

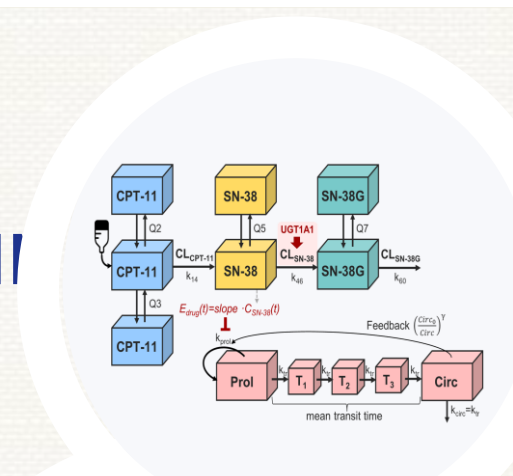
Modellierung in der Arzneistoffentwicklung

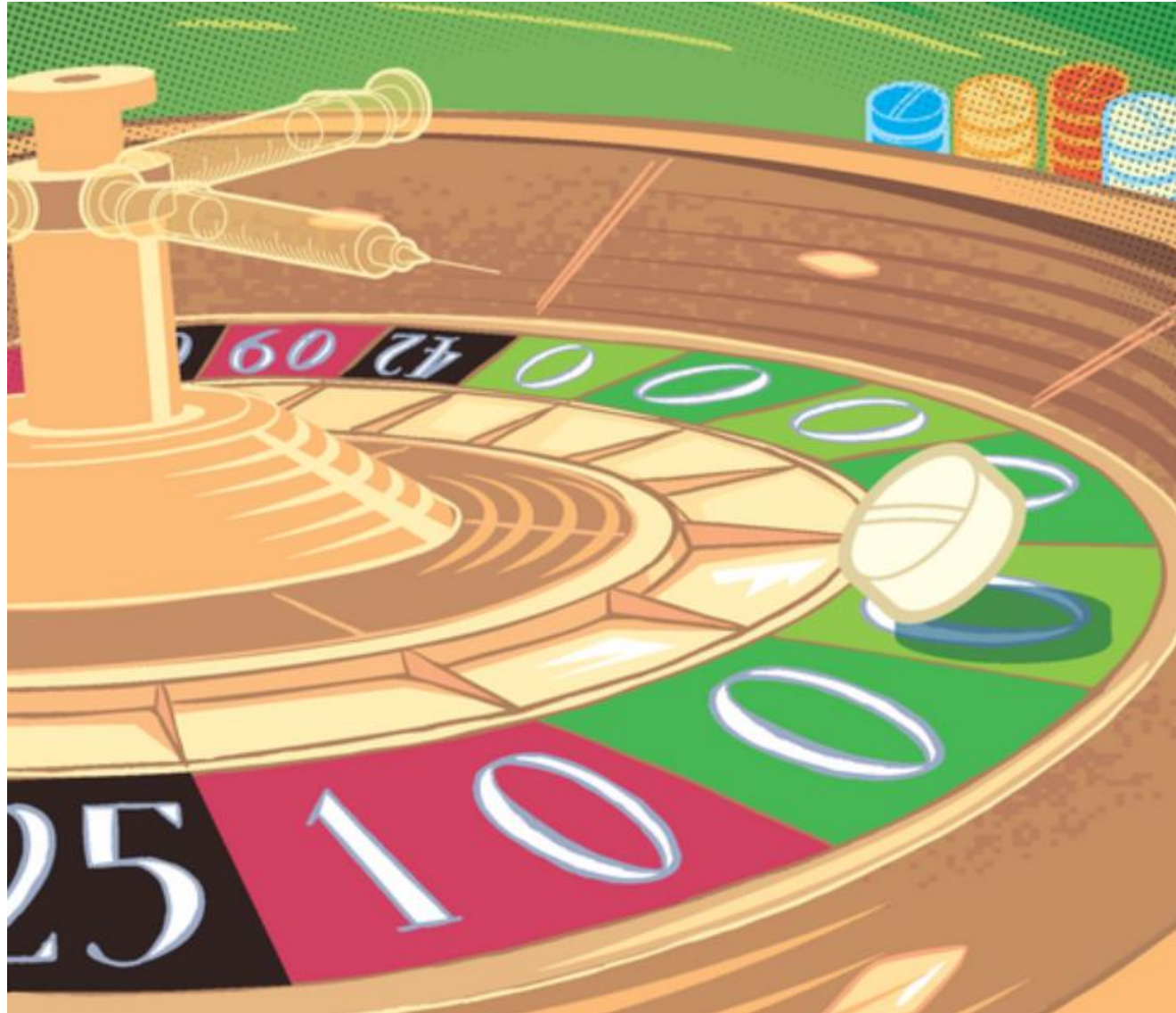
IRIS K. MINICHMAYR, MAG. PHARM. DR. RER. NAT.

Univ.Klinik für Klinische Pharmakologie, Medizinische Universität Wien

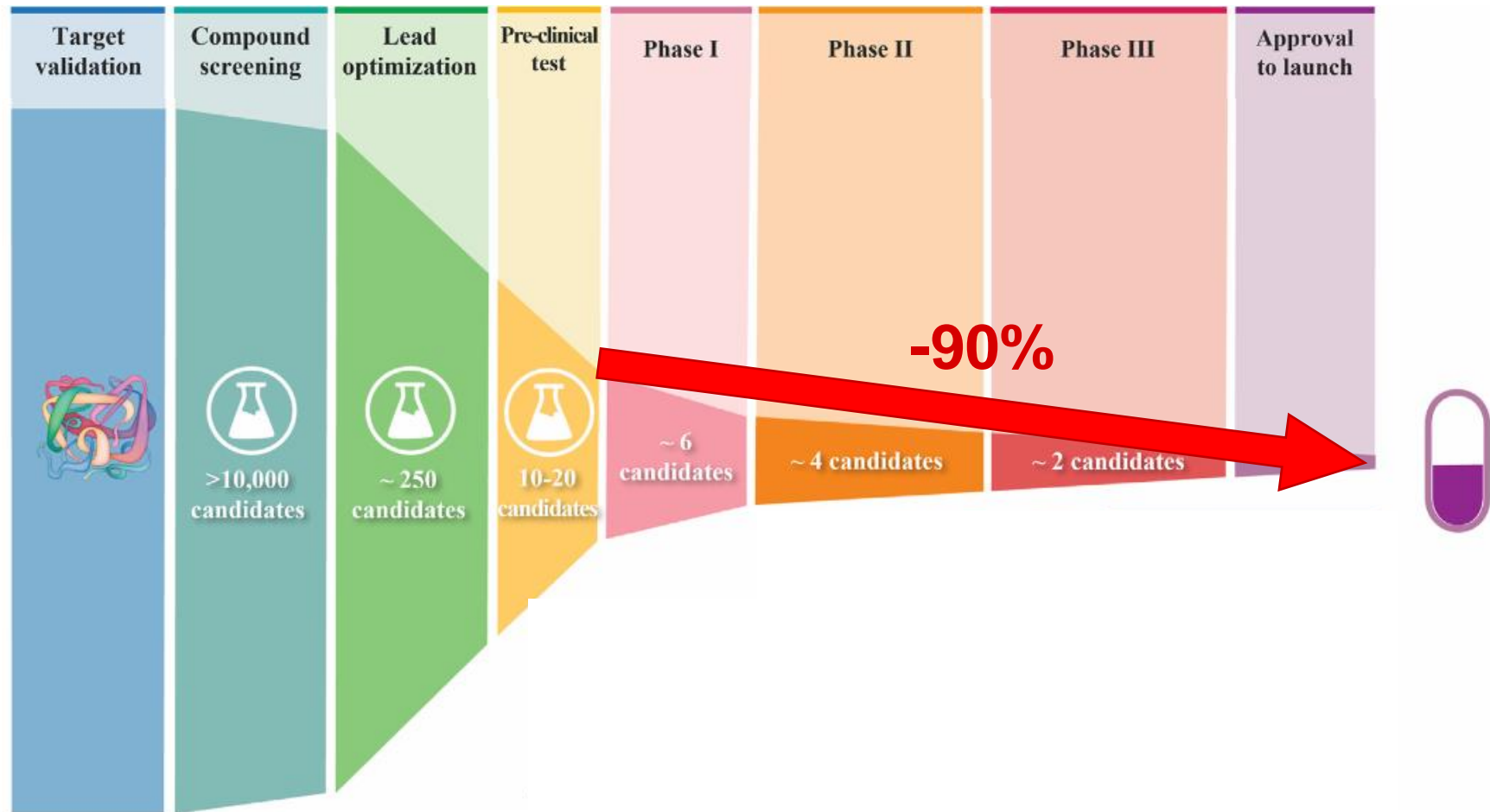
Clinical Pharmacometrics

GPMed Fortbildung, 28. September 2023

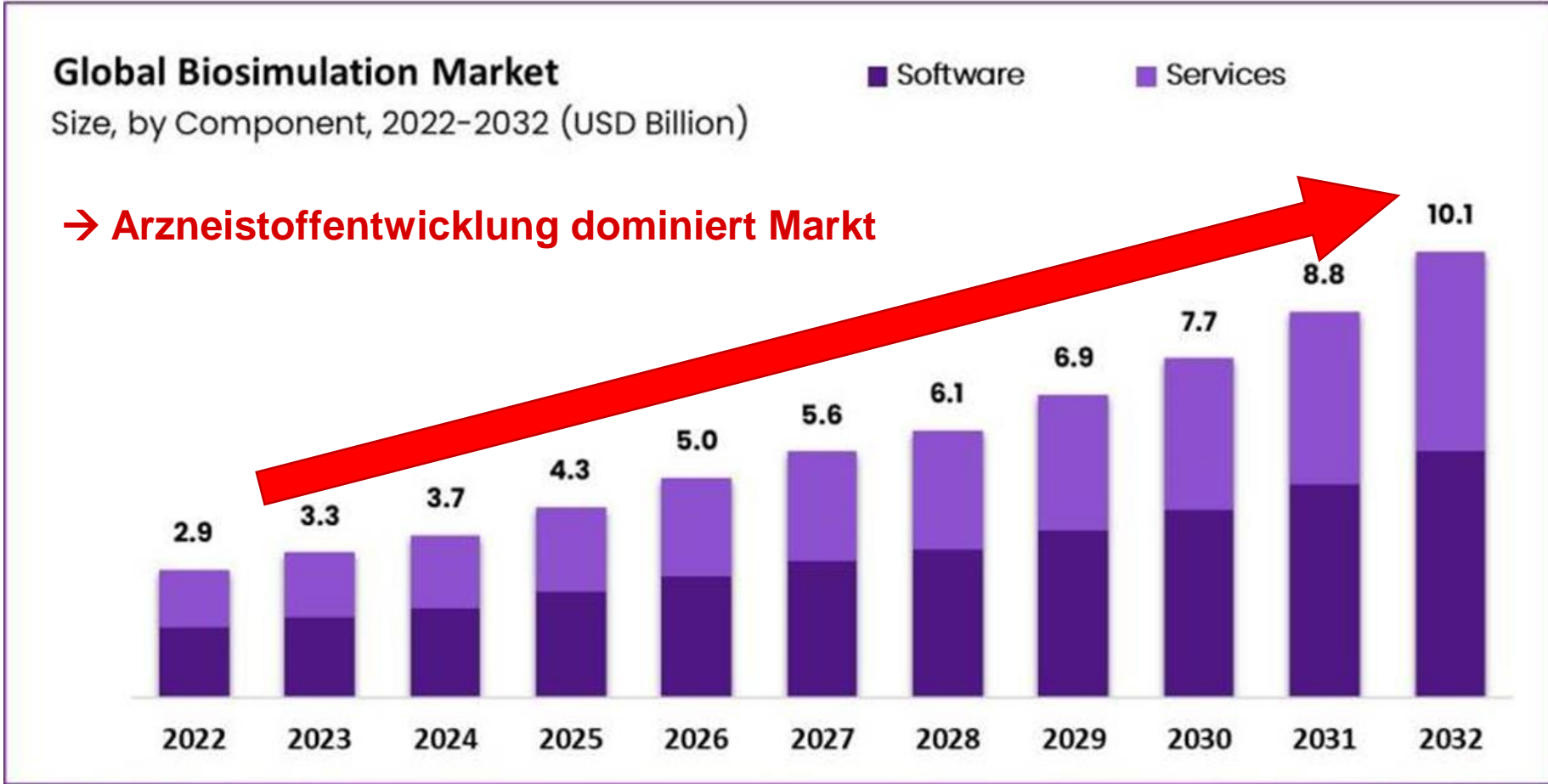




CPT Cover; van der Graaf.
Clin Pharmacol Ther. 111:5
(2022)

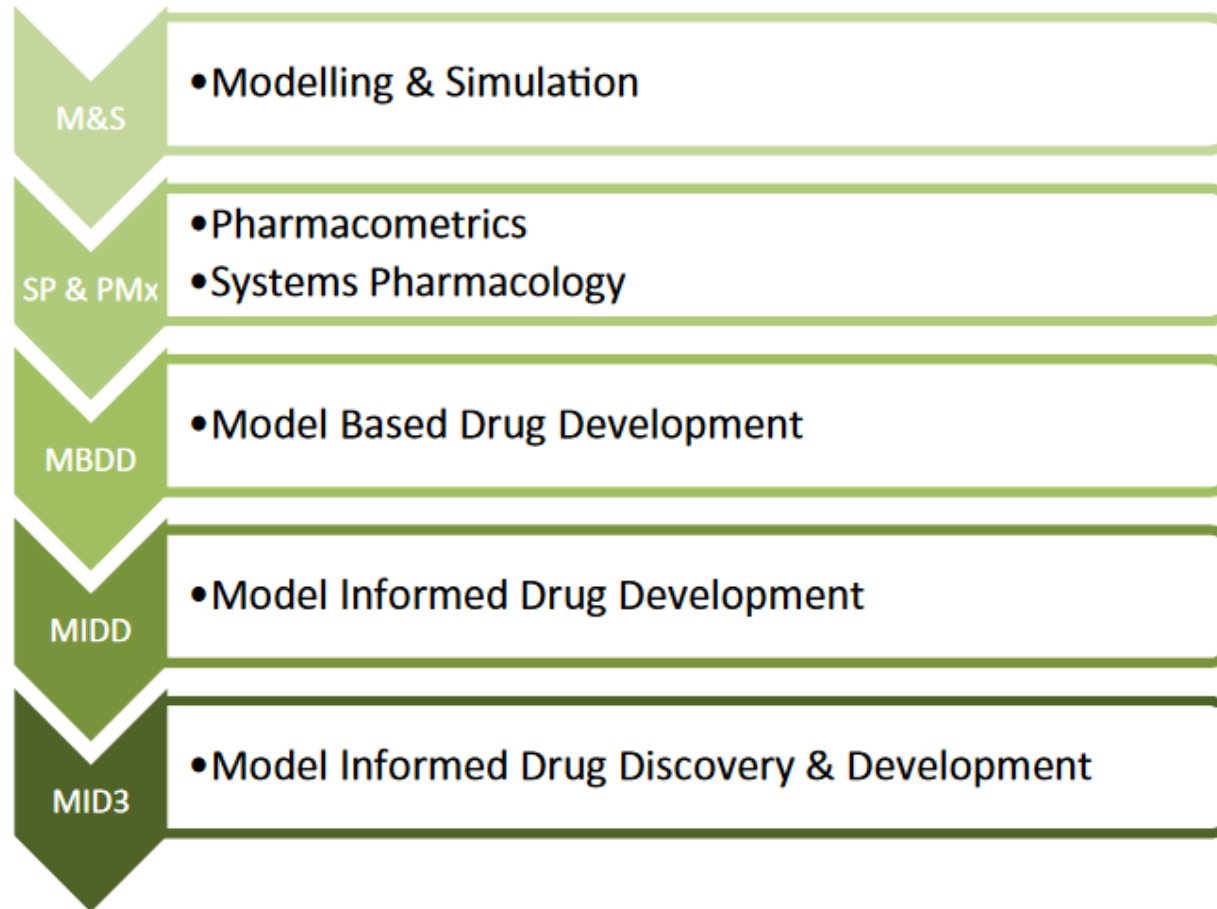


Sun D et al. Acta Pharm Sin B. 2022 Jul;12(7):3049-3062.



<https://www.enterpriseappstoday.com/news/biosimulation-market-growth-usd-10-1-billion-in-2032-at-13-7-cagr-global-analysis-by-market-us.html>

Begrifflichkeiten

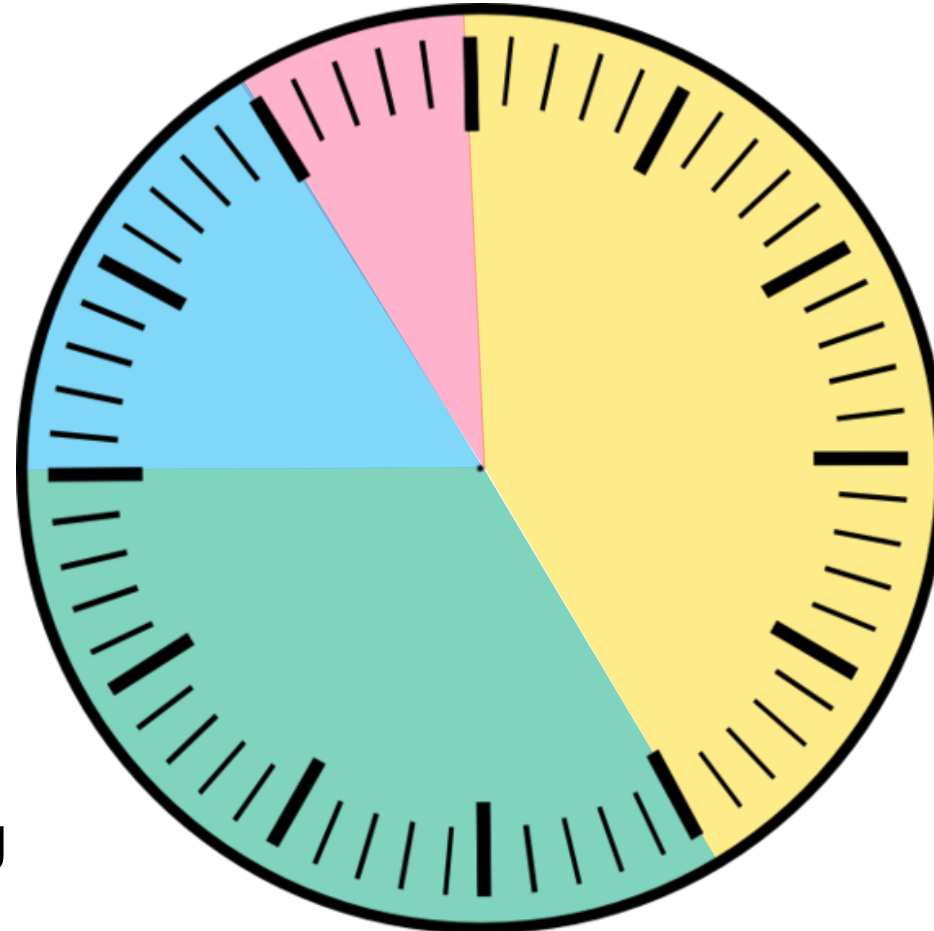


EFPIA MID3 Workgroup: SF Marshall. CPT Pharmacometrics Syst. Pharmacol. (2016) 5, 93–122

MID3

➤ **Perspektiven**

➤ **Zulassung**



➤ **Modelle und Simulationen**

➤ **Arzneistoffentwicklung**

‘Modell’



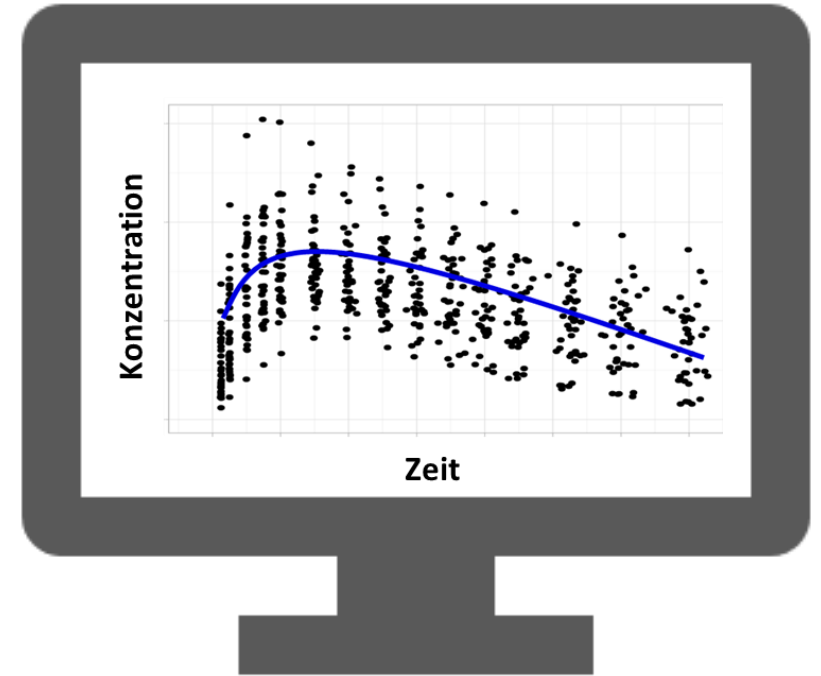
<https://shop.wienerlinien.at/uploads/product/0/425/small.jpg>



https://assets.vogue.in/photos/5d288836e2f0130008fa5d30/1:1/w_1080,h_1080,c_limit/mode!%20nidhi%20sunil.jpg

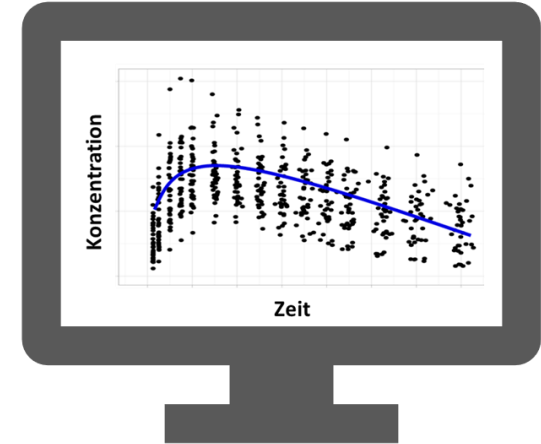


https://img.zeit.de/wissen/geschichte/2015-03/josephinum-anatomisches-modell/wide_1000x562_desktop_scale_2

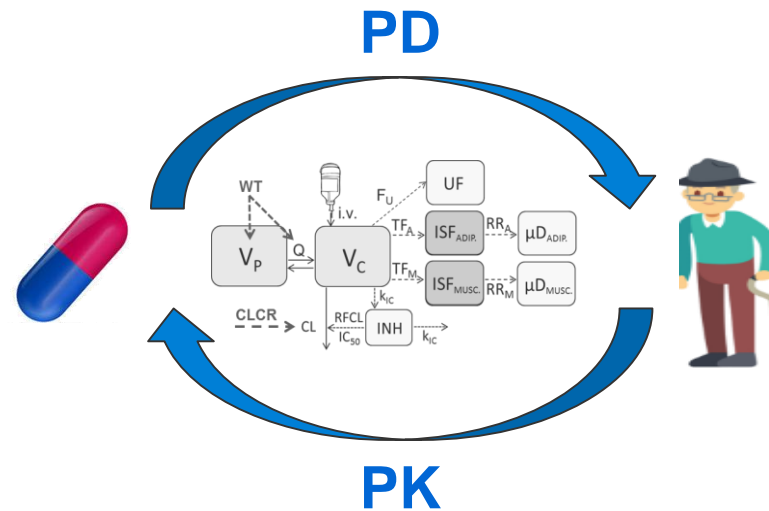


Mathematische/statistische Modelle

- **Quantifizierung** und **Vorhersage** von **Interaktionen** zwischen **Arzneistoff – Patient – Krankheit**



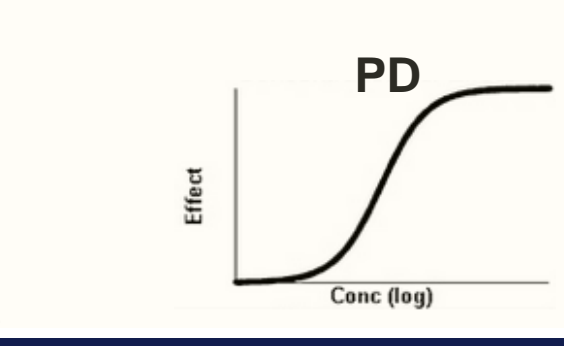
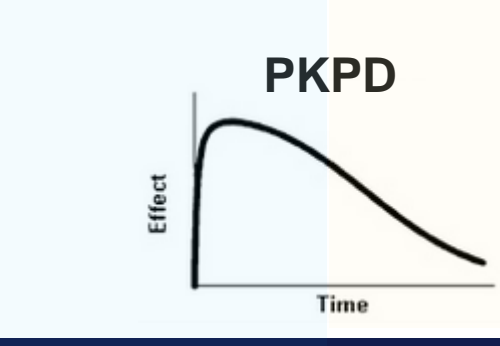
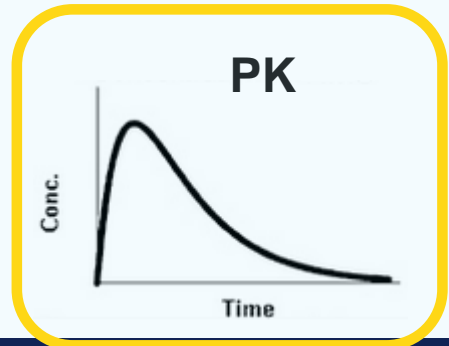
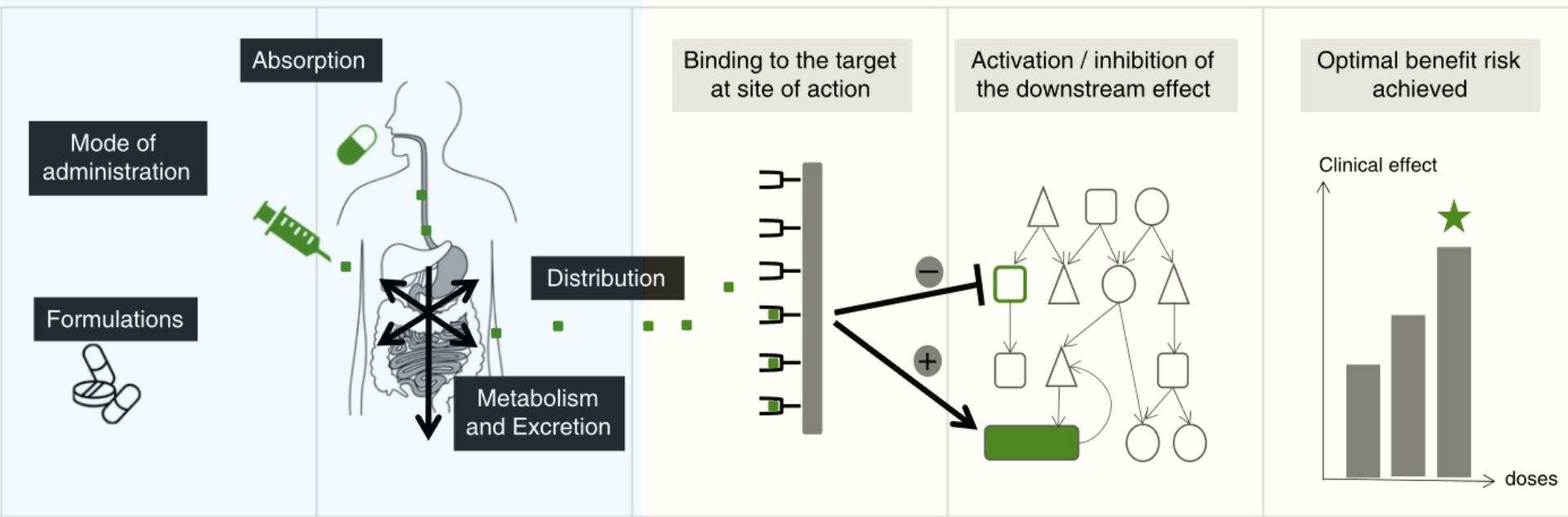
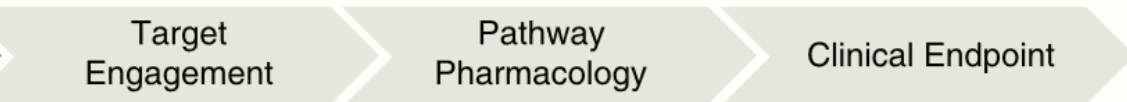
- **Pharmakometrie**



- **Exposition**
- **Wirksamkeit/Toxizität**
- **Krankheitsverläufe**

Pharmacokinetics (PK)

Pharmacodynamic (PD)

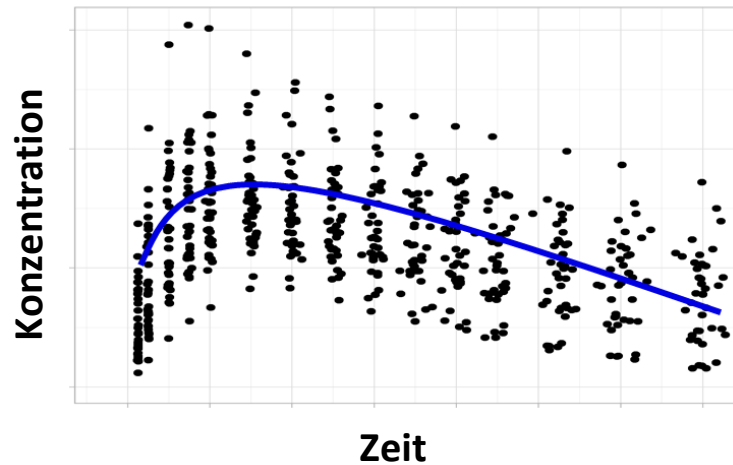


Egnell et al. Syst Med: 2:243 (2021)

Derendorf, Meibohm. Pharm Res 16: 176-185 (1999)

Mathematische/statistische Modelle

z.B. Populations-PK Modelle

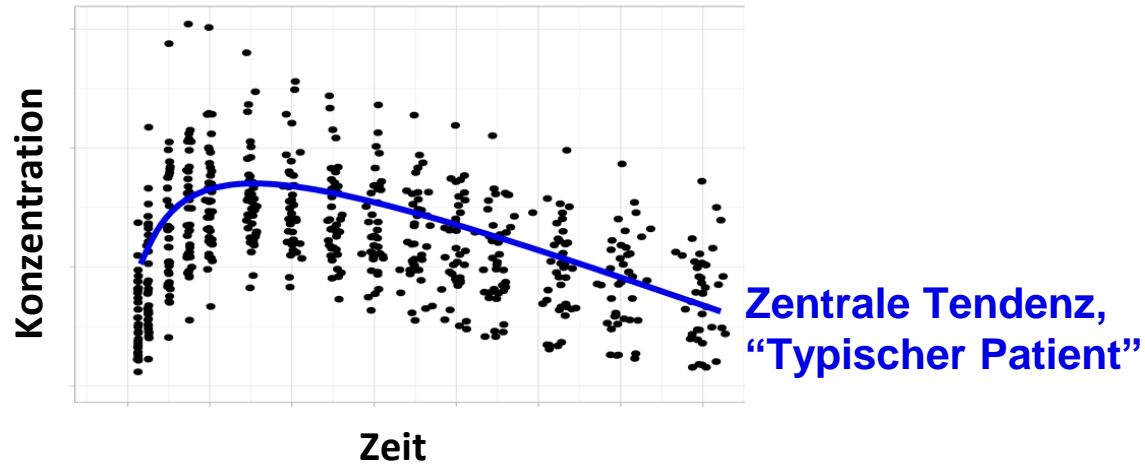


$$\begin{aligned} \text{DADT}(1) &= -KA \cdot A(1) \\ \text{DADT}(2) &= -(K23) \cdot A(2) + K32 \cdot A(3) + KA \cdot A(1) - A(2) \cdot K20 \cdot \text{INH} \\ \text{DADT}(3) &= K23 \cdot A(2) - K32 \cdot A(3) \\ \text{DADT}(4) &= \text{CSC} \cdot \text{REC1} \\ \text{DADT}(5) &= \text{KIC} \cdot ((A(2)/V2) - A(5)) \end{aligned}$$

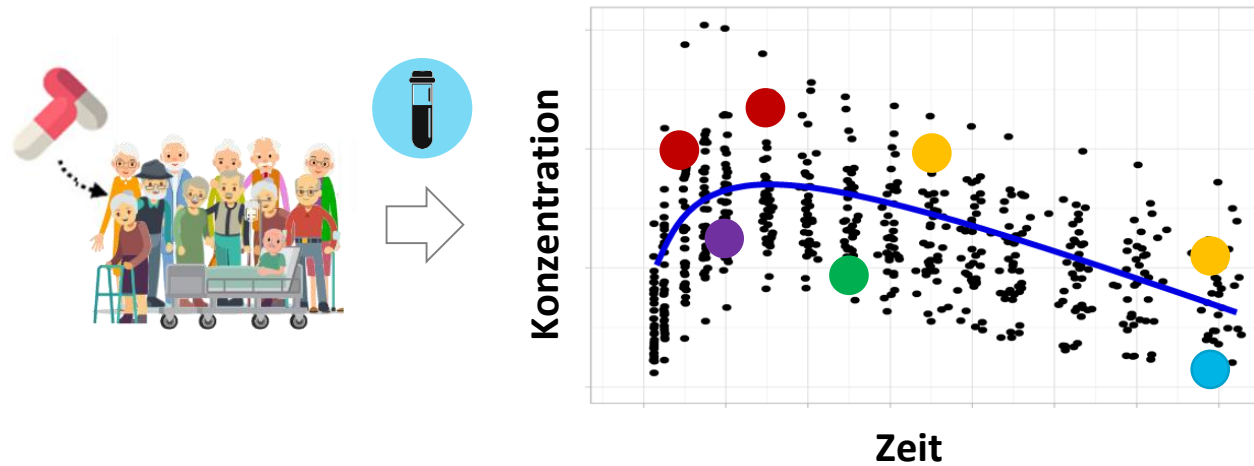
- **Beschreiben** ein **biologisches/physiologisches System**
 - in **Datensatz** beobachtet
 - oft **Zeitverläufe**, wiederholte Messungen
- **Mathematische Gleichungen**
 - Beschreiben und Verknüpfen verschiedene Informationen

→ **Verständnis des Systems** ↑

Populationspharmakokinetisches Modell

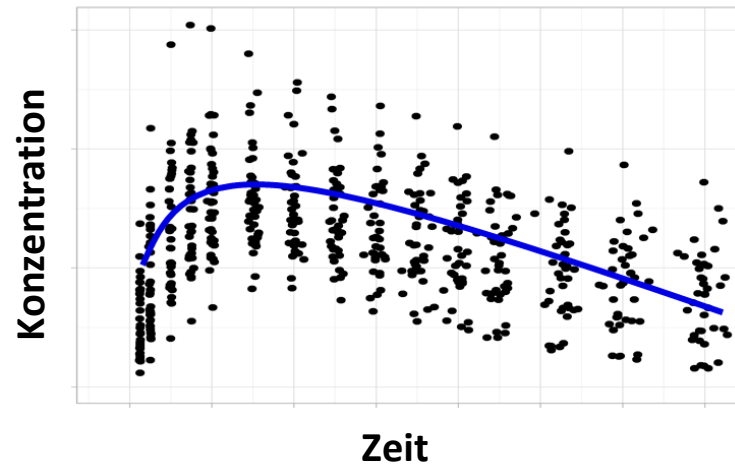


Populationspharmakokinetisches Modell



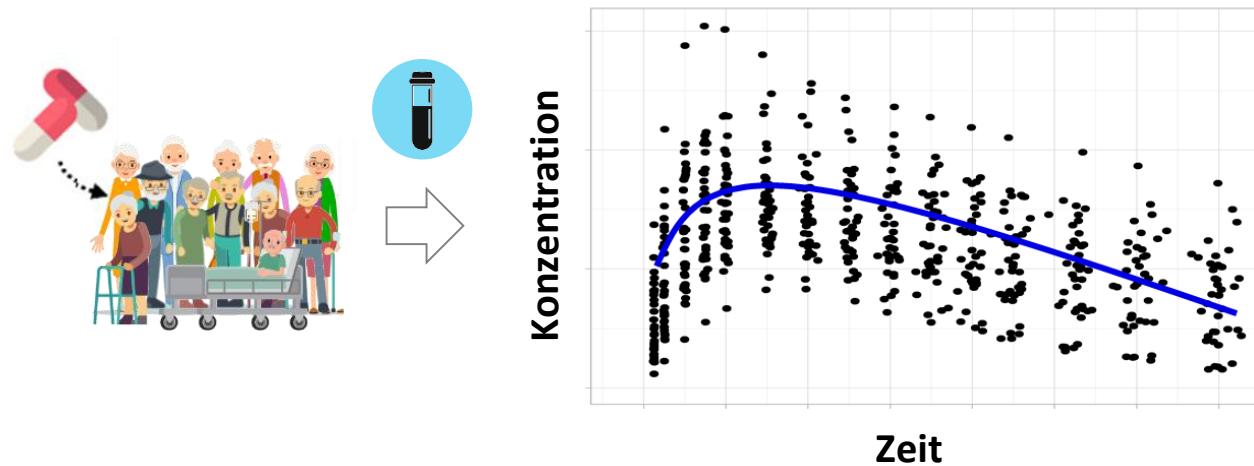
- **Gleichzeitige** Analyse **aller Daten** aller Patient:innen
 - **Dichte** und *spärliche* Daten
 - z.B. Pädiatrie

Populationspharmakokinetisches Modell



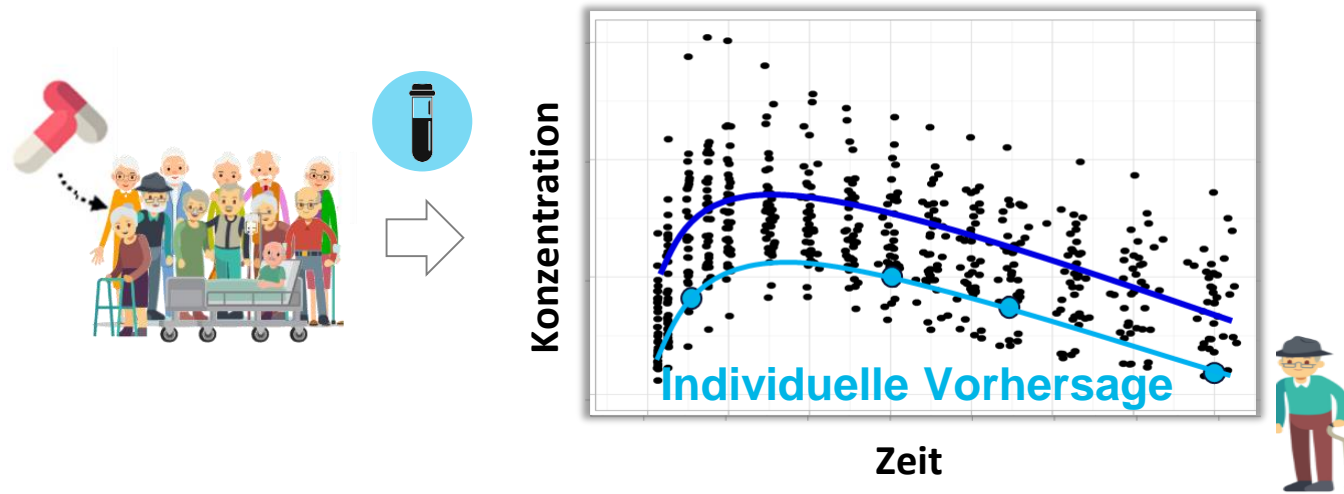
- **Gleichzeitige** Analyse **aller Daten** **aller Patient:innen**
 - Dichte und spärliche Daten
- **Charakterisierung von *nichtlinearer* *Pharmakokinetik***

Populationspharmakokinetisches Modell



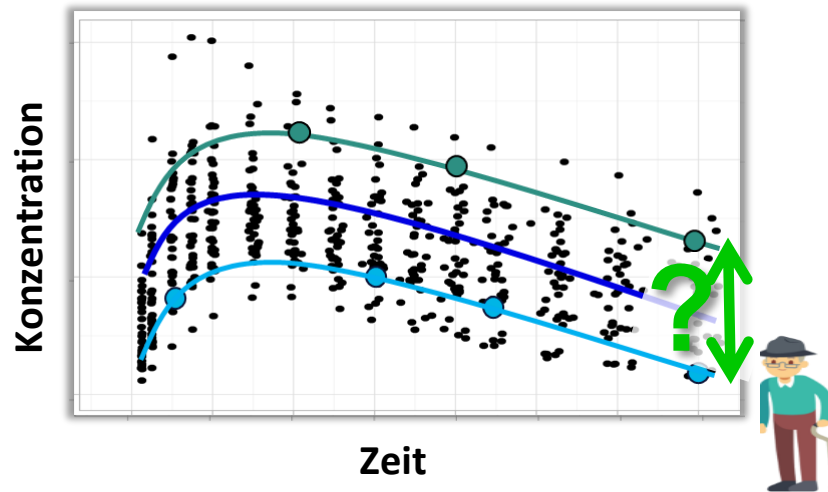
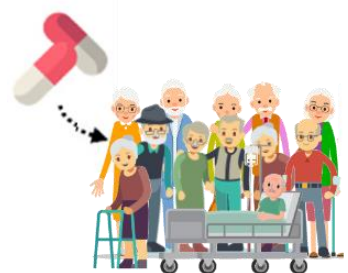
- **Gleichzeitige** Analyse **aller Daten** aller Patient:innen
- **Poolen von Daten möglich**, z.B.
 - Verschiedene Populationen
 - Alle Daten einer Crossover-Studie
 - Verschiedene Applikationswege
 - Arzneistoff + Metaboliten
 - Verschiedene Phasen

Populationspharmakokinetisches Modell



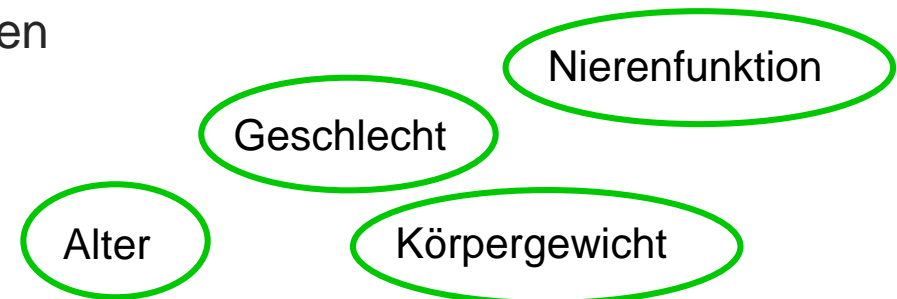
- **Gleichzeitige** Analyse **aller Daten** aller Patient:innen
- **Information über individuelle:n Patient:in** bleibt erhalten
 - **Therapie-Individualisierung**

Populationspharmakokinetisches Modell

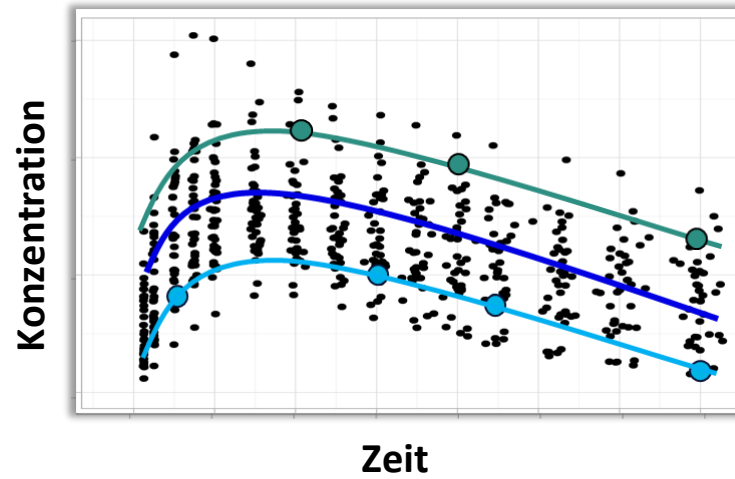
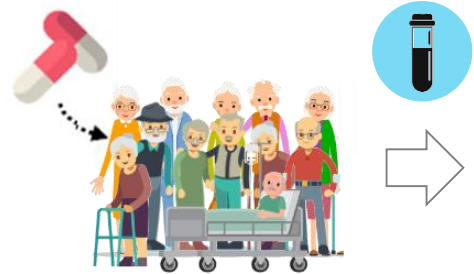


- **Gleichzeitige** Analyse **aller Daten** aller Patient:innen
- **Information über individuelle:n Patient:in** bleibt erhalten

- **Quantifizierung von Variabilität** zwischen Patient:innen
- **Erklärung von Variabilität** mit **Kovariaten**



Populationspharmakokinetisches Modell

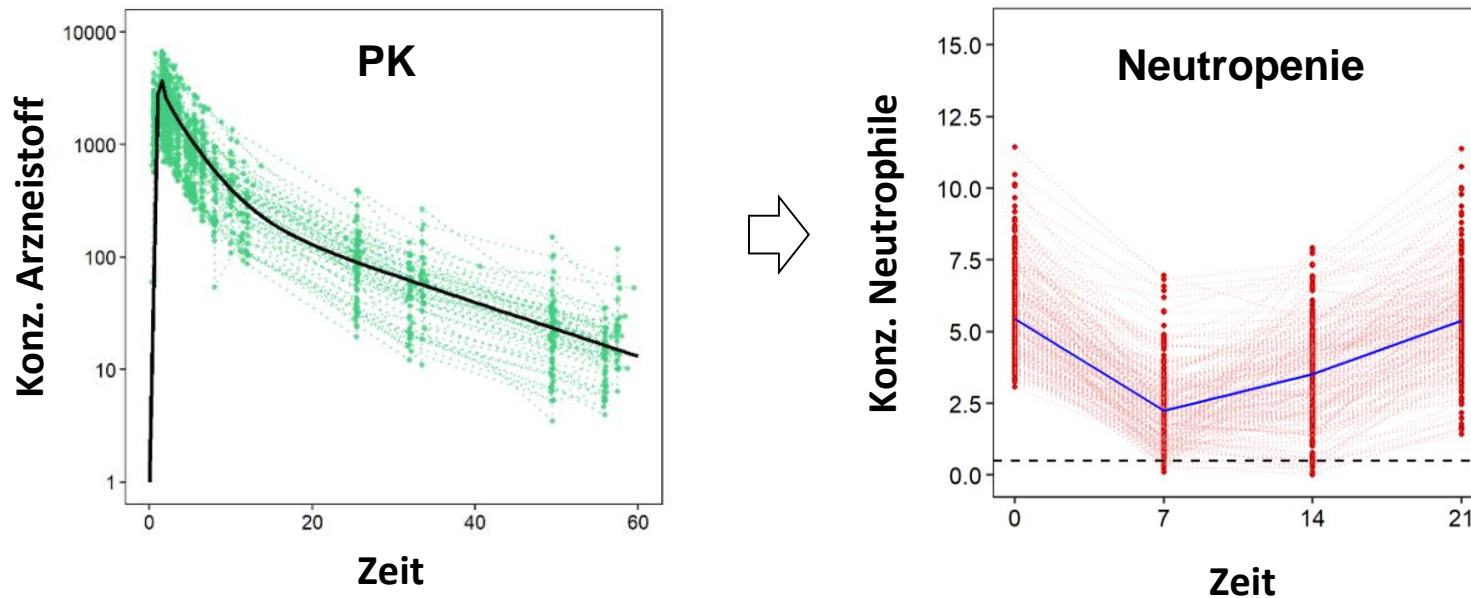


- 'Empirische' Modelle
 - Datengetrieben

PopulationsPKPD (pharmakodynamische) Modelle

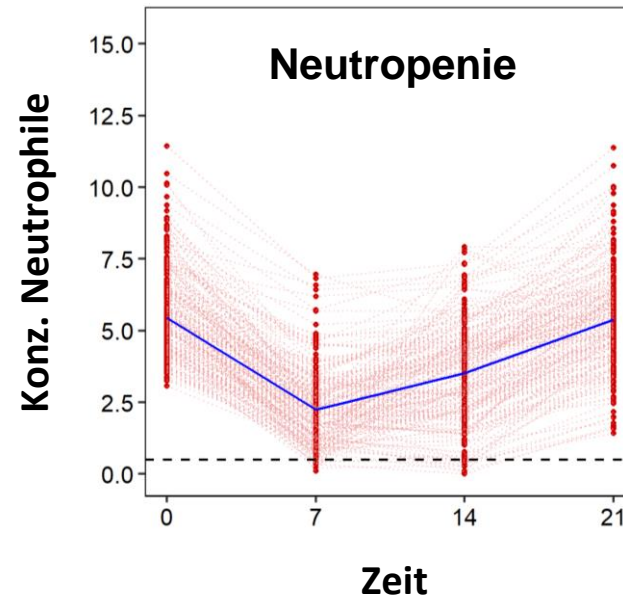
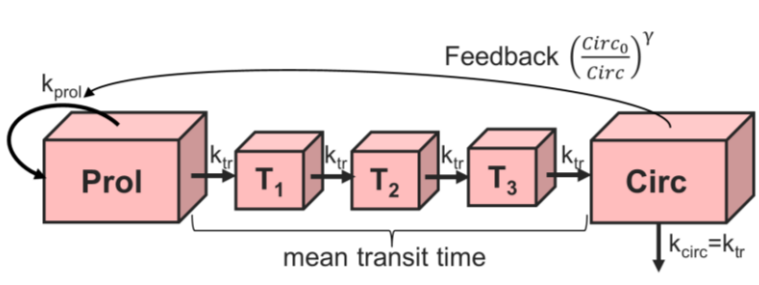
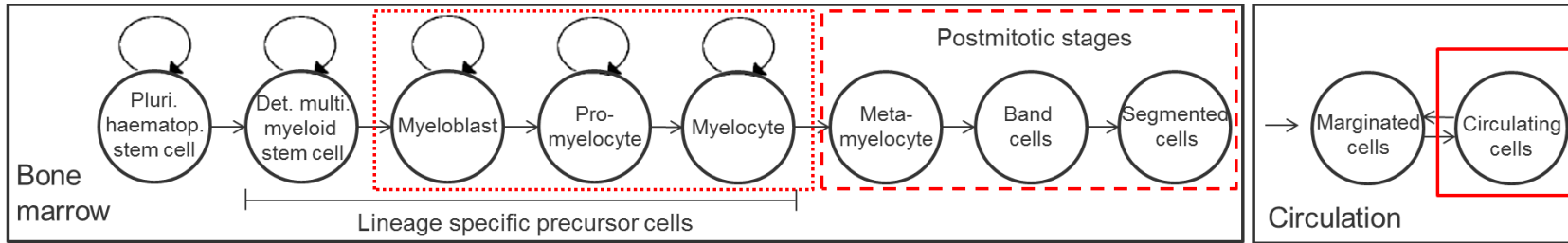
- **Arzneistoffexposition** \leftrightarrow **Effekt (erwünschte und unerwünschte Wirkungen)**
- Biomarkerverläufe, klinisches Ansprechen

Neutropenie nach Chemotherapie



Minichmayr IK, Karlsson MO, Jönsson S. Pharm Res. 2021 Apr;38(4):593-605.

PopulationsPKPD (pharmakodynamische) Modelle



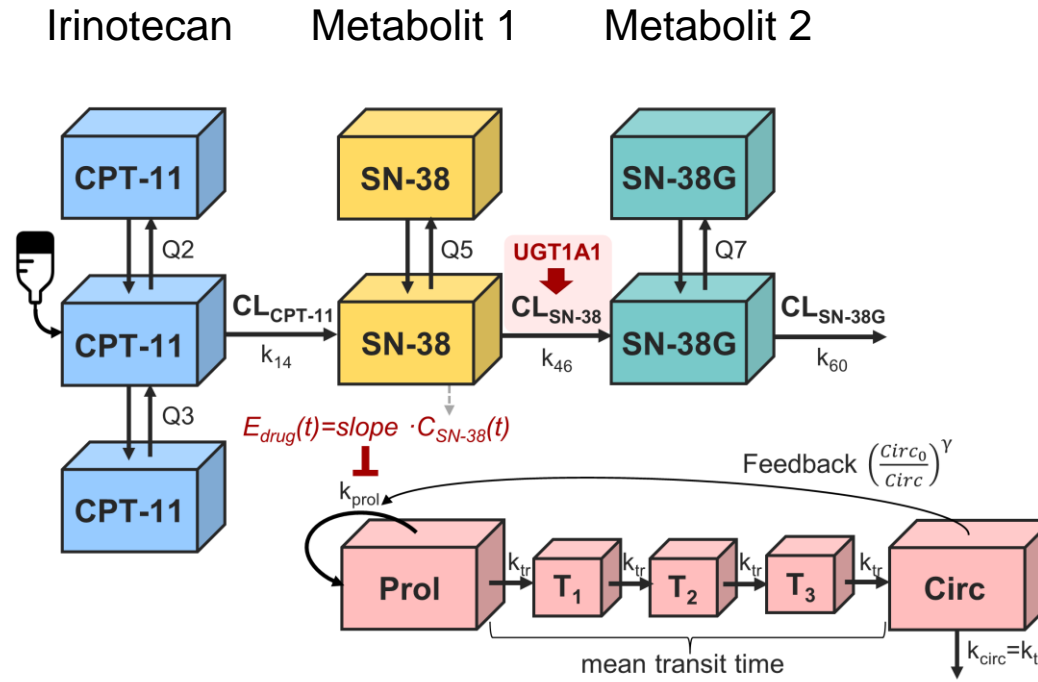
- **Semimechanistische Modelle**

- Berücksichtigen zugrundeliegende Mechanismen, physiologische Prozesse

Minichmayr IK Pharm Res.
2021 Apr;38(4):593

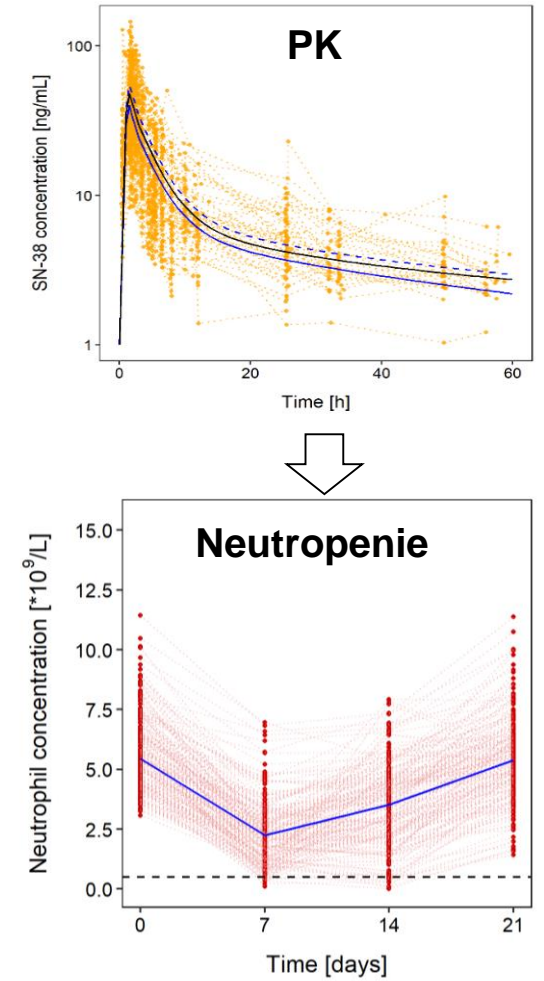
PKPD Modell für Myelotoxizität

PK Modell

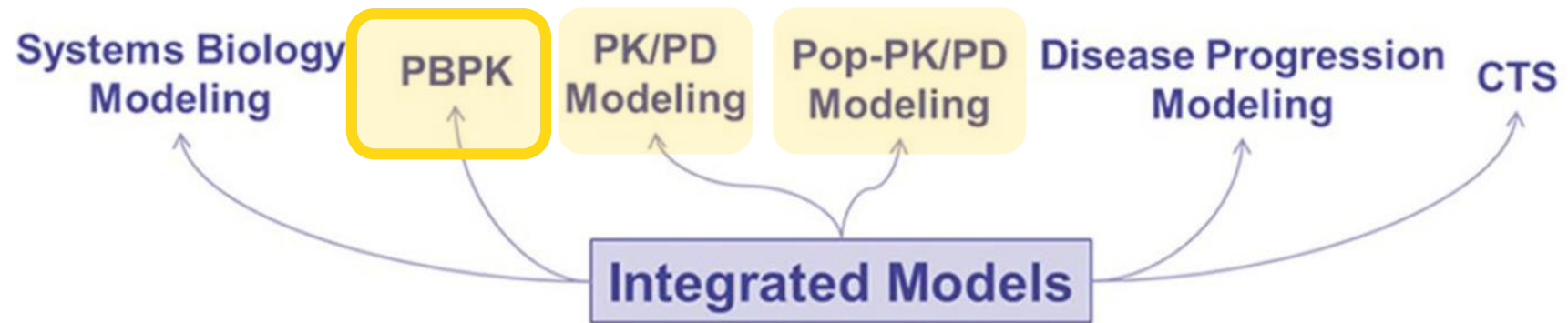


PD Modell

Neutropenie



Modelle in MID3



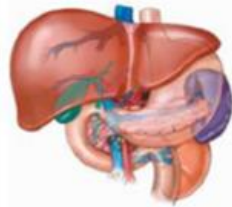
Barrett. The AAPS Journal (2023) 25:70

PBPK Modelle

- **Physiologie-Basierte Pharmako-Kinetische Modelle**



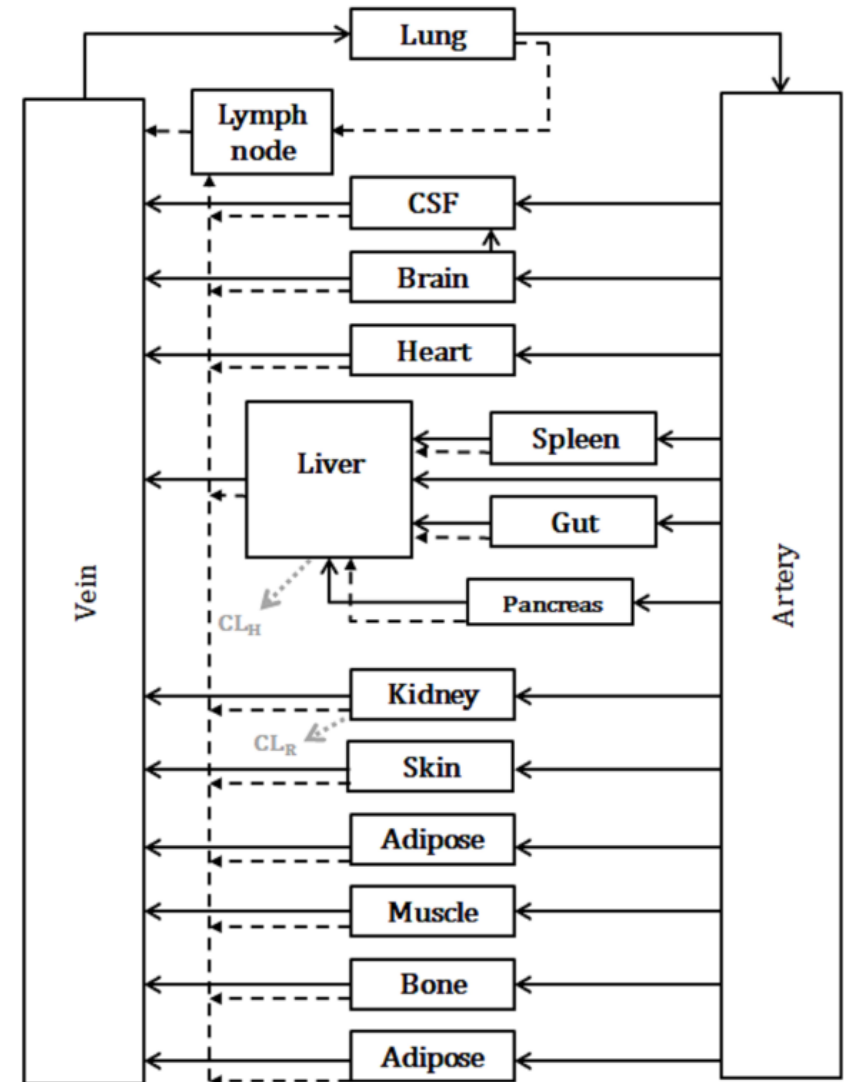
Molecular weight
 pKa
 LogD/LogP
 pH-solubility profile
 Dissolution
 Particle size
 Dosage form
 Dosing regimen
 Permeability
 K_M , V_{max}
 f_{up} , B:P, f_{uinc}



Gastrointestinal transit time
 Gastric pH
 Bile salt concentration
 Organ size and the associated tissue types
 Blood flow
 Drug metabolizing enzymes
 Drug transporters
 Plasma protein
 Hematocrit

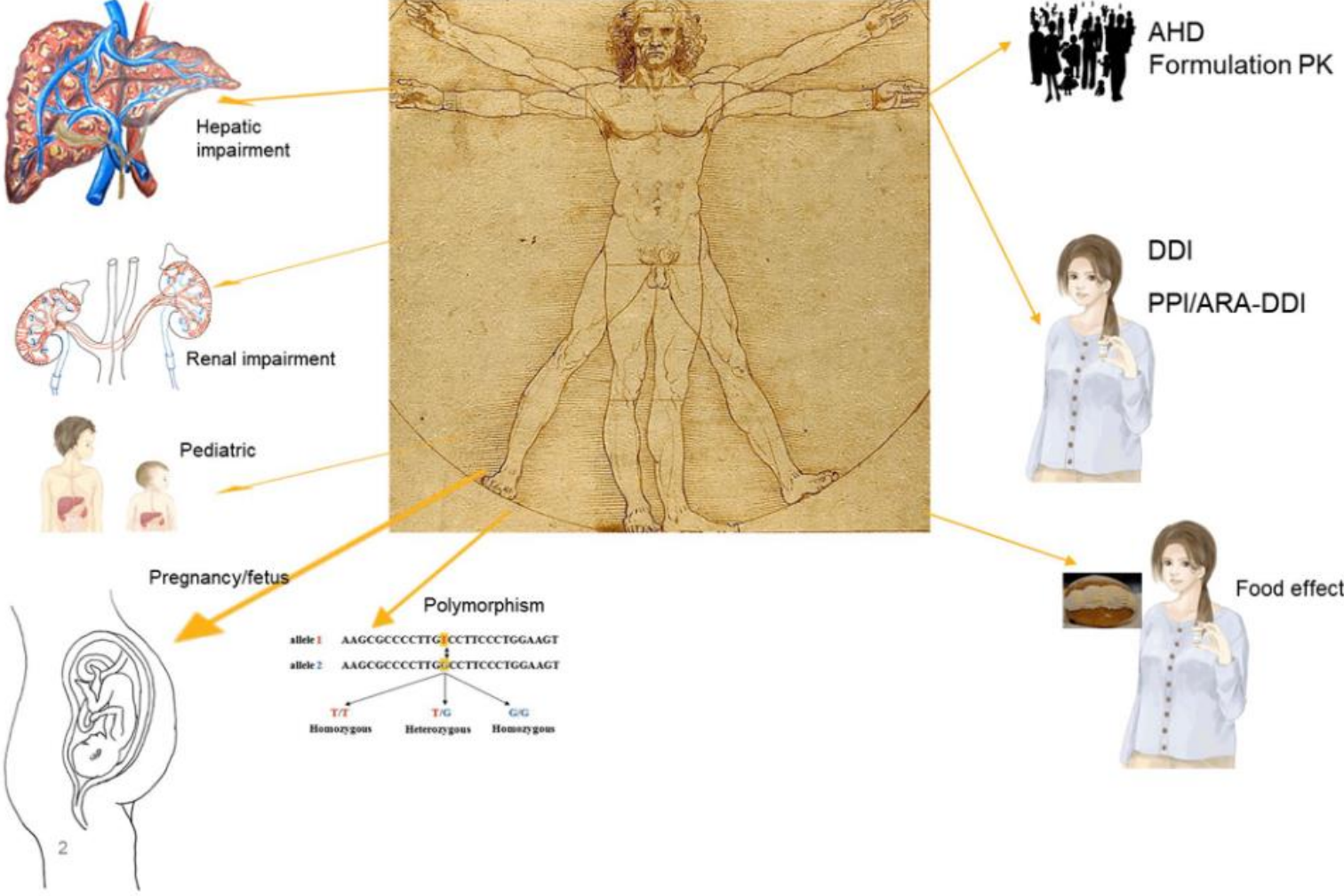


Age
 Weight
 Height
 Sex
 Genetics
 Race
 Disease



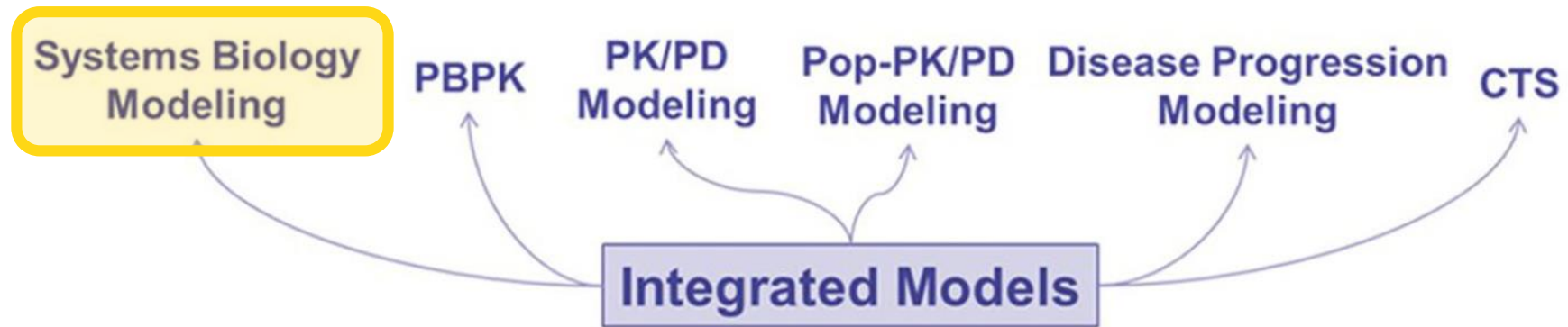
Lim. Transl Clin Pharmacol. 2019;27(1):19-23

PBPK Modelle



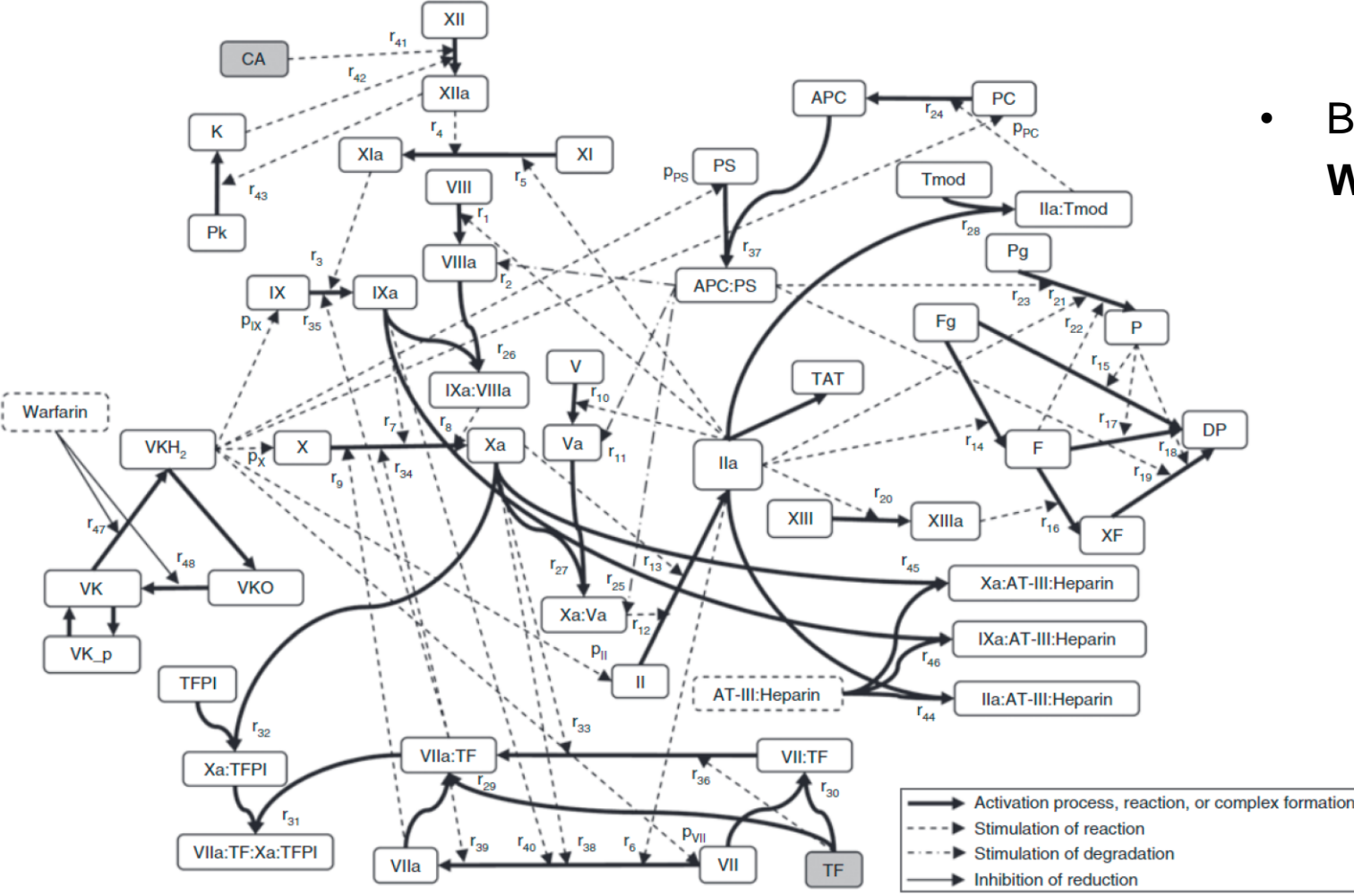
Lin et al. Pharmaceutical Research (2022) 39:1701–1731

Modelle in MID3



Barrett. The AAPS Journal (2023) 25:70

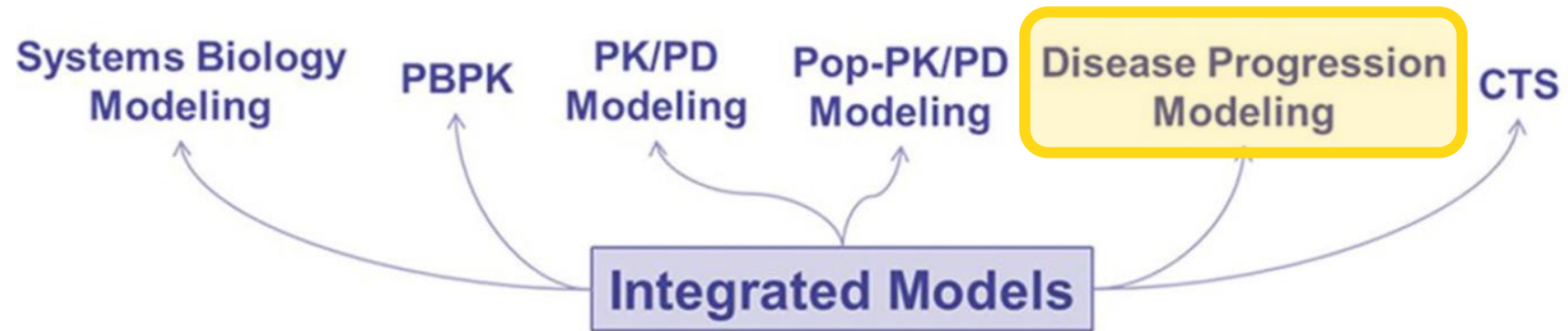
System-Biologie/Pharmakologie Modelle



- Besseres Verständnis des Systems und Wirkmechanismus von Arzneistoffen

Chung et al. Pharmaceutics 2023, 15(3), 918

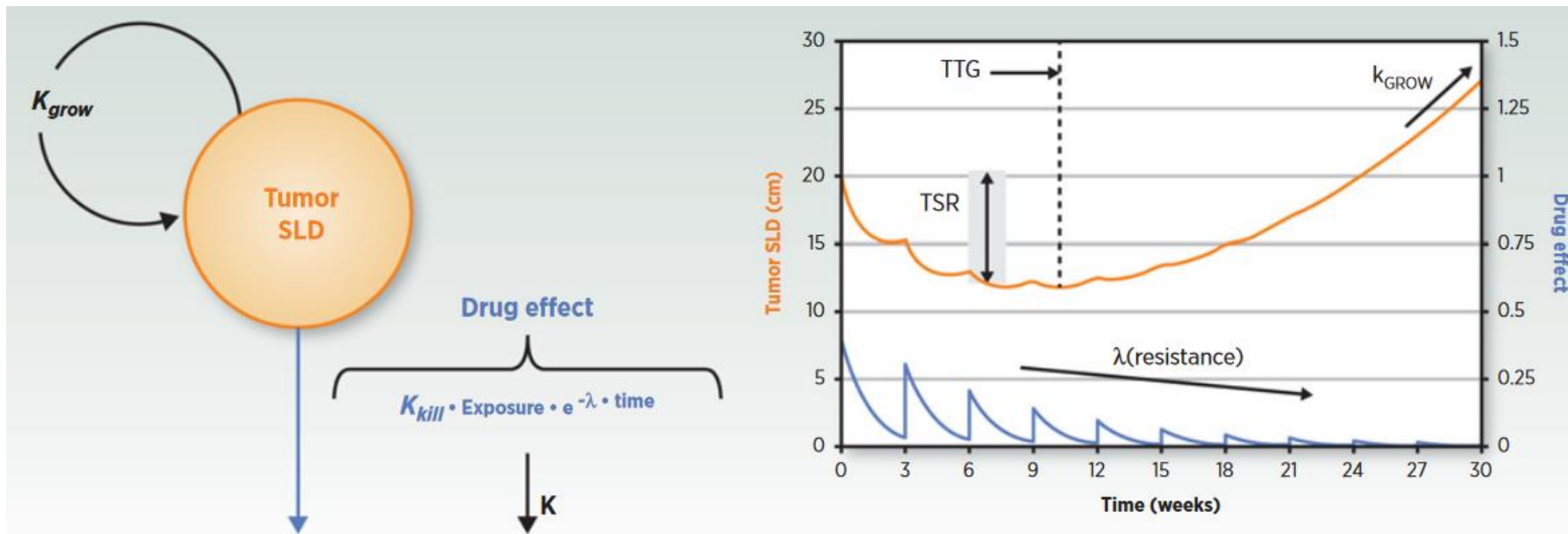
Modelle in MID3



Barrett. The AAPS Journal (2023) 25:70

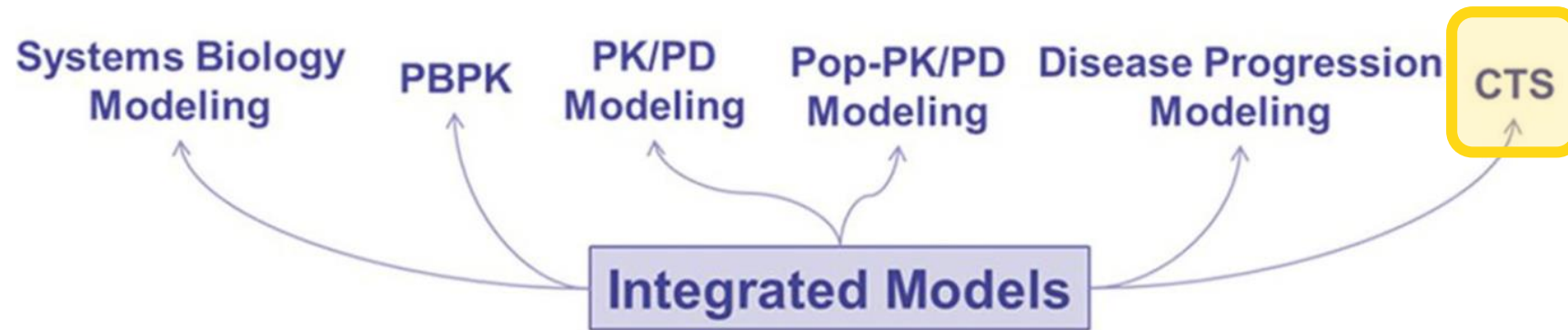
Krankheitsverlaufs-Modelle

- z.B. Tumordynamik



Bruno et al. Clin Cancer Res 2020;26:1787–95

Modelle in MID3



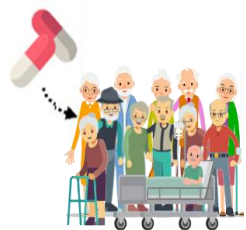
Barrett. The AAPS Journal (2023) 25:70

Modellierung und Simulation

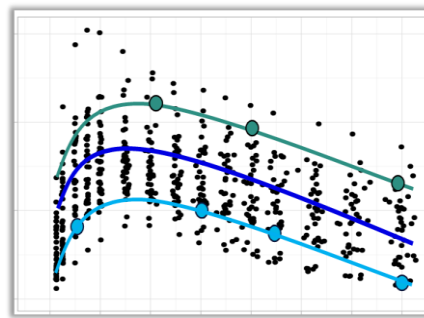
Simulationen

“Was wäre wenn...?”

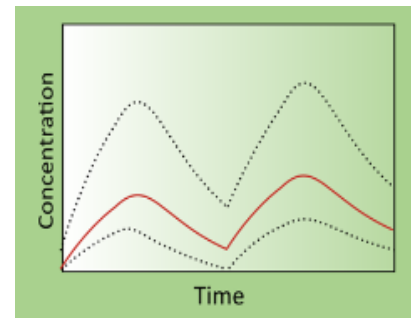
Populations-PK Modell



Konzentration



Zeit



Tängden, T. et al. *Int. Care Med* 43, 1021–1032 (2017)



https://play.googleusercontent.com/APJpPvzMcCo0uLj_R0jg0VdLrLrYysICRvVOkg5wuz2BJ0VHFKeyXzzzIQ

Vorhersage
neuer Szenarien



Entscheidungsfindung

Studie:

- 50 Patient:innen
- Oral Gabe
- 500 mg
- Alle 12 Stunden

Was wäre wenn **alle 8 Stunden**?

Was wäre wenn **Behandlungsdauer** 4 Wochen?

Was wäre wenn **Nierenfunktion** ↓?

Wieviele Samples sind ausreichend?

Was wäre wenn **n=500** Patient:innen?

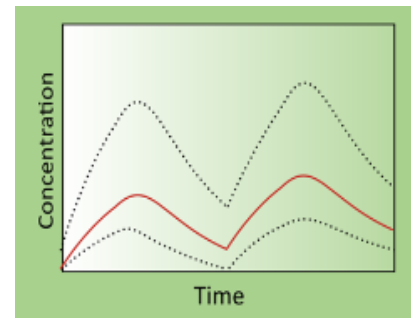
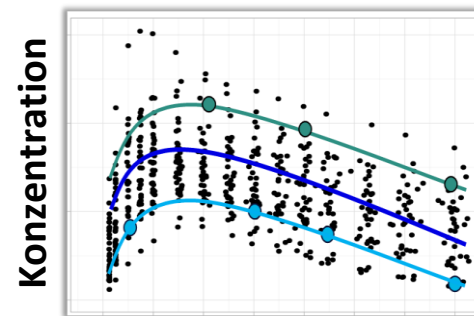
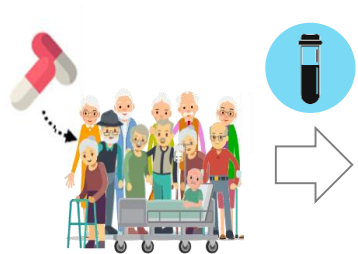
Was wäre wenn **Dosis** 750 mg?

Modellierung und Simulation

Simulationen

“Was wäre wenn...?”

Populations-PK Modell



Tängdén, T. et al. *Int. Care Med* 43, 1021–1032 (2017)



https://play.googleusercontent.com/APjP0vzMcCo0uLj_R3jg0VdLrLrYys4CRVvOKgswmz2BJ0VHFKeyXzzz1Q

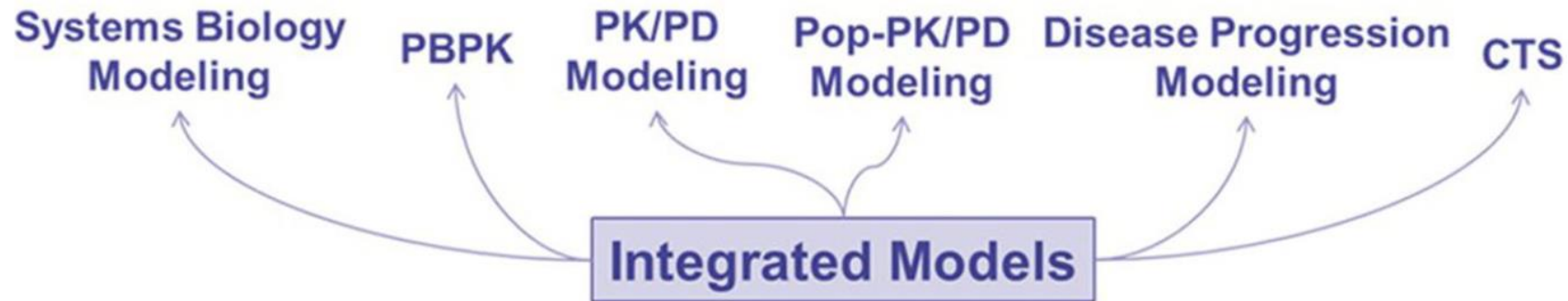
Vorhersage
neuer Szenarien



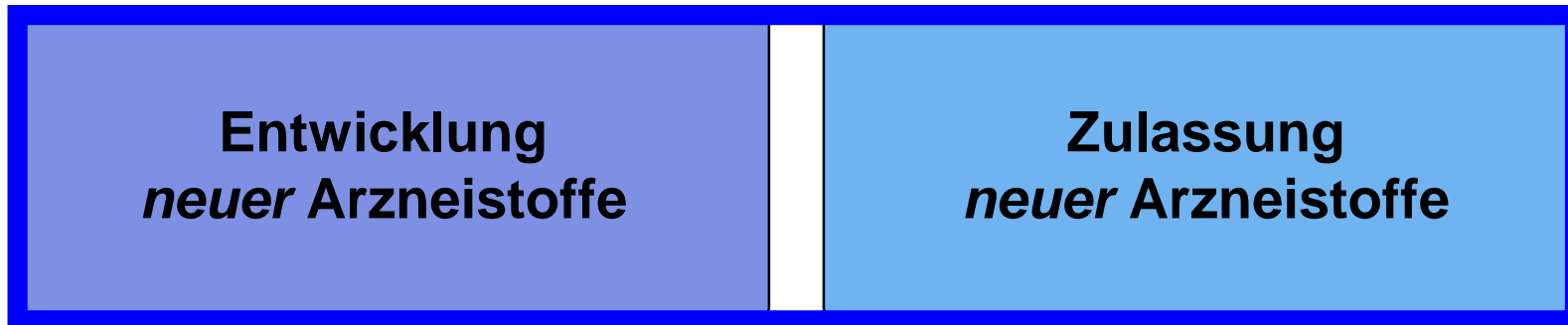
Entscheidungsfindung

- **Simulationen klinischer Studien ('Clinical trial simulations') → Outcome**
 - Studiendesign, Experimente planen
 - Informationsgrad und Effizienz ↑

Anwendungen

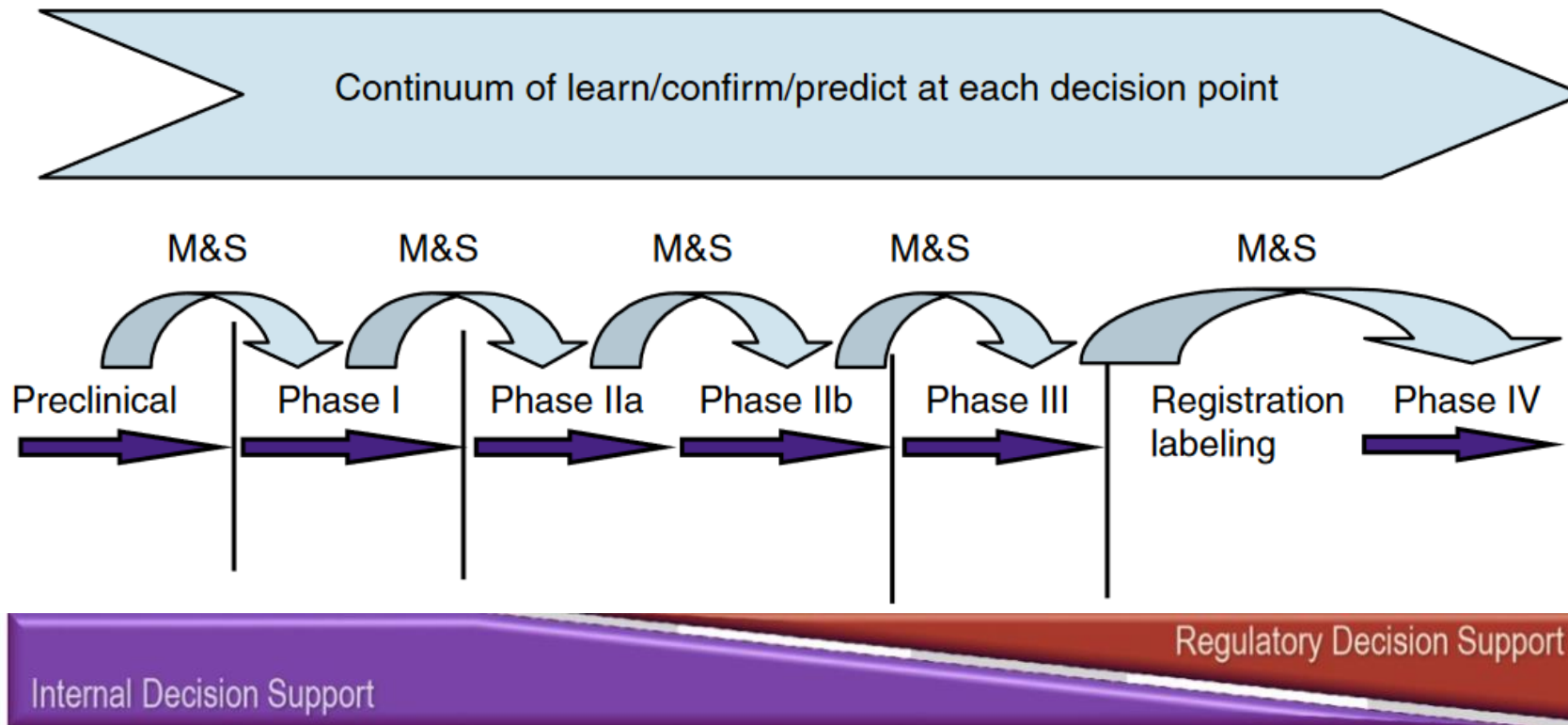


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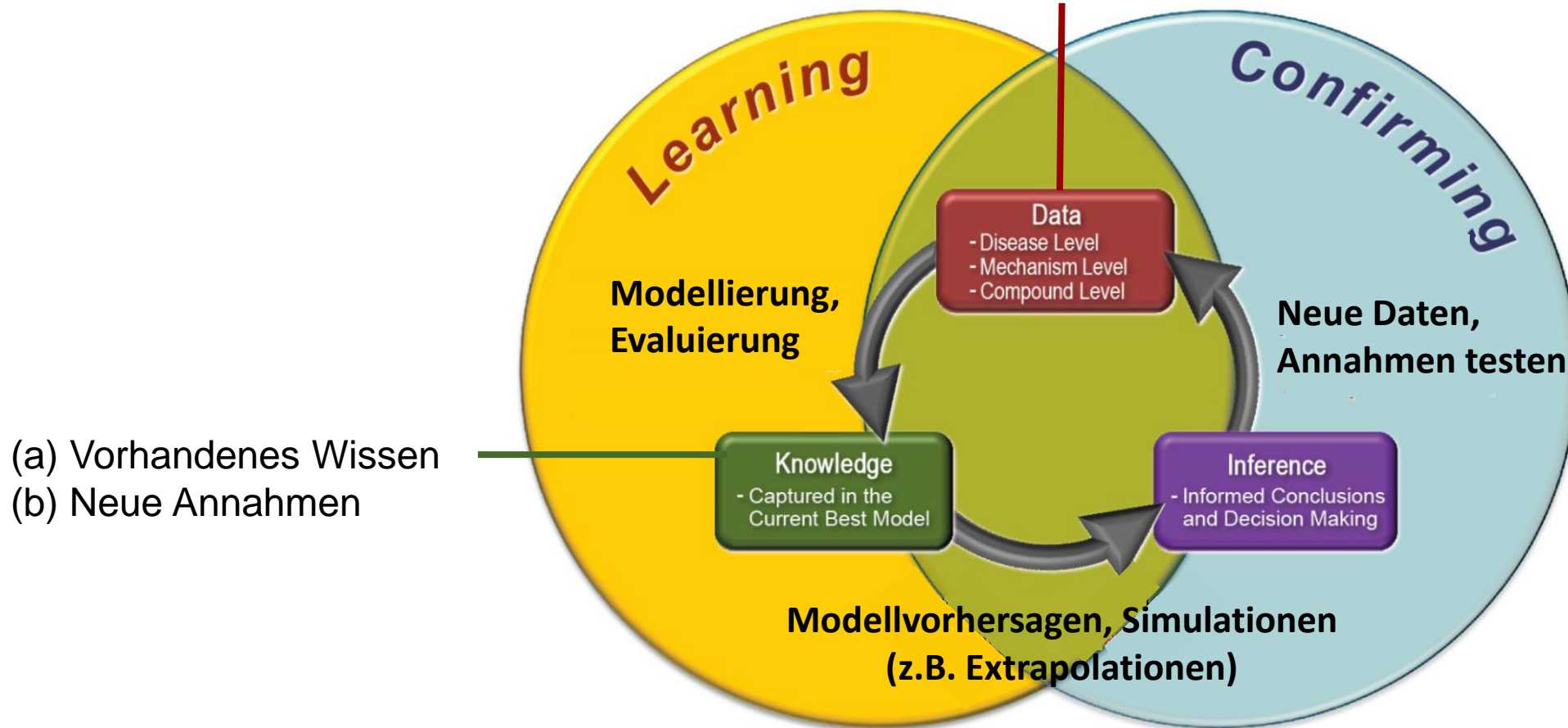
Barrett. The AAPS Journal (2023) 25:70

Modellierung in der Arzneistoffentwicklung



Lalonde et al. Clin Pharmacol Ther. 82:1 (2007)

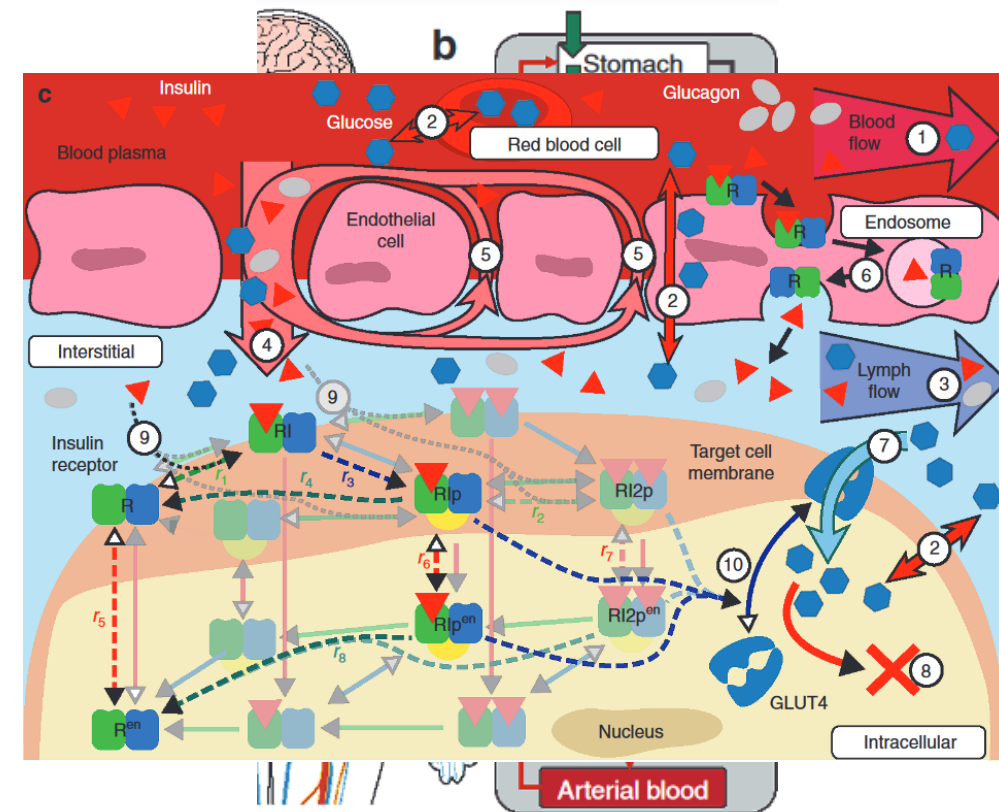
Spezifische Frage,
Wissenslücke



EFPIA MID3 Workgroup: SF Marshall. CPT Pharmacometrics Syst. Pharmacol. (2016) 5, 93–122



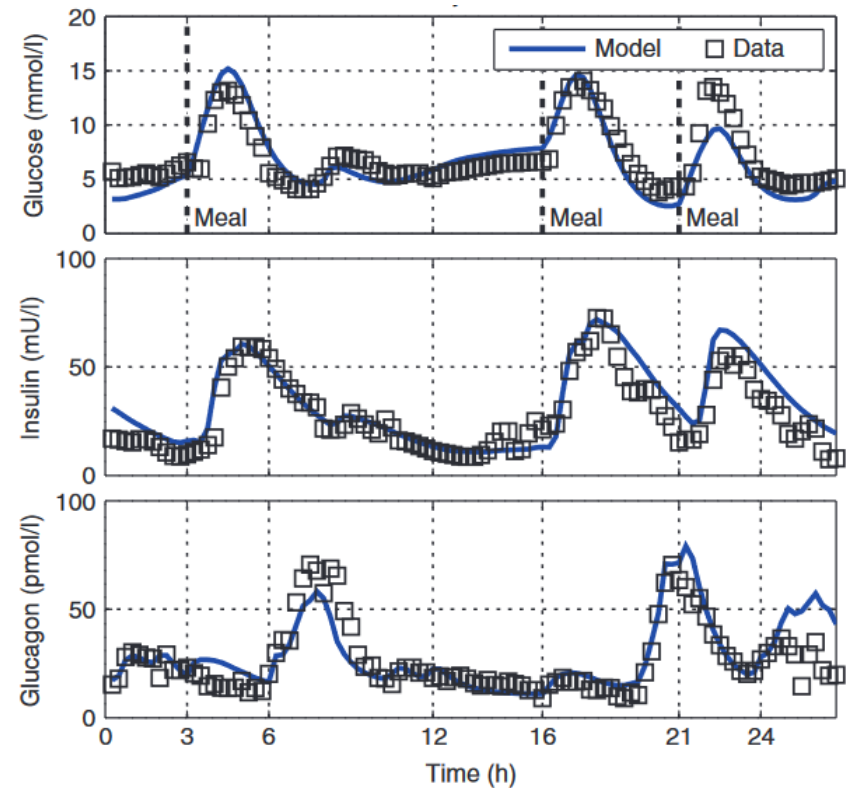
- **Target-Identifizierung**
 - **Besseres (mechanistisches) Verständnis** von Targetmodulierung, PK, Toxizität
 - **Glucose-Insulin-Glucagon Modell**
 - Neue Strategien für Diabetestherapie



EFPIA MID3 Workgroup: SF Marshall. CPT Pharmacometrics Syst. Pharmacol. (2016) 5, 93–122
 Schaller et al. CPT: Pharmacometrics & Systems Pharmacology (2013) 2, e65



- **Target-Identifizierung**
 - **Besseres (mechanistisches) Verständnis** von Targetmodulierung, PK, Toxizität
 - **Glucose-Insulin-Glucagon Modell**
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EFPIA MID3 Workgroup: SF Marshall. CPT Pharmacometrics Syst. Pharmacol. (2016) 5, 93–122
 Schaller et al. CPT: Pharmacometrics & Systems Pharmacology (2013) 2, e65



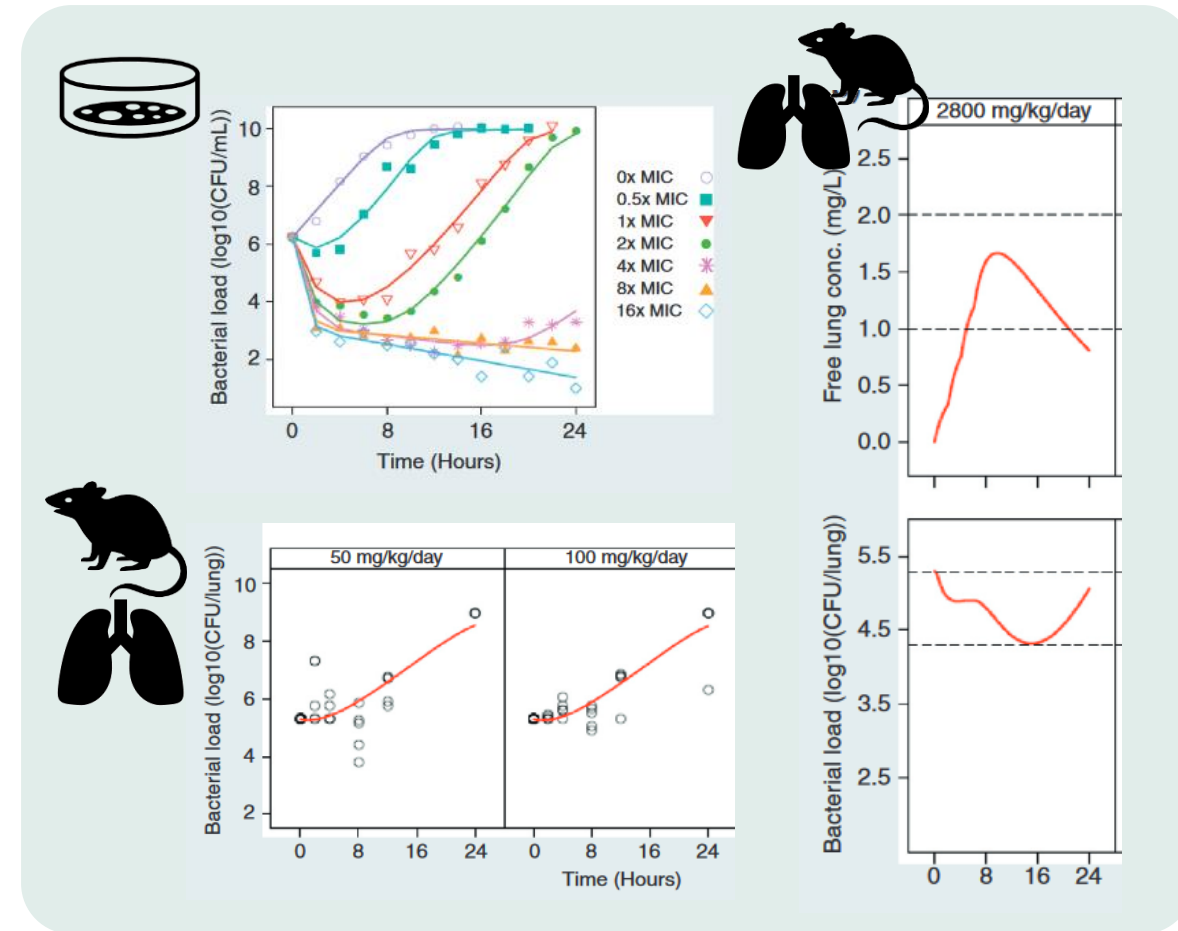
- **Kandidatenvergleich, -selektion**
- Human-PK, Dosisvorhersage
- Erwünschte/unerwünschte Effekte



- **Bakterienmodell**
- In vitro–in vivo Korrelation

https://upload.wikimedia.org/wikipedia/commons/thumb/2/2f/Zeichen_206_-_Halt%21_Vorfahrt_gew%C3%A4hren%21_StVO_1970.svg/1200px-Zeichen_206_-_Halt%21_Vorfahrt_gew%C3%A4hren%21_StVO_1970.svg.png

Visser et al. Drug Discovery Today, 18, 15/16, 2013
 EFPIA MID3 Workgroup: SF Marshall. CPT Pharmacometrics Syst. Pharmacol. (2016) 5, 93–122





- **Optimierung des Studiendesigns**

→ Sample size, informative Sampling Zeitpunkte

Indication	MBDD approach adopted	Efficiencies gained over historical designs and analysis
Thromboembolism	Omit phase IIa, model-based adaptive phase IIb design	2,750 Fewer patients, 1 year shorter study duration
Hot flashes	Model-based dose-response relationship	1,000 Fewer patients, 1 year shorter study duration
Diabetes	Prior data supplementation, model-based dose-response relationship, sequential design	760 Fewer patients, 1 year shorter study duration
Diabetes	Prior data supplementation, model-based dose-response relationship	120 Fewer patients, 1 year shorter study duration
Reflux	Model-based dose-response relationship	1,025 Fewer patients, 1 year shorter study duration
Rheumatoid arthritis	Model-based dose-response relationship	437 Fewer patients, increased probability of success
Global anxiety disorder	Omit phase IIb	260 Fewer patients, 1 year shorter study duration
Lower urinary tract symptoms	Meta-analysis	Increased probability of success

<https://www.vecteezy.com/vector-art/6662132-growth-product-icon-vector-operational-excellence-symbol-cost-efficiency-sign-for-your-web-site-design-logo-app-ui-illustration>

<https://cdn4.vectorstock.com/i/1000x1000/89/48/hourglass-icon-waiting-symbol-loading-time-vector-40708948.jpg>

<https://static.thenounproject.com/png/449456-200.png>

EFPIA MID3 Workgroup: SF Marshall. CPT Pharmacometrics Syst. Pharmacol. (2016) 5, 93–122, Milligan. CIn Pharmacol Ther. 93, 6 (2013)



- **ADME Charakterisierung**

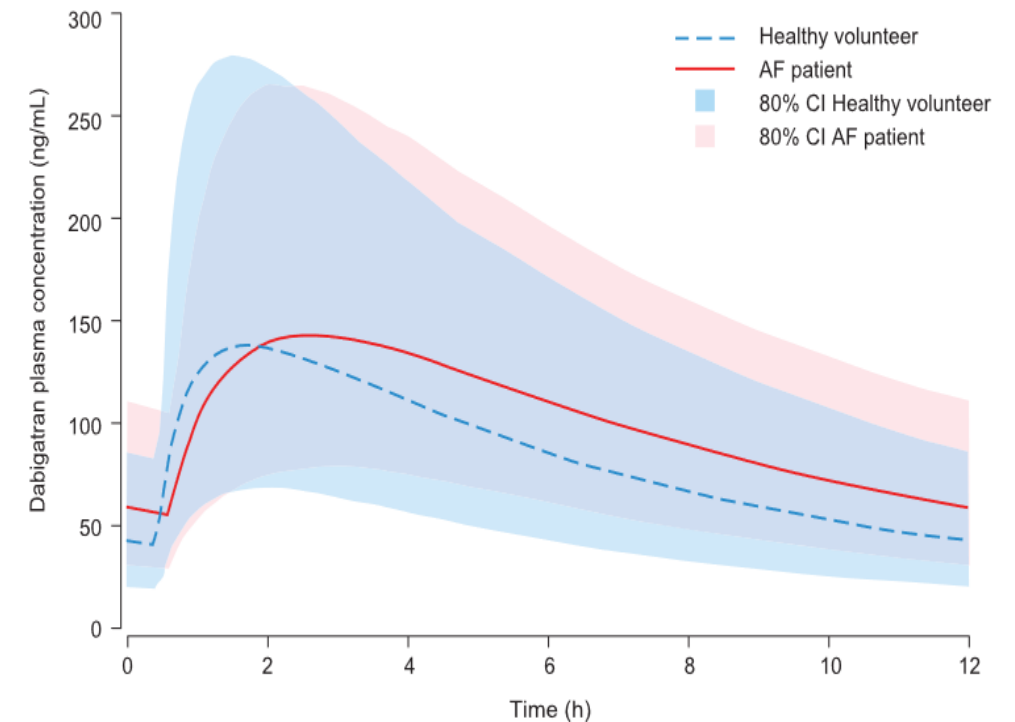
- **Einflussfaktoren → PK + Variabilität**

- Organfunktionsstörung, DDI, Formulierungsänderungen

→ Dosisanpassung?

- **PK und PD Vergleich Gesunde vs. Patient:innen mit Vorhofflimmern**

- Nierenfunktion als einziger klinisch relevanter Parameter für PK

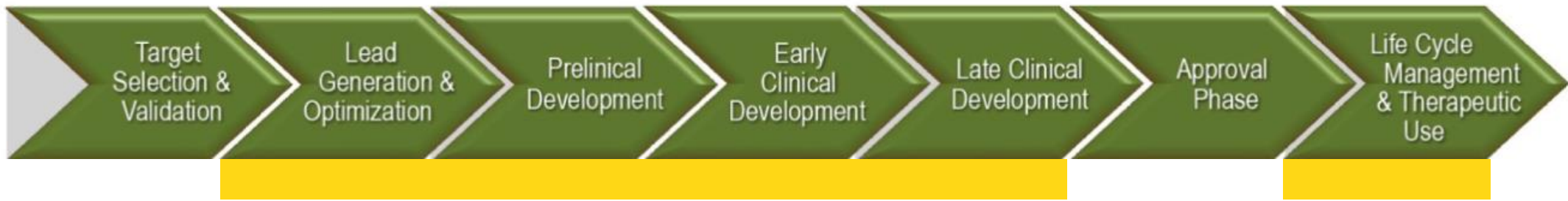


Dansirikul et al. Thrombosis and Haemostasis 107.4/2012

EFPIA MID3 Workgroup: SF Marshall. CPT Pharmacometrics Syst. Pharmacol. (2016) 5, 93–122



- **Nutzen-Risiko Charakterisierung, Outcome-Vorhersage**
 - Kandidatenauswahl, Dosisoptimierung etc.
 - Go/No-Go Entscheidungen
 - **Risiko für QTc Verlängerung:** Hund → Patient:innen
 - Neutropenie: **Monotherapie-Studien → Kombinationstherapie → Studiendesign**
 - HbA1c: **Kurze Studie → Langfristiger Outcome**



- **Vergleichsprodukte / Standardtherapie –**
Differenzierungs- und Kommerzialisierungsstrategien

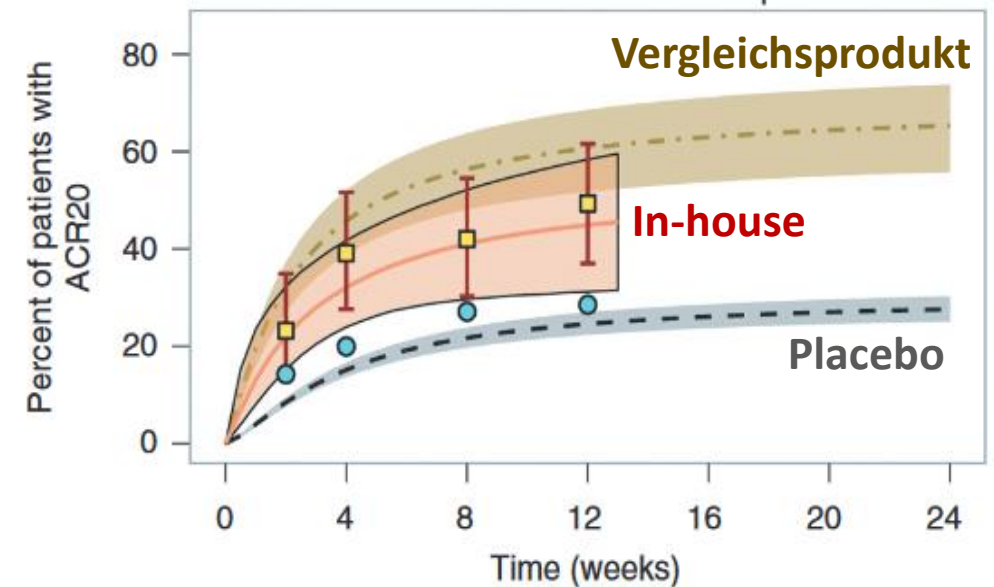


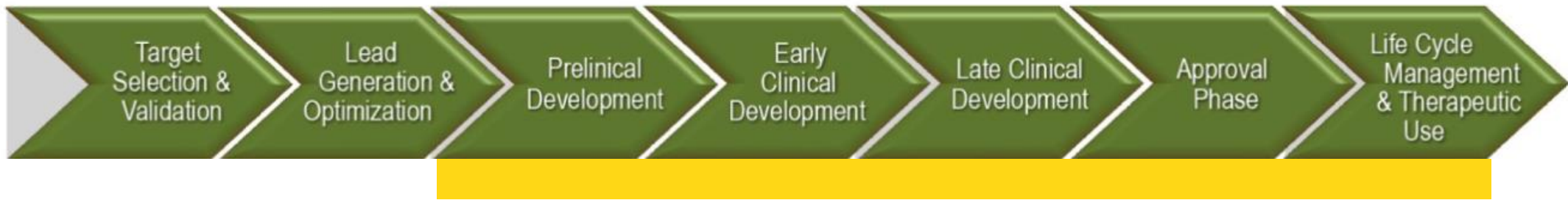
- **In-house Daten** ↔ **publizierte Daten** von zugelassenen Therapien
→ Keine zusätzlichen Benefits

https://upload.wikimedia.org/wikipedia/commons/thumb/2/2f/Zeichen_206_-_Halt%21_Vorfahrt_gew%C3%A4hren%21_StVO_1970.svg/1200px-Zeichen_206_-_Halt%21_Vorfahrt_gew%C3%A4hren%21_StVO_1970.svg.png

Pharmacol Ther. 2012 Sep;92(3):352-9.

EFPIA MID3 Workgroup: SF Marshall. CPT Pharmacometrics Syst. Pharmacol. (2016) 5, 93–122



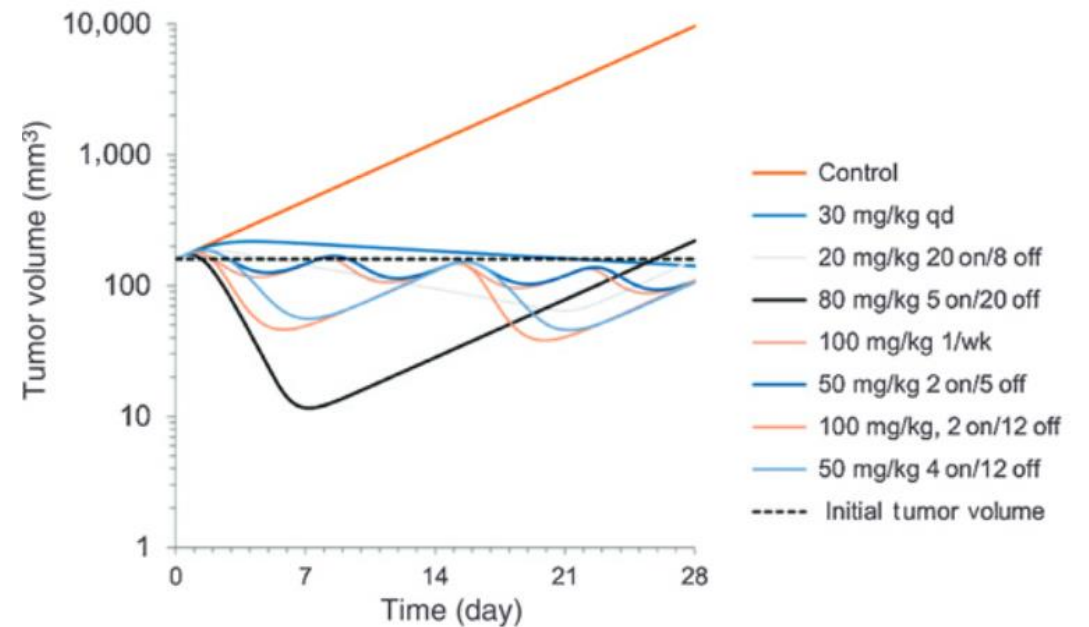


- **Dosierungsauswahl, Empfehlungen für Fachinformation**

- Interpolation/Extrapolation

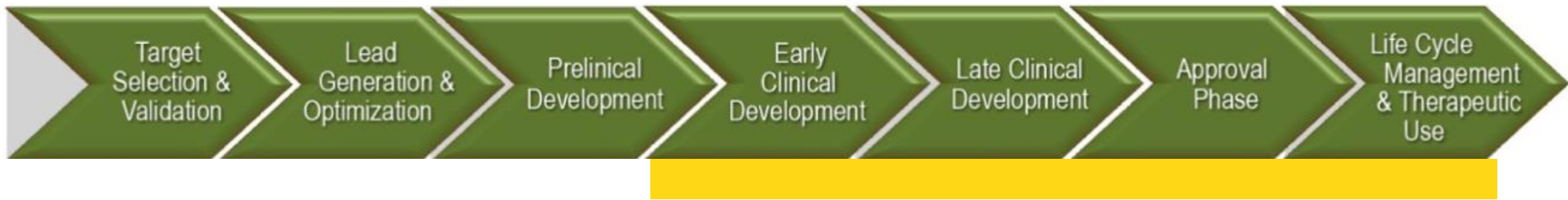
→ Optimale Dosis

- **Präklinische Daten → Phase I Dosierungsschema**

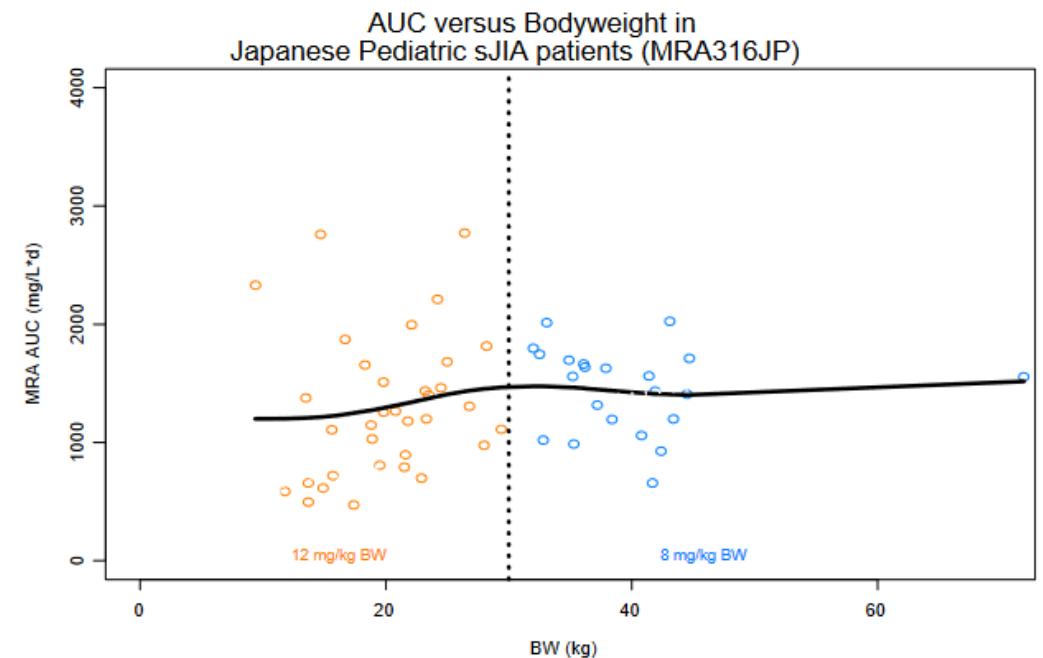


Higgins B, et al. Clin Cancer Res. 2014 Jul15;20(14):3742-52.

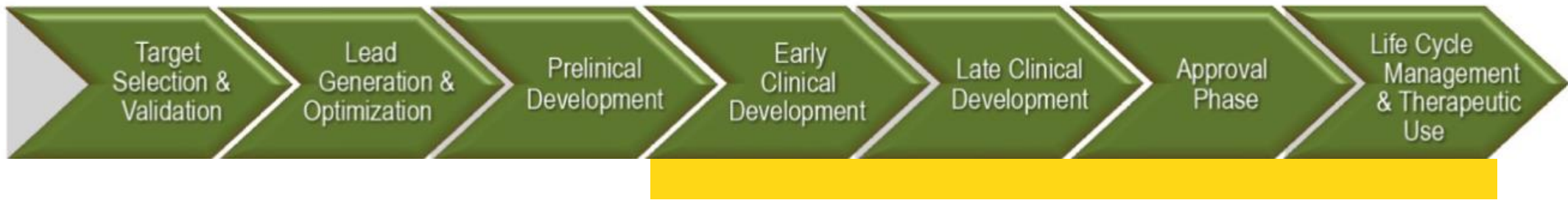
EFPIA MID3 Workgroup: SF Marshall. CPT Pharmacometrics Syst. Pharmacol. (2016) 5, 93–122



- **Selektion von Patientenpopulation, ‘Bridging’ zwischen Populationen** (pädiatrische, ältere, fettleibige Patient:innen)
 - PK, Wirksamkeit, Sicherheit



https://www.ema.europa.eu/en/documents/presentation/presentation-case-study-title-improvement-clinical-benefit-sub-sub-group-paediatric-systemic_en.pdf EFPIA MID3 Workgroup: SF Marshall. CPT Pharmacometrics Syst. Pharmacol. (2016) 5, 93–122



- **Selektion von Patientenpopulation, ‘Bridging’ zwischen Populationen**
 - **Dosierung von Patient:innen mit schwerer Niereninsuffizienz**

Table 10 Impact of Renal Impairment on Dabigatran Pharmacokinetics

Renal Function	CrCl (mL/min)	Increase in AUC	Increase in C _{max}	t _{1/2} (h)
Normal	≥ 80	1×	1×	13
Mild	50-80	1.5×	1.1×	15
Moderate	30-50	3.2×	1.7×	18
Severe ⁺	15-30	6.3×	2.1×	27

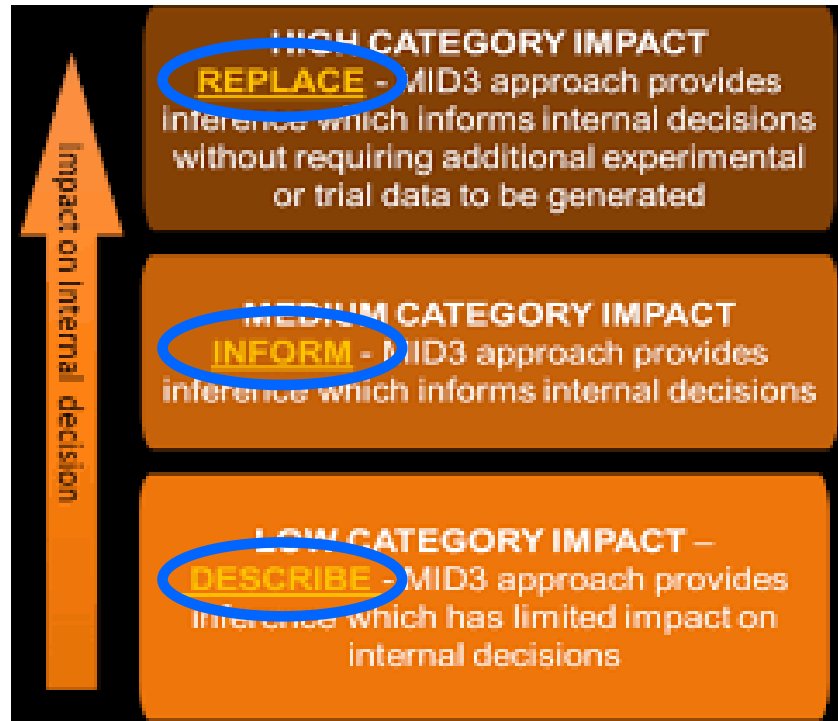
⁺Patients with severe renal impairment were not studied in RE-LY, RE-COVER and RE-NOVATE II. Dosing recommendations in subjects with severe renal impairment are based on pharmacokinetic modeling [see *Dosage and Administration* (2.2, 2.4) and *Use in Specific Populations* (8.6)].

Lehr et al. Clin Pharmacol. 2012 Sep;52(9):1373-8.

PRADAXA- dabigatran etexilate mesylate capsule Boehringer Ingelheim Pharmaceuticals Inc.

EFPIA MID3 Workgroup: SF Marshall. CPT Pharmacometrics Syst. Pharmacol. (2016) 5, 93–122

MID3 - Impact



- Pradaxa[®]:

Table 10 Impact of Renal Impairment on Dabigatran Pharmacokinetics

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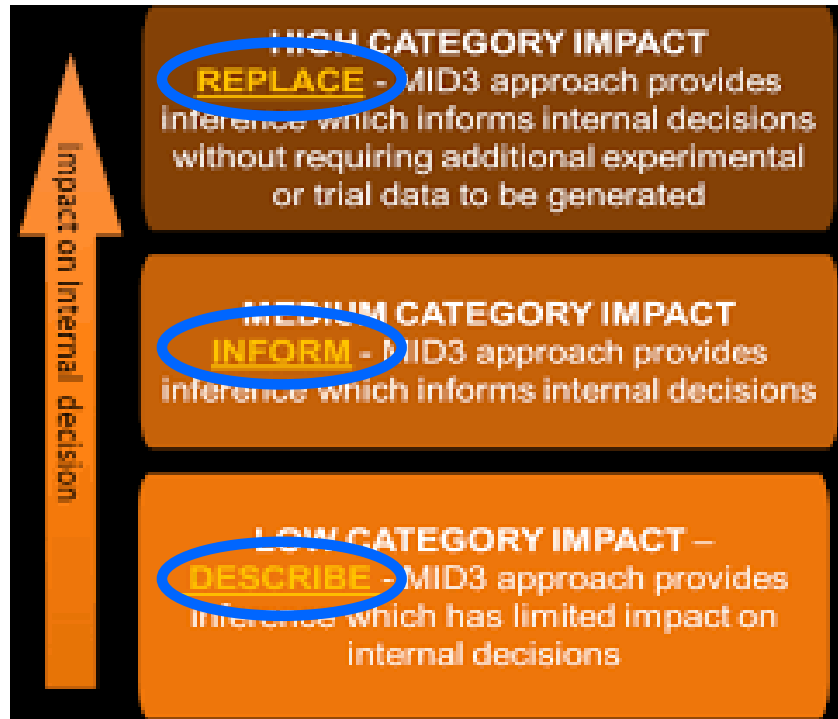
[†]Patients with severe renal impairment were not studied in RE-LY, RE-COVER and RE-NOVATE II. Dosing recommendations in subjects with severe renal impairment are based on pharmacokinetic modeling [see *Dosage and Administration (2.2, 2.4) and Use in Specific Populations (8.6)*].

https://www.psiweb.org/docs/default-source/default-document-library/02-mid3-extrapolation-psi-november-2017-final.pdf?sfvrsn=2789dfdb_0

PRADAXA- dabigatran etexilate mesylate capsule Boehringer Ingelheim Pharmaceuticals Inc.

MID3 → Zulassung

- **Impact in R&D**



- **Impact in der Zulassung**



https://www.psiweb.org/docs/default-source/default-document-library/02-mid3-extrapolation-psi-november-2017-final.pdf?sfvrsn=2789dfdb_0



3.2.5. Optimise capabilities in modelling, simulation and extrapolation

PERSPECTIVE

Quantitative Modeling and Simulation in PMDA: A Japanese Regulatory Perspective

M Sato*, Y Ochiai, S Kijima, N Nagai, Y Ando, M Shikano and Y Nomura

PERSPECTIVE

Model Informed Drug Development and Regulation in China: Challenges and Opportunities

Li Li¹, Hongcan Han¹, Jun Wang¹, Chunmin Wei¹, Yuzhu Wang¹, Min Li¹, Yu Zhou¹ and Jinbo Yang^{1,*}



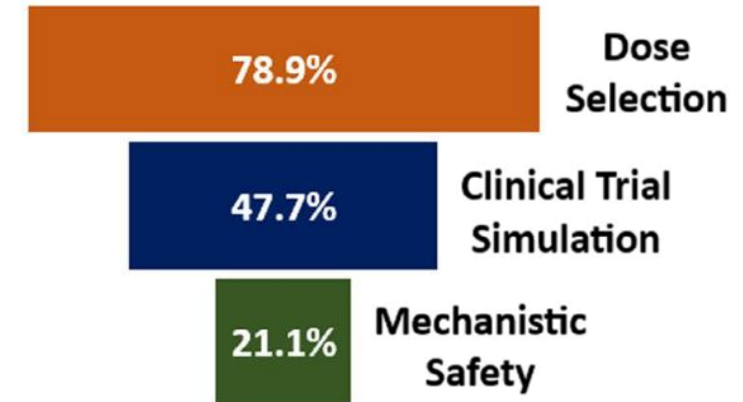
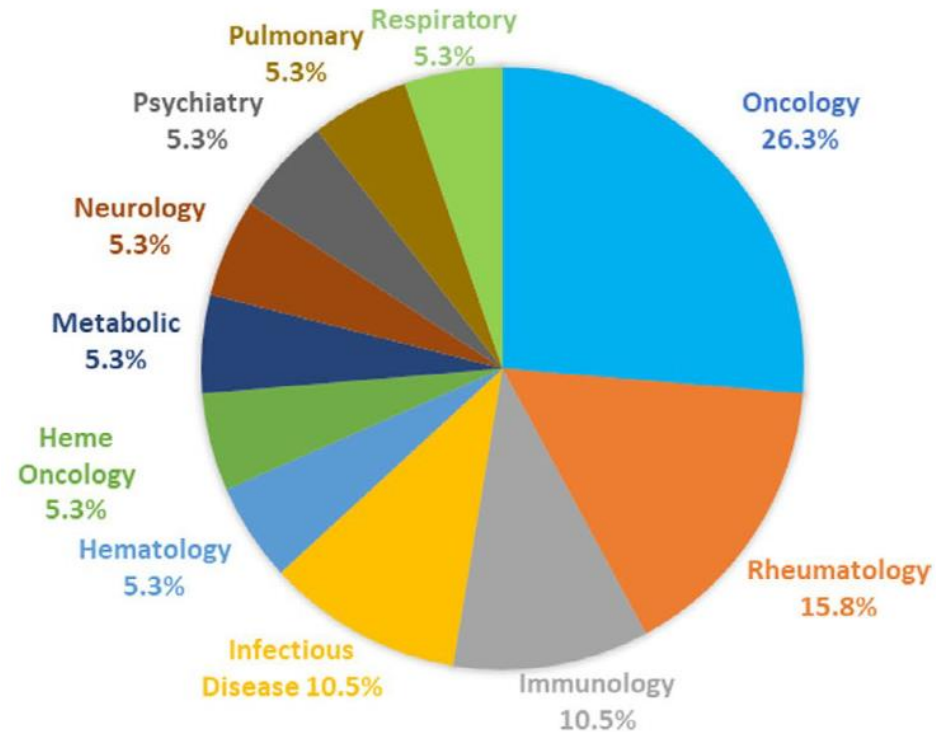
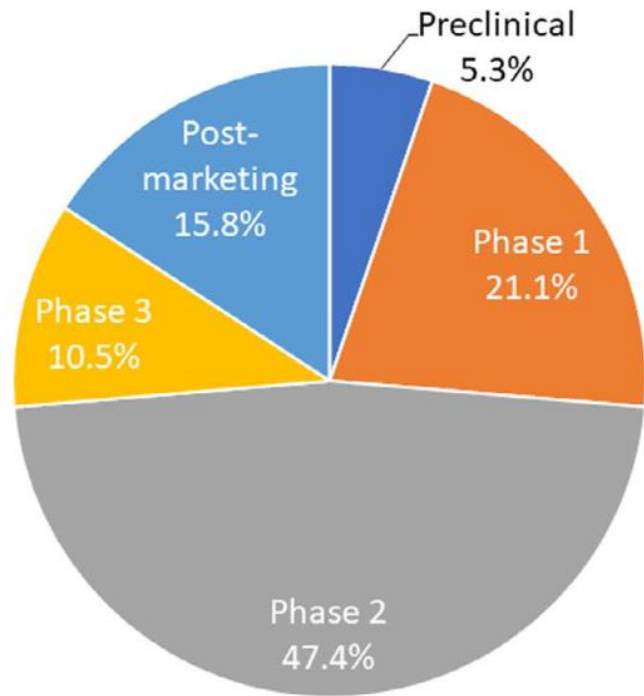
Model-Informed Drug Development Paired Meeting Program

https://www.ema.europa.eu/en/documents/report/emas-regulatory-science-strategy-2025-mid-point-achievements-end-2022_en.pdf

<https://www.fda.gov/drugs/development-resources/model-informed-drug-development-paired-meeting-program>



Model-Informed Drug Development Paired Meeting Program



Galluppi et al. Clin Pharmacol Ther. 110:1172 (2021)

MID3 → Zulassung

- **Scientific Advice**
 - Dosisregimes, Studiendesigns, Endpunkte, Datengrundlage für Nutzen-Risiko-Entscheidungen
- **Pädiatrischer Prüfplan**
- **Zulassungsantrag**
 - Fachinformation
- **Post-Marketing**
 - Signaldetektion, Lifecycle Management
 - Neue Indikationen

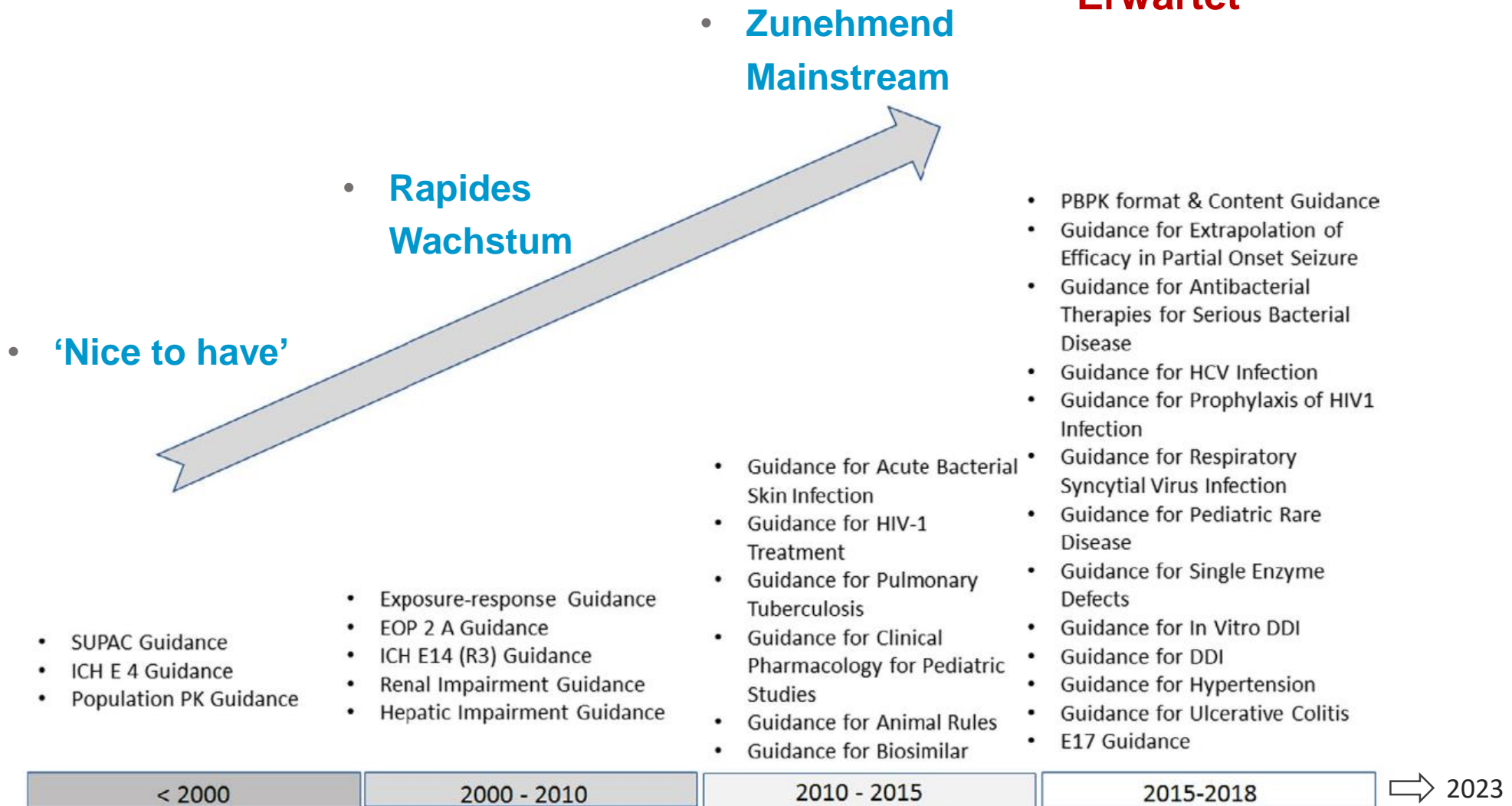
Population Pharmacokinetics Guidance for Industry

*Additional copies are available from:
Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov*

<https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs>

U.S. FDA Population Pharmacokinetics Guidance for Industry (Feb 2022)

MID3 → Zulassung



Zhu et al. Clin Pharmacol Ther. 106:1 2019)

EMA Regulatory Science to 2025

Strategic reflection



3.2.5. Optimise capabilities in modelling, simulation and extrapolation

Core recommendations	Underlying actions
Optimise capabilities in modelling, simulation and extrapolation	<ul style="list-style-type: none"> Enhance modelling and simulation and extrapolation use across the product lifecycle and leverage the outcome of EU projects;
	<ul style="list-style-type: none"> Develop guidance and standards on the use of AI in modelling and simulation for regulatory submissions;
	<ul style="list-style-type: none"> Deploy advances in RWD, modelling, simulation and extrapolation to benefit special populations particularly neglected patient populations;
	<ul style="list-style-type: none"> Promote development and international harmonisation of methods and standards via a multi-stakeholder platform;
	<ul style="list-style-type: none"> Increase capability and redesign the operations of relevant working parties to ensure wider knowledge exchange: <ul style="list-style-type: none"> Invest in Centres of Excellence in regulatory science at an EU level, to work with regulatory agencies to provide training and research on modelling & simulation tools; Enhance collaboration with external partners/consortia with expertise in modelling and simulation, and EU funded or co-funded projects e.g. IMI, Horizon 2020;
	<ul style="list-style-type: none"> Investigate possibilities for conducting modelling and simulation analyses to address key regulatory questions as part of product specific assessment or development of guidelines and policies;
	<ul style="list-style-type: none"> Consider working with stakeholders to foster data sharing through developing data standards and platforms for data exchange.

Zusammenfassung



<https://cdn-icons-png.flaticon.com/128/4599/4599675.png>



<https://www.vecteezy.com/vector-art/6662132-growth-product-icon-vector-operational-excellence-symbol-cost-efficiency-sign-for-your-web-site-design-logo-app-ui-illustration>



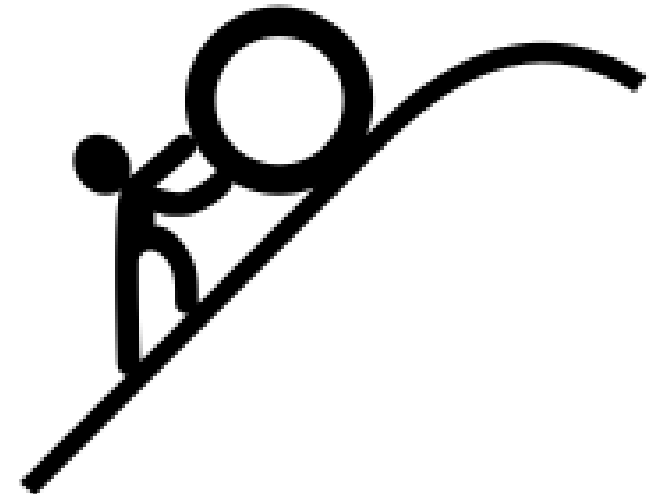
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<https://static.thenounproject.com/png/449456-200.png>

Herausforderungen

- Potentiell ↑ **Zeitaufwand für Voruntersuchungen** vor Studienbeginn
- **Skepsis gegenüber Änderungen** in Routine
- **Kommunikation** zwischen internen Unternehmensbereichen
- **IT Infrastruktur**
- **Datenverfügbarkeit und Qualität**
- **Komplexität** biologischer Systeme
 - Komplexität von Modellen, Modellentwicklung
- **Modellvalidierung und Standardisierung**
- Qualifizierte, erfahrene **Fachkräfte**



<https://thenounproject.com/browse/icons/term/challenge/>

Perspektiven

- MID3 für neue Therapiemodalitäten

Opportunities and challenges for applying model-informed drug development approaches to gene therapies

Artur Belov¹ | Kimberly Schultz² | Richard Forshee¹ | Million A. Tegenge^{1,2,3}

Application of Pharmacokinetic-Pharmacodynamic Modeling and Simulation for Antibody-Drug Conjugate Development

Aman P. Singh • Young G. Shin • Dhaval K. Shah

Pembrolizumab: Role of Modeling and Simulation in Bringing a Novel Immunotherapy to Patients With Melanoma

R de Greef^{1,2}, J Elassaiss-Schaap^{1,3}, M Chatterjee¹, DC Turner¹, M Ahamadi¹, M Forman¹, D Cutler¹, DP de Alwis¹, A Kondic^{1*} and J Stone¹

Model-informed drug development of autologous CAR-T cell therapy: Strategies to optimize CAR-T cell exposure leveraging cell kinetic/dynamic modeling

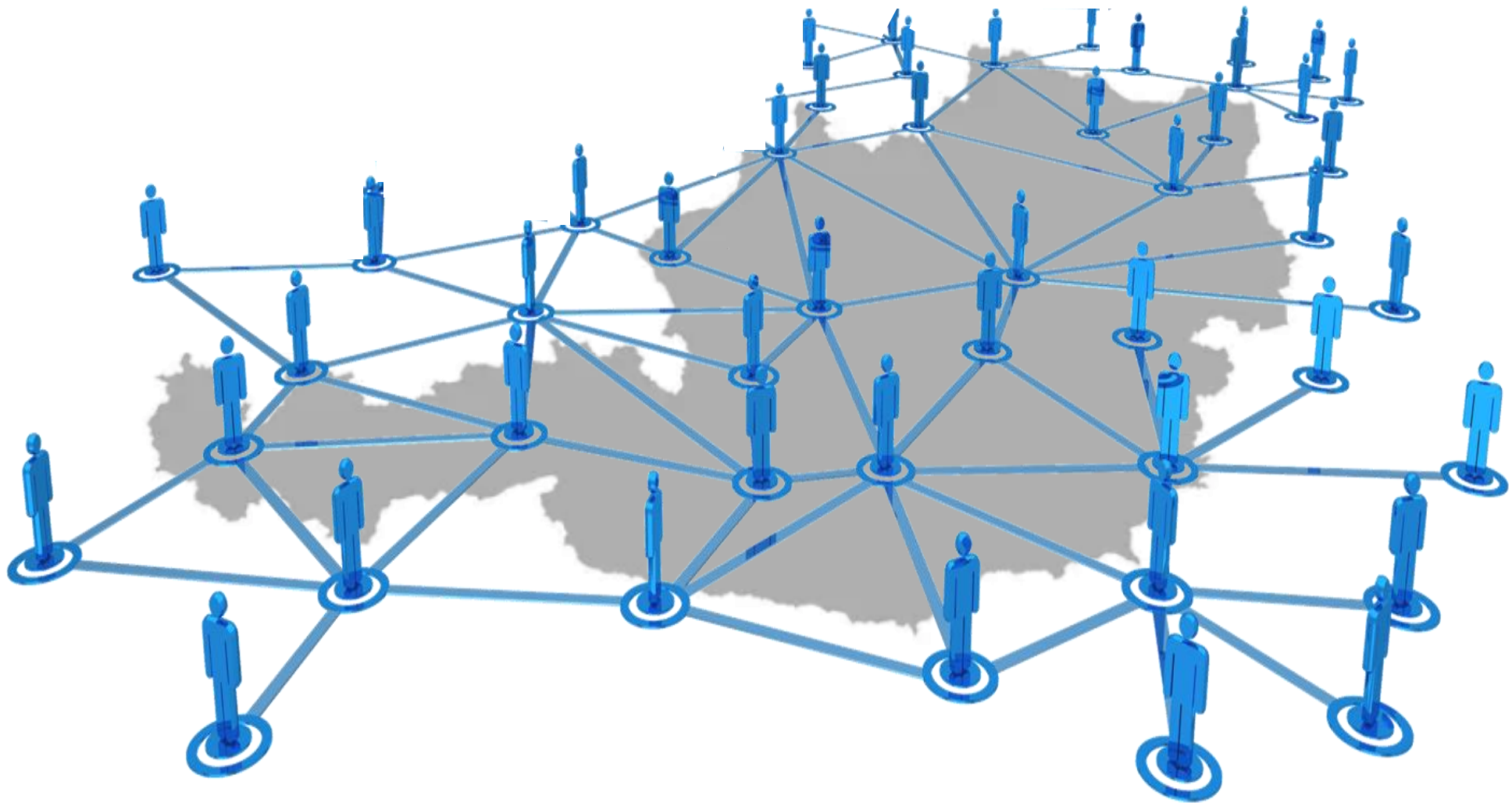
Anna M. Mc Laughlin¹ | Peter A. Milligan¹ | Cassian Yee^{2,3} | Martin Bergstrand¹

The Utility of Modeling and Simulation Approaches to Evaluate Immunogenicity Effect on the Therapeutic Protein Pharmacokinetics

Juan Jose Perez Ruixo,¹ Peiming Ma,¹ and Andrew T. Chow^{1,2}

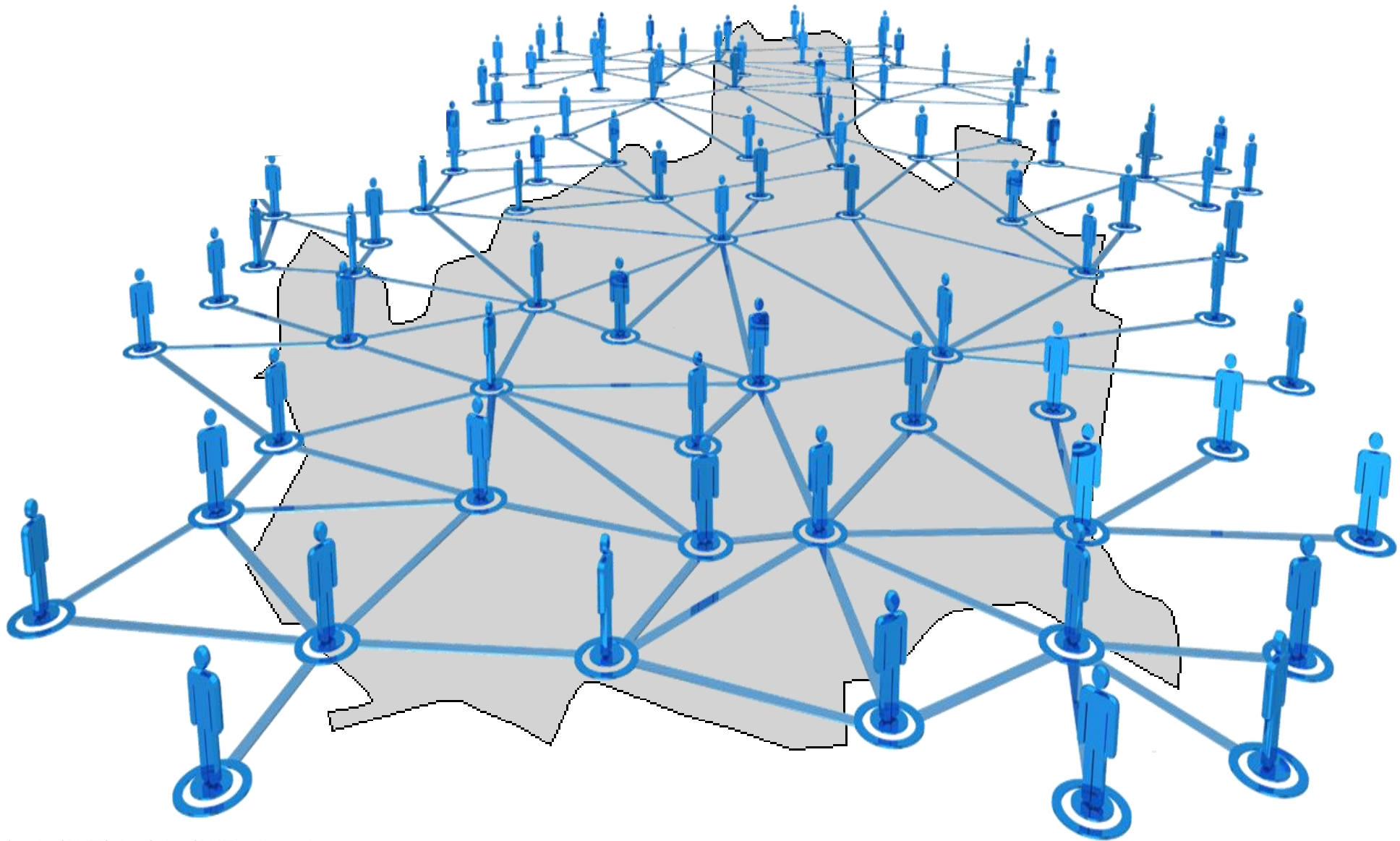
- AI und Machine Learning
- Kollaborationen





<https://www.vectorstock.com/royalty-free-vector/map-austria-administrative-regions-and-areas-vector-31166324>

<https://zabulionis.files.wordpress.com/2014/06/people-network.jpg>



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<https://zabulionis.files.wordpress.com/2014/06/people-network.jpg>



Univ.Klinik für Klinische Pharmakologie
iris.minichmayr@meduniwien.ac.at

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<https://zabulionis.files.wordpress.com/2014/06/people-network.jpg>