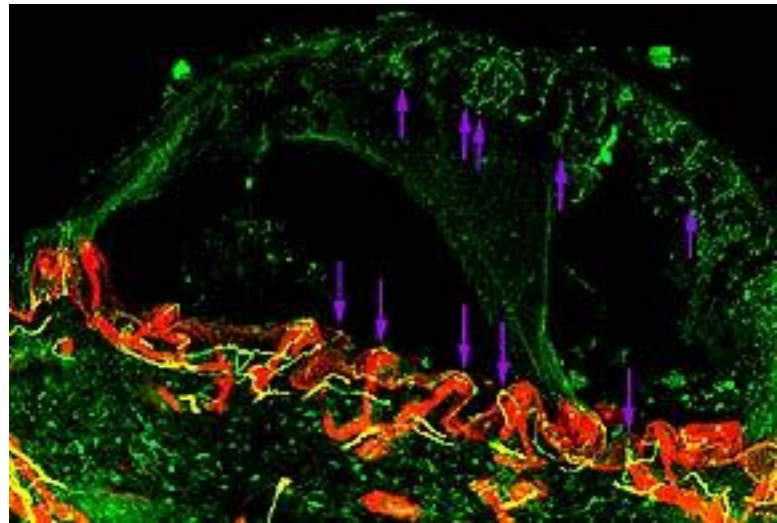
## Optimal II:

Anatomisch – Histologische Zuordnung

## Optimal III:

Invasivität und Schmerz für Probanden

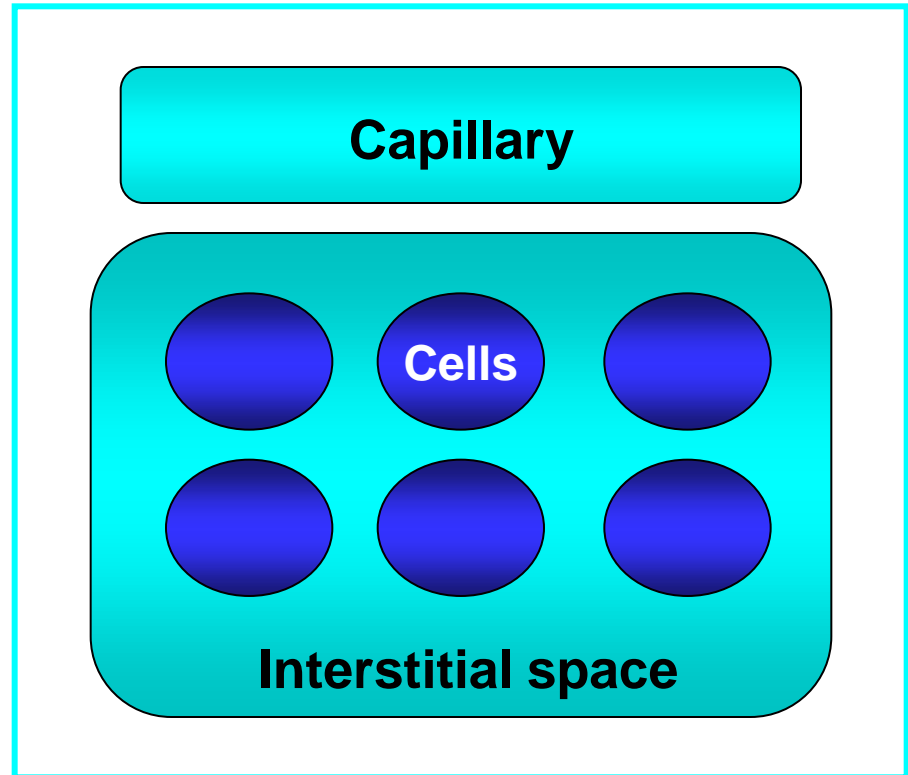
# Skin Blister





# Biopsie:

Vermischung verschiedener Kompartimente



# EMA Points to consider on PK and PD in the development of antibacterial medicinal products

- ▶ *“...include measurement of human tissue and body fluid concentrations.”*
- ▶ *“...unreliable information is generated from assays of drug concentration in whole tissues (e.g. homogenates)”*

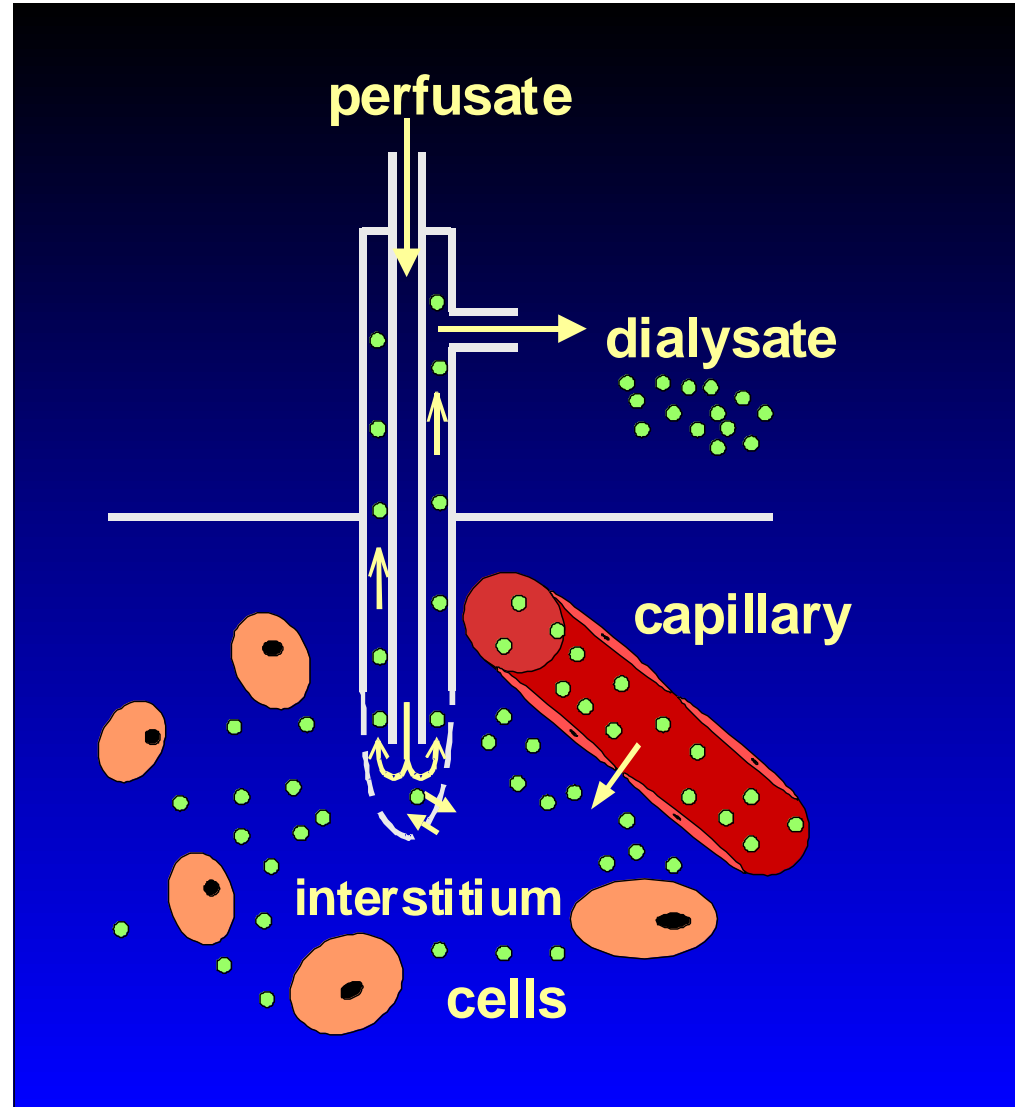
# Biopsie



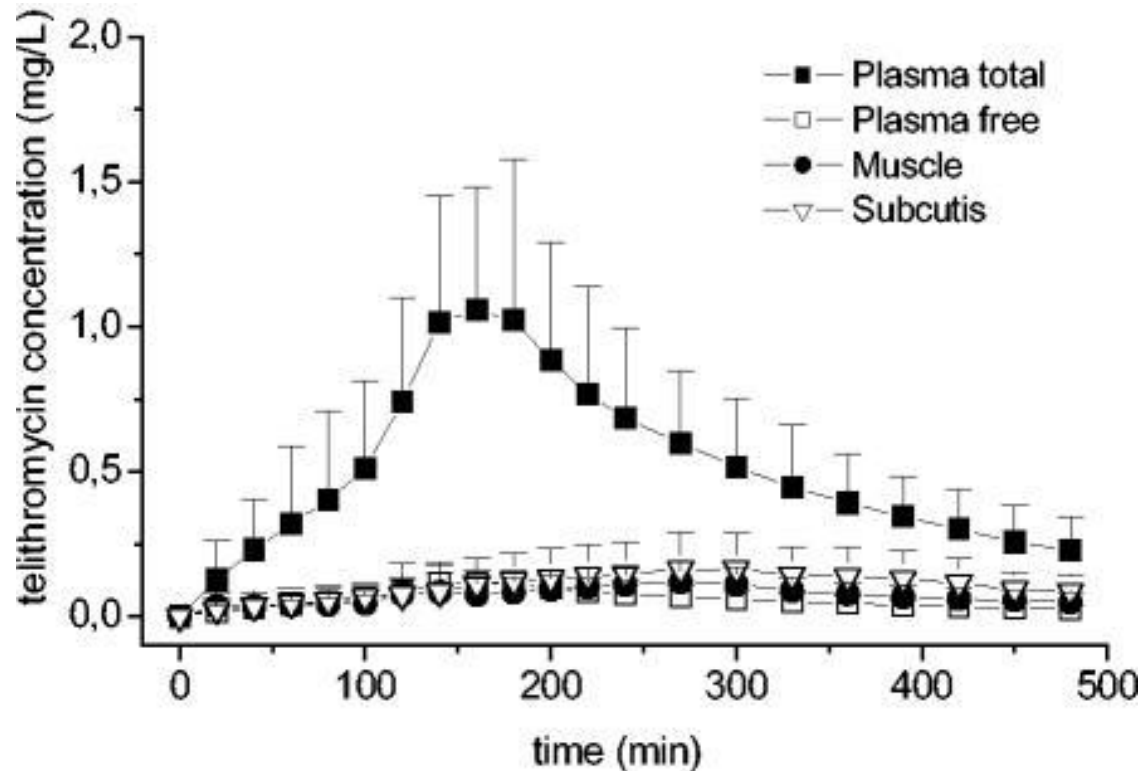
	$C_{\max}$ tonsill (mg/L)	$C_{\max}$ tonsill/ $p_{\max}$ Plasma
Azithromycin	5.5	13.8
Clarithromycin	6.7	3.72
Roxithromycin	2.2	0.28
Telithromycin	3.95	3.4

Fraschini F. J Antimicrob Chemother 1991  
Foulds G. J Antimicrob Chemother 1993  
Gehanno P. Int J Antimicrob Agents 2003

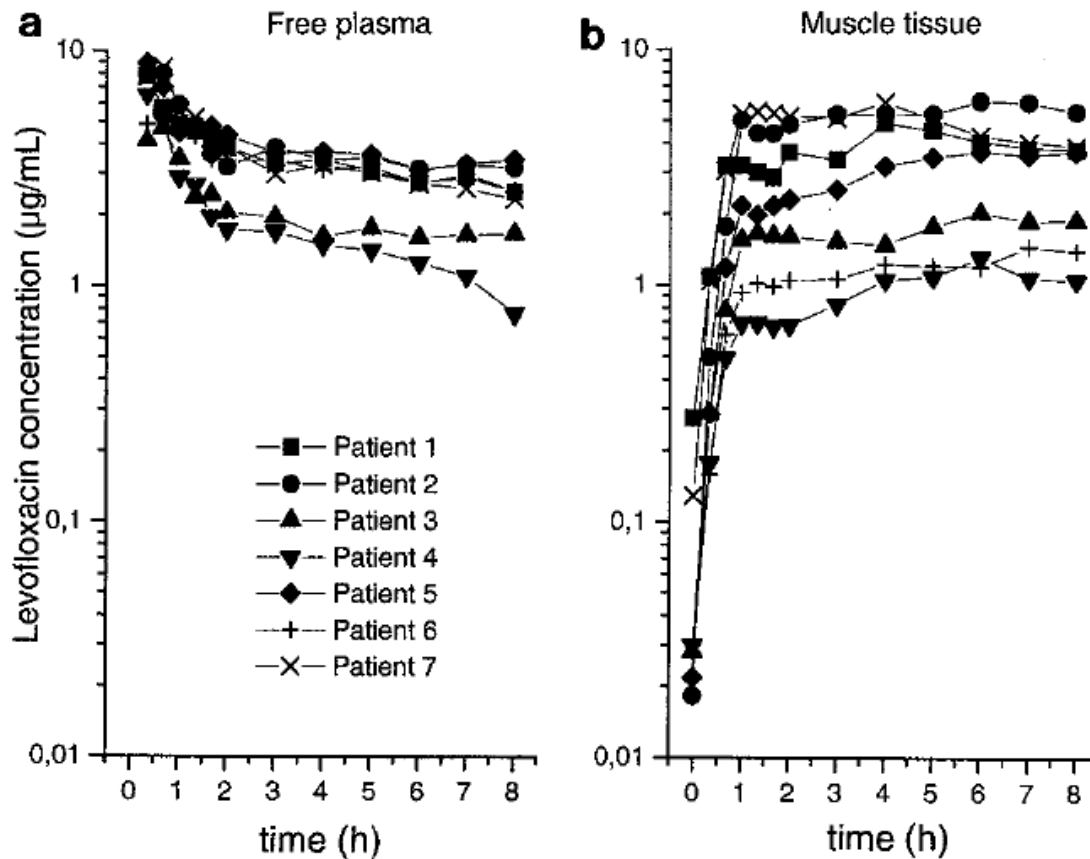
# Microdialyse



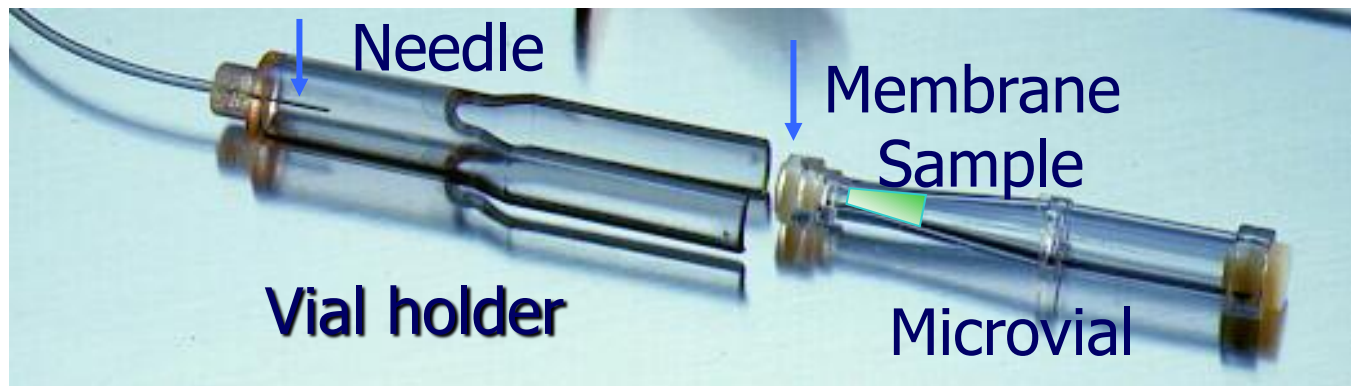
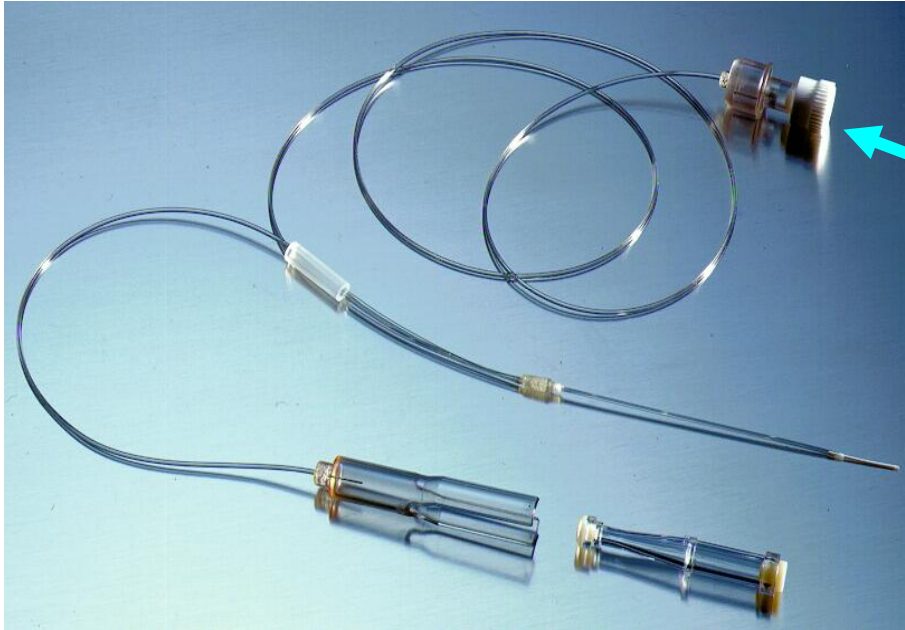
# Telithromycin 800mg



# Individual penetration of levofloxacin in ICU patients

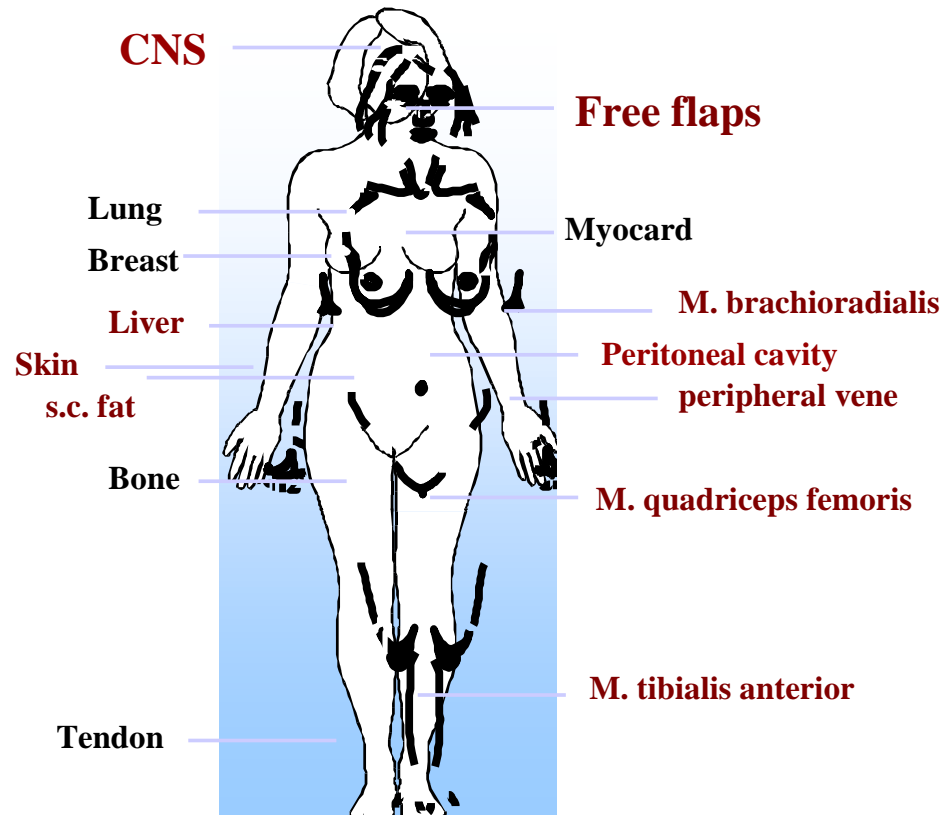


# Ausrüstung



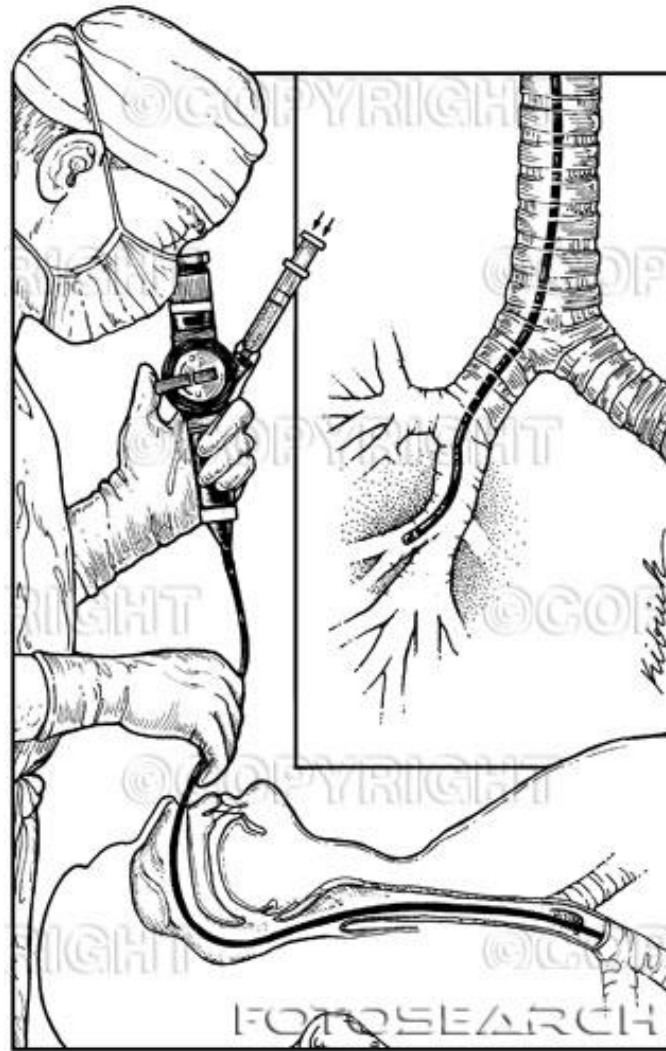
# Wo ist Mikrodialyse möglich?

**Red:**  
**CE certified**

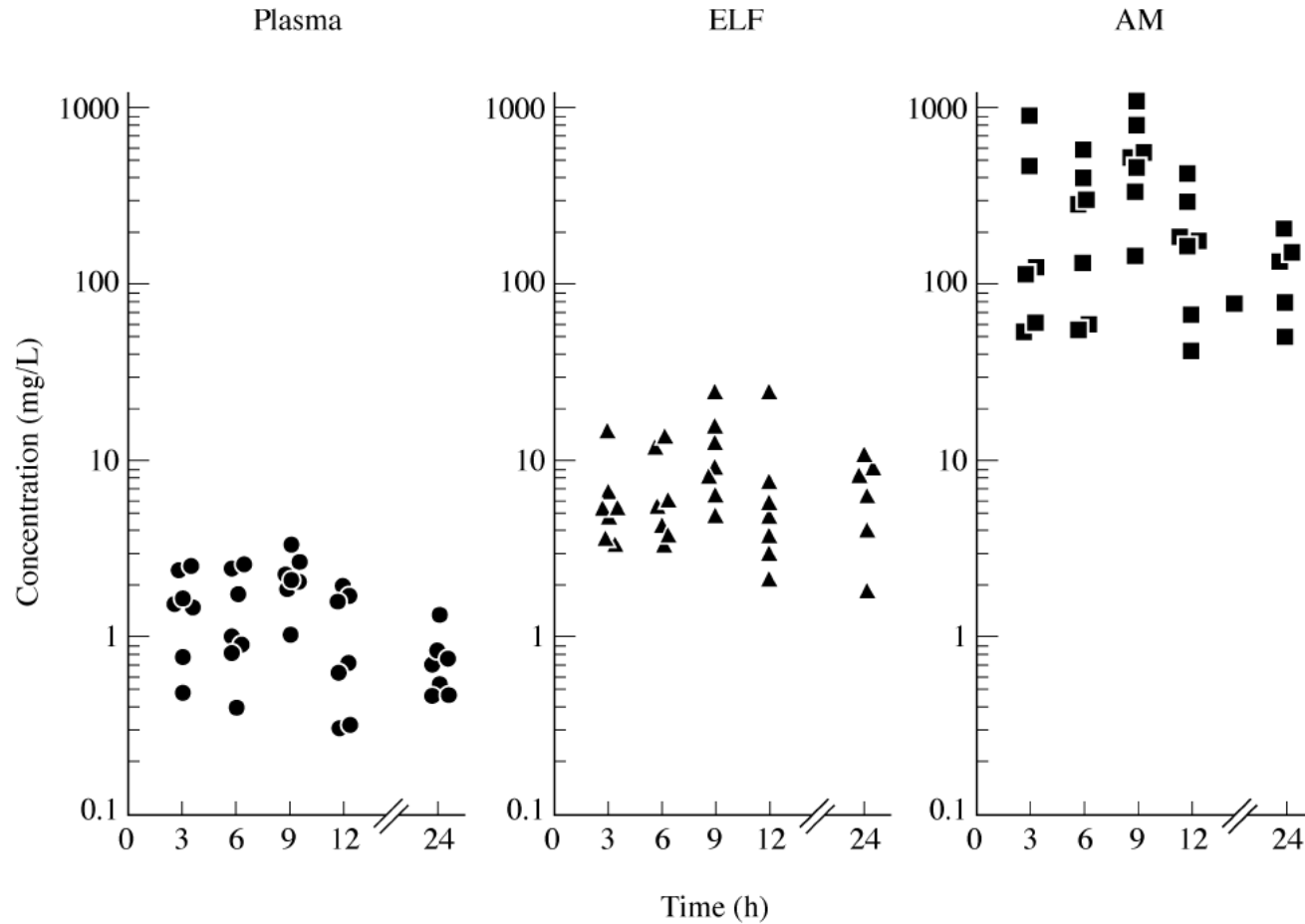




# Bronchoalveolar Lavage (BAL)



# Clarithromycin





# PET

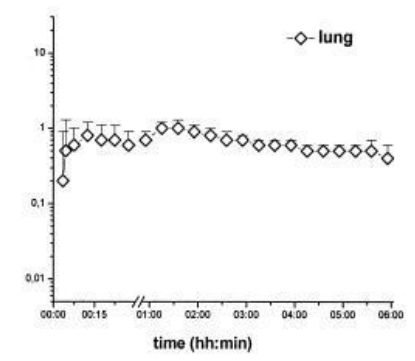
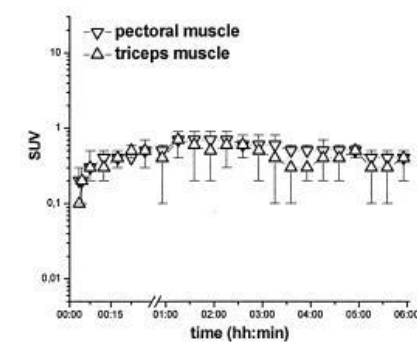
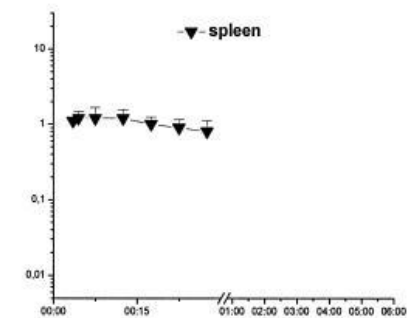
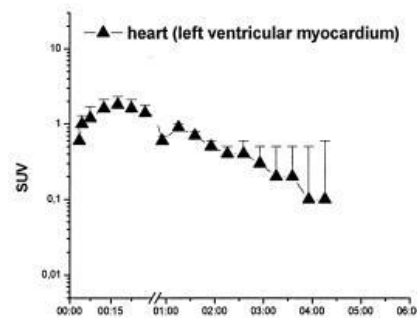
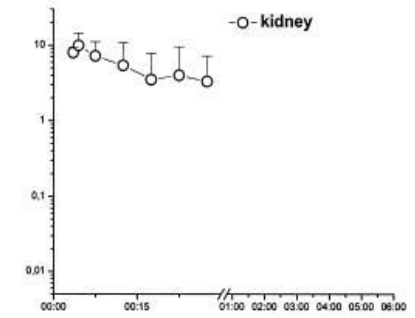
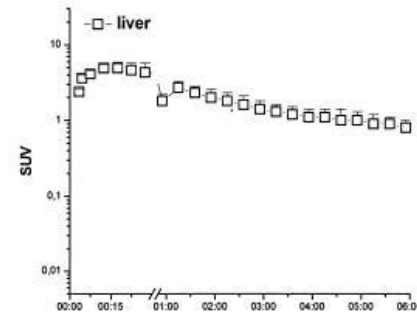
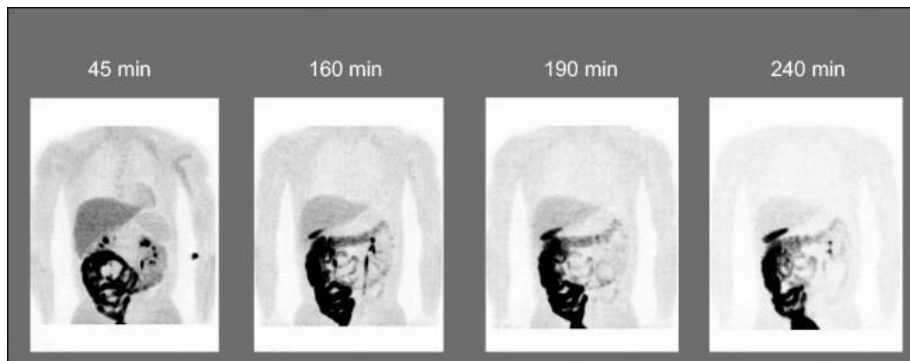
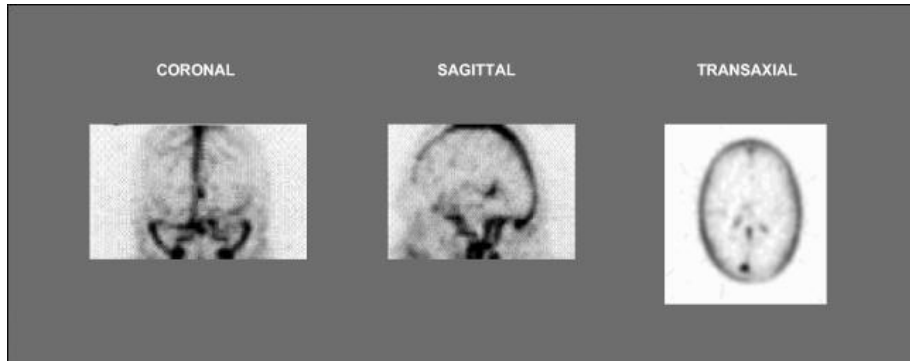
ARCS, Radiopharmaka



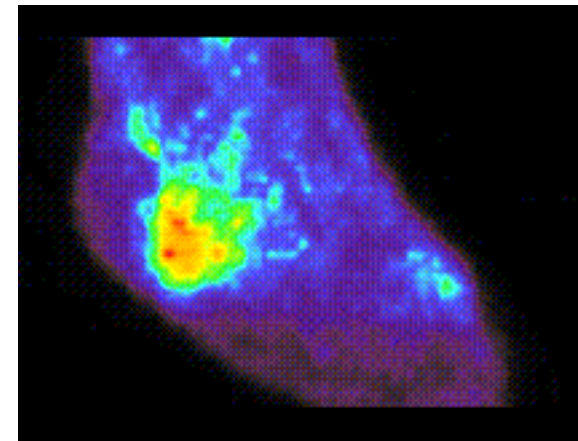
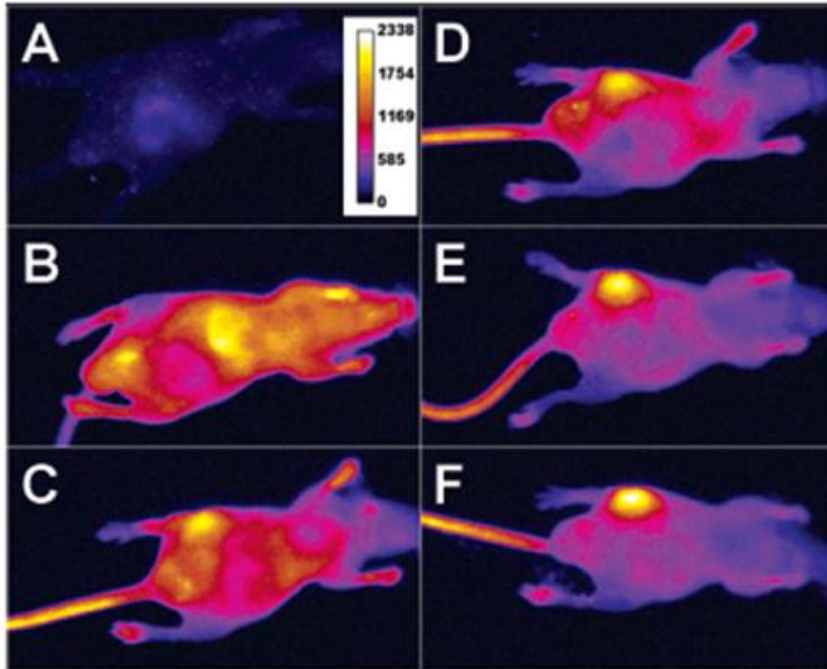
## Physical characteristics of radionuclides used in PET imaging<sup>a</sup>

Radionuclide	Half-life	Common forms
$^{15}\text{O}$	2 min	$^{15}\text{O}_{2}$ , $\text{C}^{15}\text{O}_{2}$ , $\text{C}^{15}\text{O}$
$^{13}\text{N}$	10 min	$^{13}\text{NH}_{3}$ , $^{13}\text{N}_{2}$
$^{11}\text{C}$	20 min	$^{11}\text{CO}_{2}$ , $^{11}\text{CO}$ , $^{11}\text{CH}$
$^{18}\text{F}$	1.8 h	$^{18}\text{F}_{2}$ , $\text{H}^{18}\text{F}$
$^{76}\text{Br}$	16.2 h	$^{76}\text{Br}_{2}$
$^{124}\text{I}$	4 days	$\text{Na}^{124}\text{I}$

# [<sup>18</sup>F]ciprofloxacin

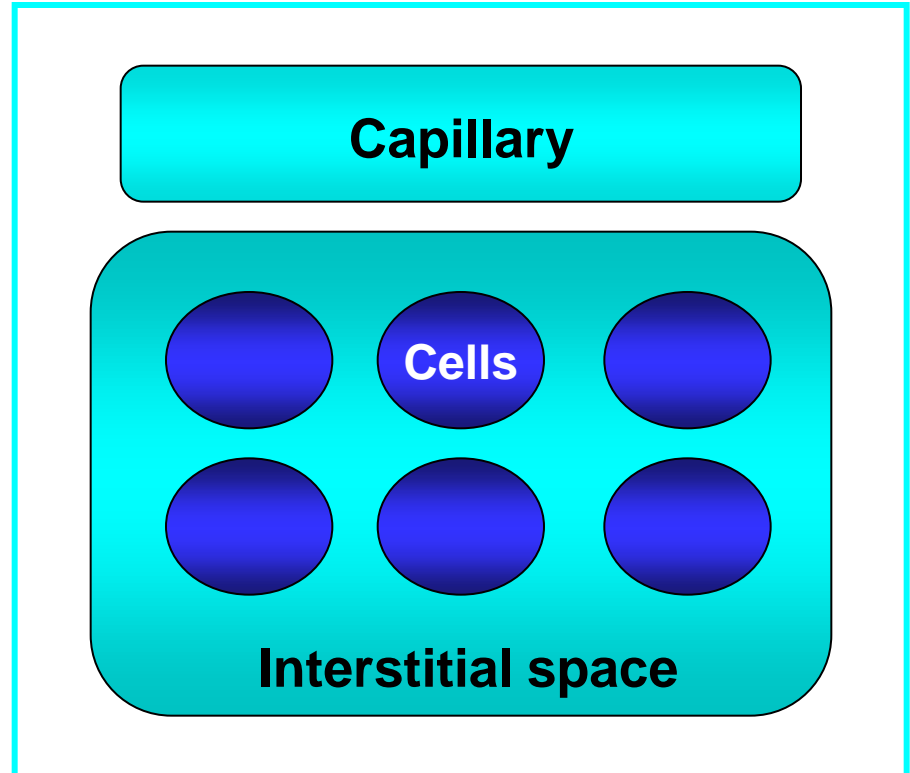


# Visualisierung von Infektionen

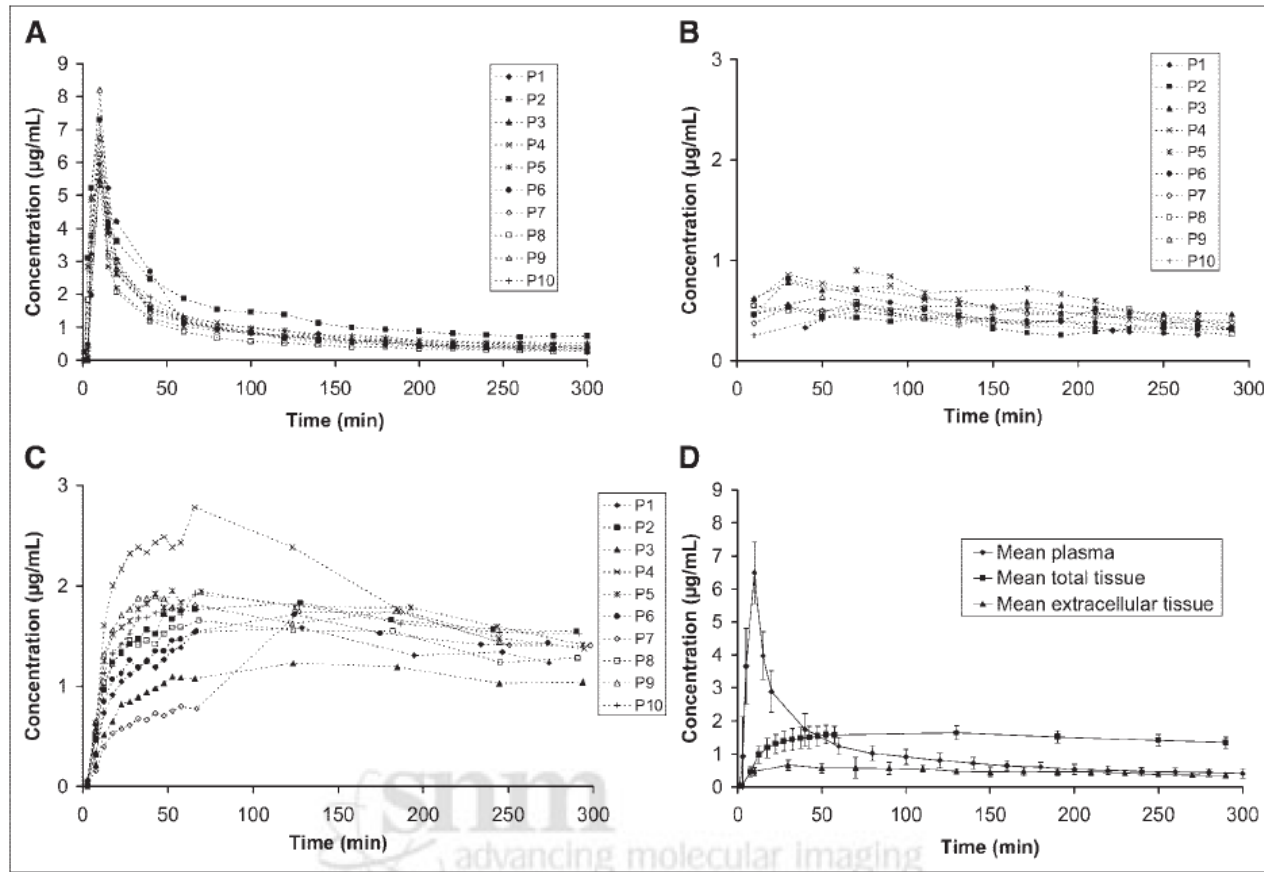


# PET:

Vermischung verschiedener Kompartimente



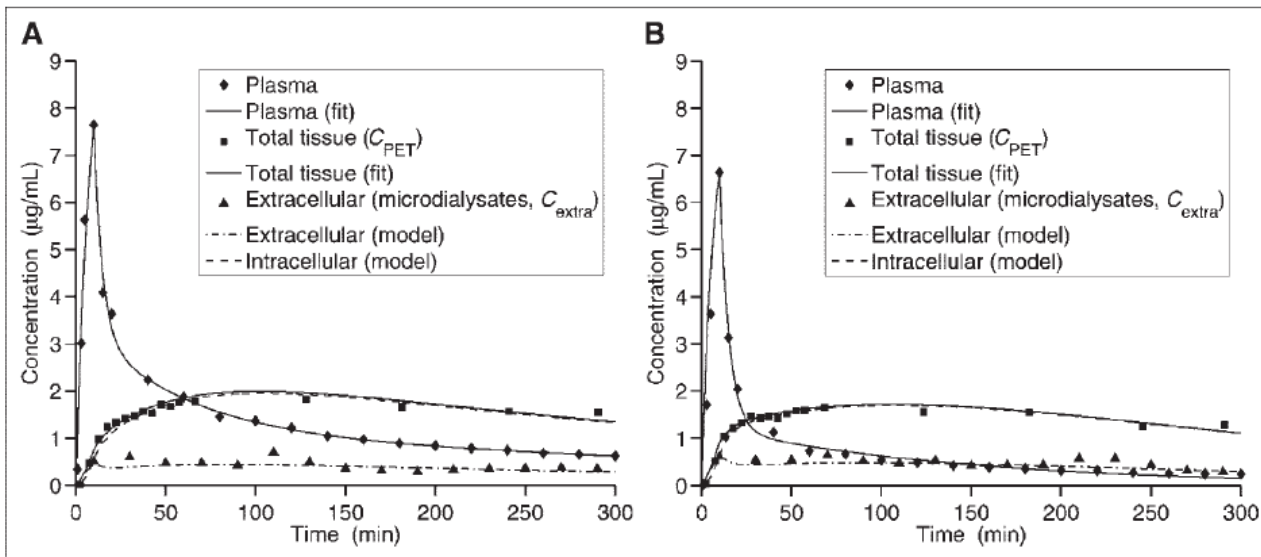
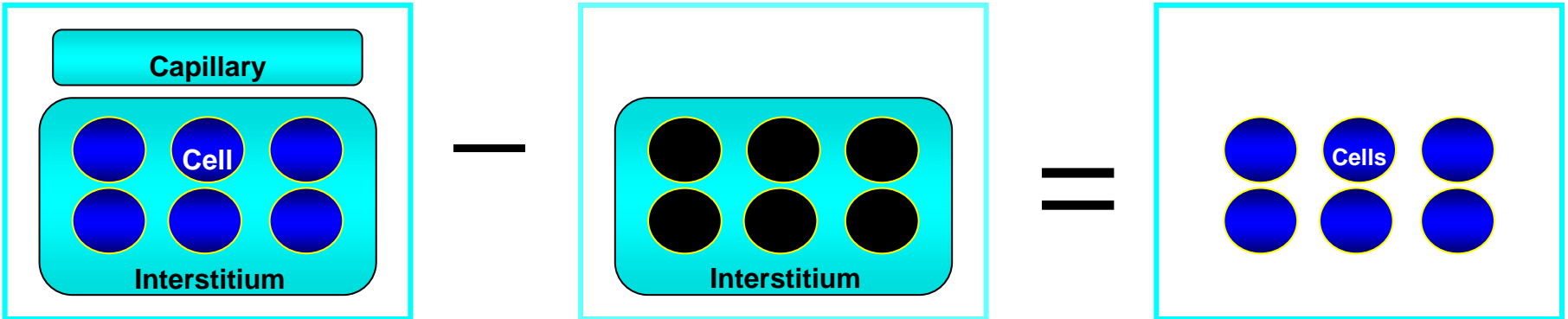
# PET + Microdialyse



**FIGURE 2.** Individual (A–C) and mean  $\pm$  SD (D) concentration–time profiles of ciprofloxacin in plasma (A), extracellular space of skeletal muscle tissue (B), and total skeletal muscle (C) measured by combined microdialysis and PET after intravenous administration of a mixture of  $687 \pm 50$  MBq of  $^{18}\text{F}$ -ciprofloxacin and 200 mg of unlabeled ciprofloxacin to 10 healthy male volunteers (P1–P10 indicate individual subjects).

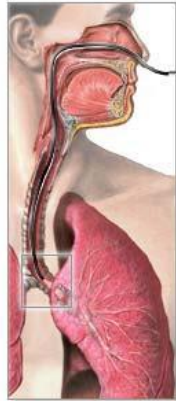


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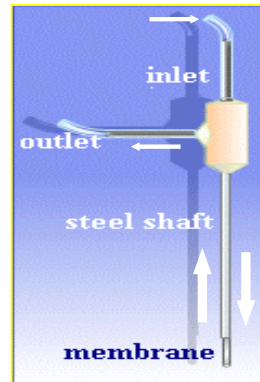


**FIGURE 3.** Blood and tissue concentration–time profiles of ciprofloxacin and fits obtained from 3-compartment, 4-rate-constant pharmacokinetic model from 2 representative subjects (A, subject 2; B, subject 8). Microdialysis data points ( $C_{extra}$ ) were corrected for extracellular protein binding.

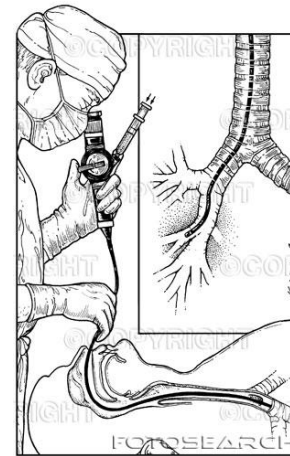
# Biopsie



# MD



# BAL



# PET



Konzentration-  
Zeit Profil

-

+

-

+/-

Anatomisch-  
Histologisch

+/-

+

+/-

+/-

Invasivität/  
Schmerz

-

+/-

-

+/-