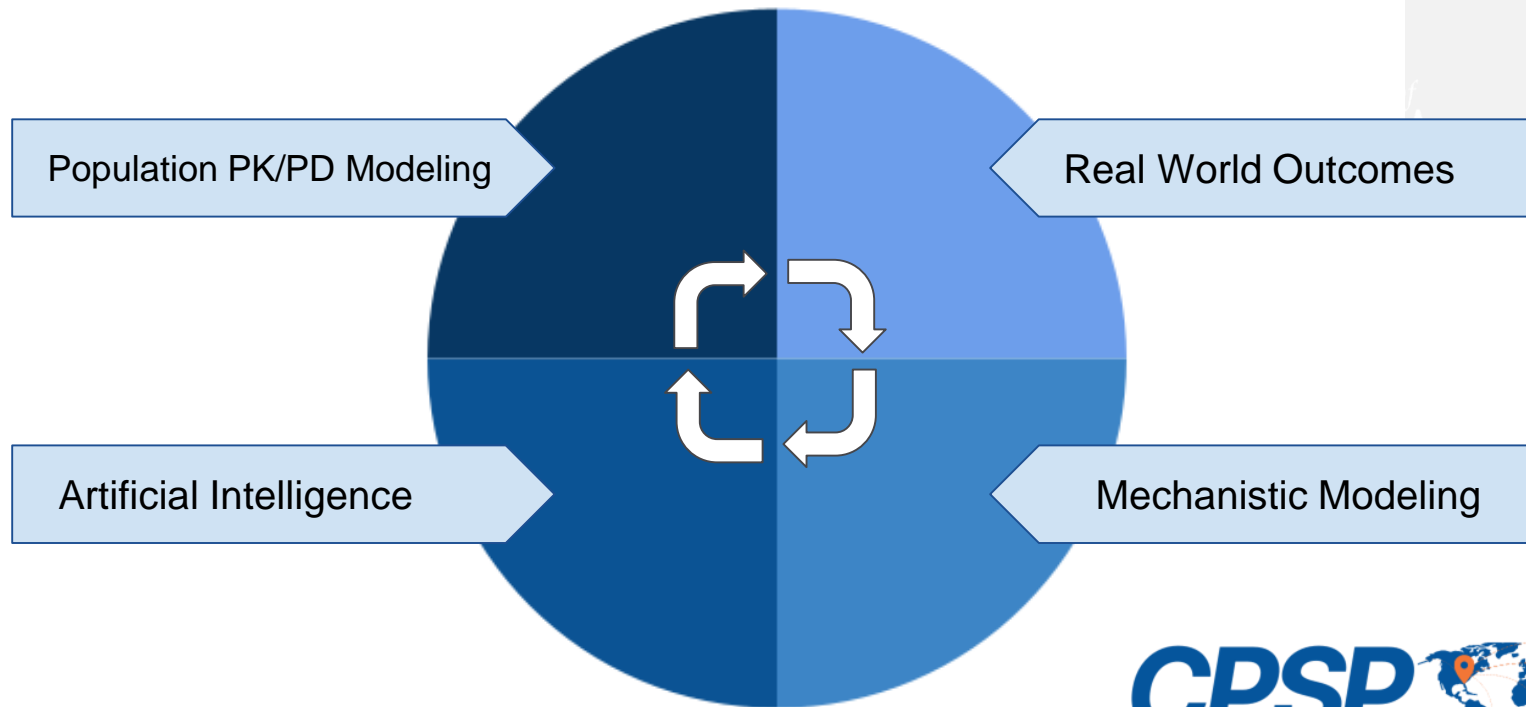# VIRTUAL PATIENT for Testing In - Silico Drug Formulations

Hans Leuenberger, PhD,

Prof. emeritus Pharmaceutical Technology University of Basel;

Adjunct Professor,

University of Florida, College of Pharmacy, Lake Nona Campus.

hans.leuenberger@ufl.edu;

PILLAR OVERVIEW

Population PK/PD Modeling

Real World Outcomes

Artificial Intelligence

Mechanistic Modeling

The Virtual Patient:
API focused Knowledge!

- **NIFEDIPINE** $C_{17}H_{18}N_2O_6$ MW 344.33
- Calcium Channel Blocker xlogP = 2.2
- **Antihypertensive Drug & Prophylactic** Treatm. of Angina Pectoris (Prinzmetal's).
- Adalat GITS (Osmotic Pump) 30/60 mg
- Nifedipine 80 mg XL Tablets (In-Silico);
- **N. Imm. Release** (too fast, **problematic**).
- **Treatment to eliminate Kidney Stones.**
- Nifedipine Ointment (topical) **for healing** **Anal Fissures** by locally increasing blood flow.
- Other indications such as anti-cancer Activity?
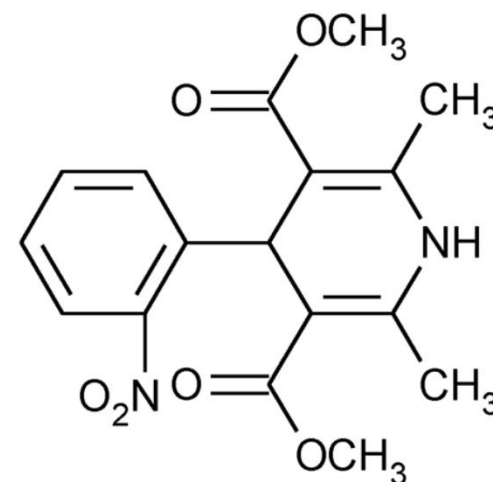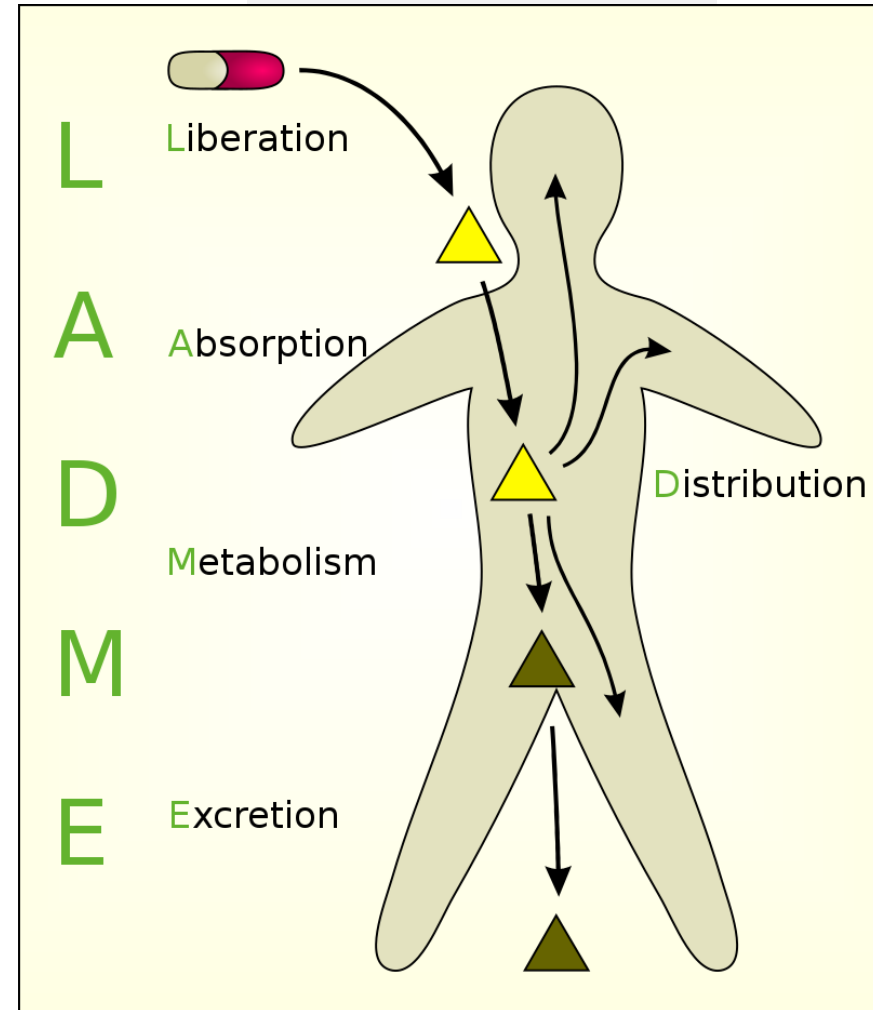
Virtual Patient: NIFEDIPINE focused knowledge based on

Pharmacokinetic PK Data
Bioavailablity: 45-56 %;
Protein Binding: 92-98 %
Elimination Half-Life: 2h;
Kidney > 50%; Biliary: 5-15%.
Pharmacodynamic PD Data
Reduction of Blood Pressure, Dilation of Blood Vessels, Higher Blood Flow, Effect on the Sympathetic Nervous System related to NIFEDIPINE Liberation
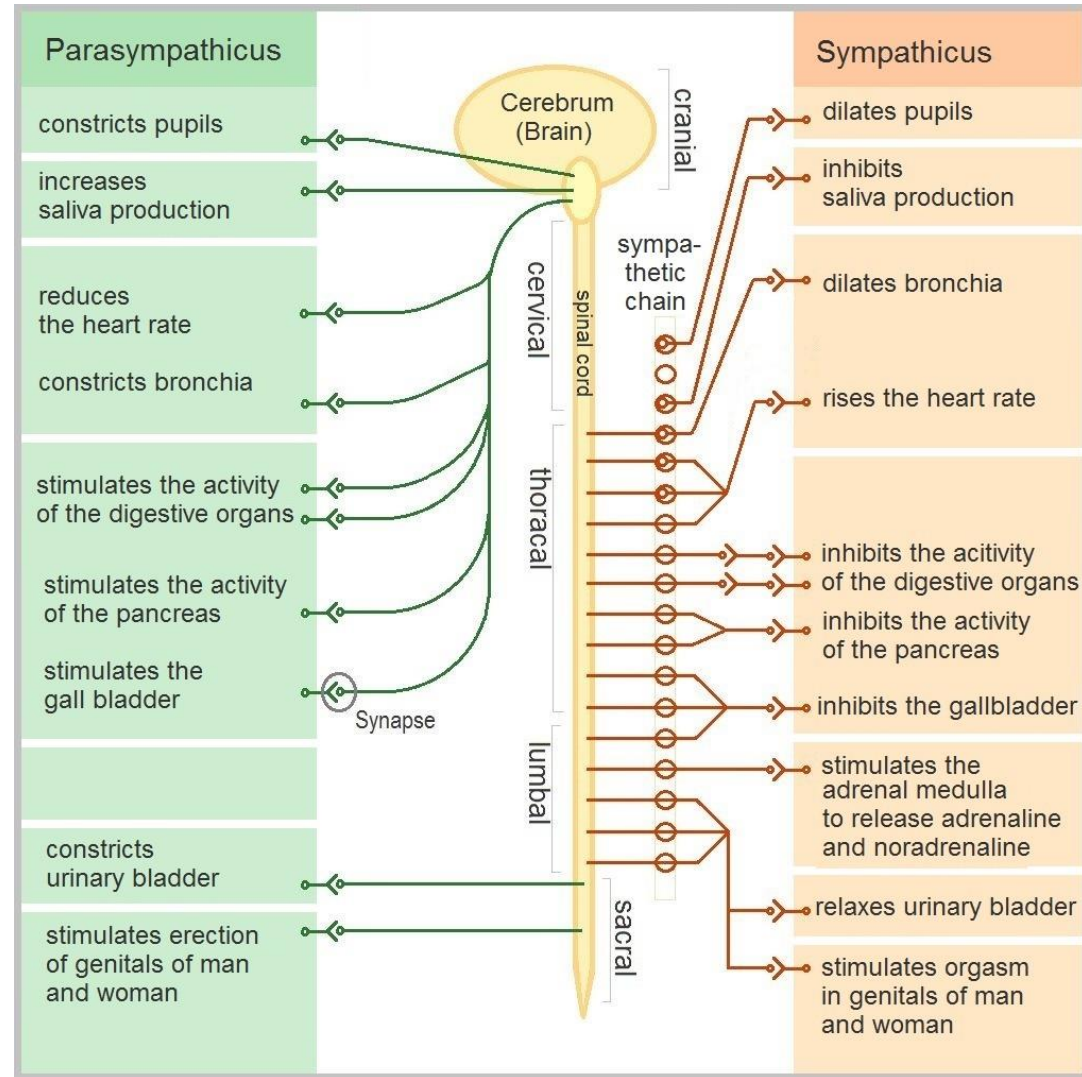

L — Liberation
A — Absorption
D — Distribution
M — Metabolism
E — Excretion

Autonomic Nervous System

Sympathetic system (Fight or Flight)

Parasympathetic syst. (Rest & Digest)

Comparison of short-acting versus extended-release Form.: Effects on hemodynamics & sympathetic activity in patients with stable coronary artery disease. (www.nature.com 2020).

Parasympathicus		Sympathicus
constricts pupils	Cerebrum (Brain)	dilates pupils
increases saliva production		inhibits saliva production
reduces the heart rate	sympa-thetic chain	dilates bronchia
constricts bronchia		rises the heart rate
stimulates the activity of the digestive organs		inhibits the acitivity of the digestive organs
stimulates the activity of the pancreas		inhibits the activity of the pancreas
stimulates the gall bladder	Synapse	inhibits the gallbladder
		stimulates the adrenal medulla to release adrenaline and noradrenaline
constricts urinary bladder		relaxes urinary bladder
stimulates erection of genitals of man and woman		stimulates orgasm in genitals of man and woman

cranial, cervical, spinal cord, thoracal, lumbar, sacral

Autonomic Nervous System

Sympathetic system (Fight or Flight): A significant fall in blood pressure and a significant increase in total body Norepinephrine spillover in both NIFEDIPINE Formulations. The ***increase in sympathetic activity*** in response to ***short-acting*** was much greater than in the *extended release* GIT Nifedipine *formulation*. **Adverse effects** in case dramatic drop in BP & peripheral vasodilation "stealing blood from other vascular beds", *tachycardia* from *norepinephrine release*. Clinically, these manifest in *neurologic events, coronary events, or myocardial ischemia. Several deaths have occurred (Ref*. Winker. *JAMA* 1996;276;1342-1343).

Autonomic Nervous System

Control of vital BP: A Redundant System is required. Thus, diff. Classes of APIs can Lower BP with differ. CNS properties.

TABLE 2. Effects of Different Classes of Antihypertensive Drugs on SNS (Centrally and Peripherally Mediated Effects)

Class	Central Effect	Peripheral Effect
Diuretics	↑	↔
Centrally acting antihypertensive drugs	↓	↓
α1 adrenergic antagonists	↑	↓
β–blockers	↓ ↔	↓
Dihydropyridines CCB	↑ ↔	↓ ↔
Nondihydropyridines CCB	↔	↓ ↔
ACE inhibitors	↓	↓
AT1 receptor antagonists	↓ ↔	↓

This table shows principal effects of different classes of antihypertensive drugs on central (cathecolamines release) and peripheral (peripheral tissue receptors activation) SNS.

The final effect on sympathetic tone is not so clear for all the antihypertensive class of drugs.

Symbols: ↑, increased effect; ↓, decreased effect; ↔, nonmodified effect.

Virtual Patient: NIFEDIPINE

Autonomic Nervous System

Evidently PK & PD data need be complemented: Bioelectric Medicine is an emerging Field*(https://feinstein.northwell.edu/institutes-researchers/bio-electronic-medicine).
Driving force is the con-vergence of advances in neuroscience, electronics, materials science, molecular medicine, and biomedical Engineering.
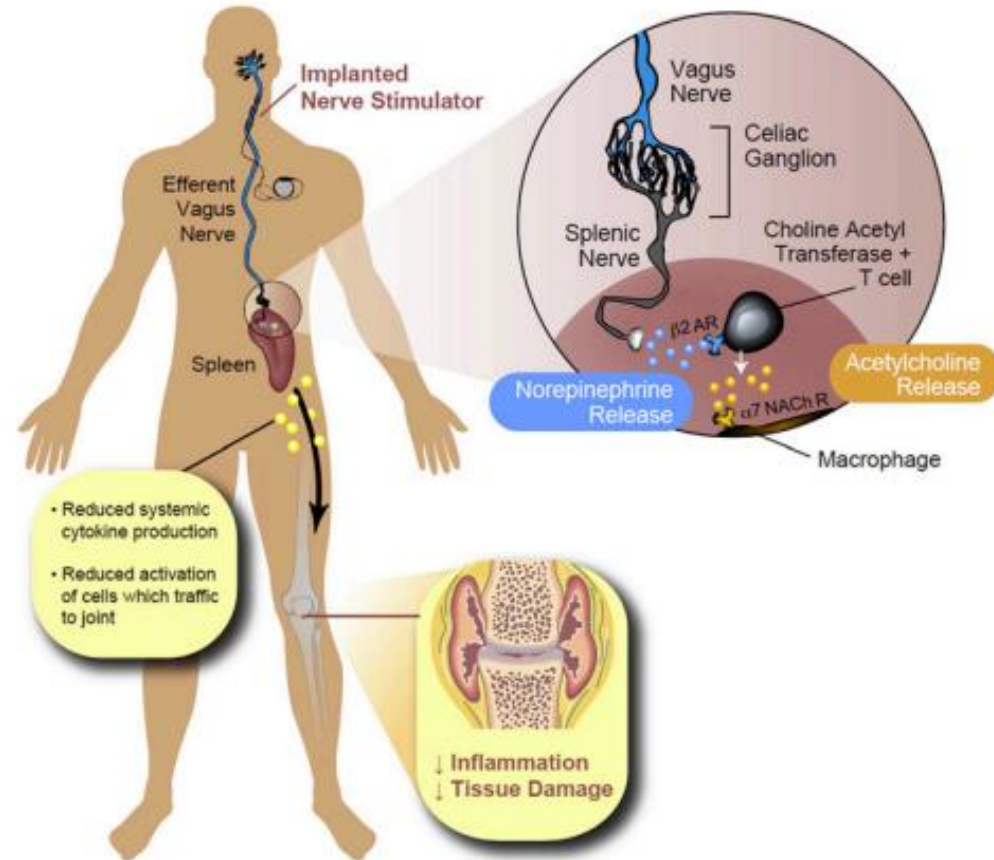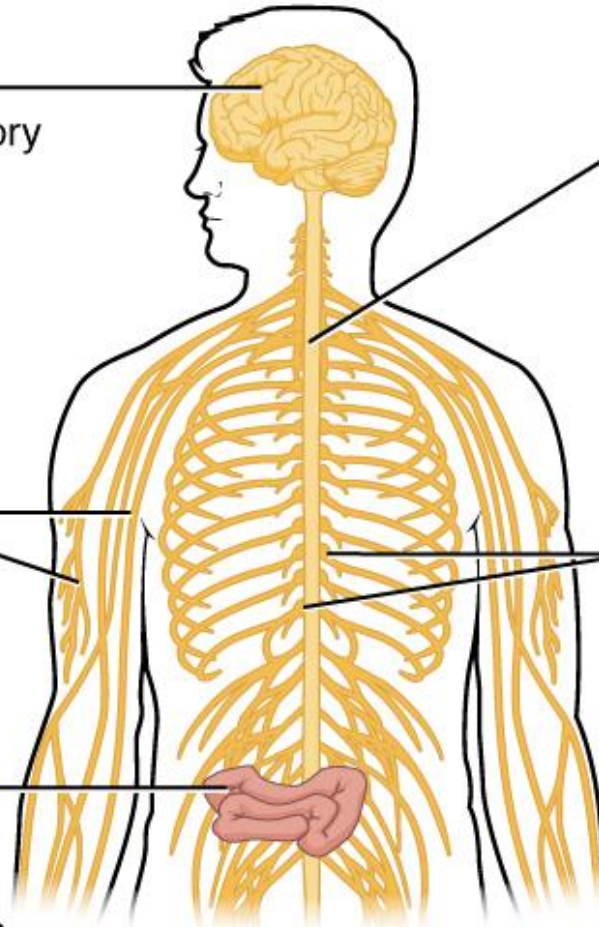
CNS & Peripheral Nervous System*

Brain (CNS)
Perception and processing of sensory stimuli (somatic/autonomic)
Execution of voluntary motor responses (somatic)
Regulation of homeostatic mechanisms (autonomic)

Spinal cord (CNS)
Initiation of reflexes from ventral horn (somatic) and lateral horn (autonomic) gray matter
Pathways for sensory and motor functions between periphery and brain (somatic/autonomic)

Nerves (PNS)
Fibers of sensory and motor neurons (somatic/autonomic)

Ganglia (PNS)
Reception of sensory stimuli by dorsal root and cranial ganglia (somatic/autonomic)
Relay of visceral motor responses by autonomic ganglia (autonomic)

Digestive tract (ENS)
The enteric nervous system (ENS), located in the digestive tract, is responsible for autonomous functions and can operate independently of the brain and spinal cord.

We need to include in our models our "Computer Wiring Network"!

*https://upload.wikimedia.org/wikipedia/commons/b/b2/1205_Somatic_Autonomic_Enteric_StructuresN.jpg

Human Being = A Supercomputer:
Study based on the work of I. Prigogine & I. Stengers

"Order out of Chaos, Man's New Dialogue with Nature"(U of M, Bantam Books,1984) and on my work in SWISS PHARMA 41 (2019) Nr. 1, 20–36,
In case of a system far from Equilibrium Conditions:

1.*(Prigogine): Transformations exist from disorder into order, leading to the creation of life: Chaos ➡ Order.*
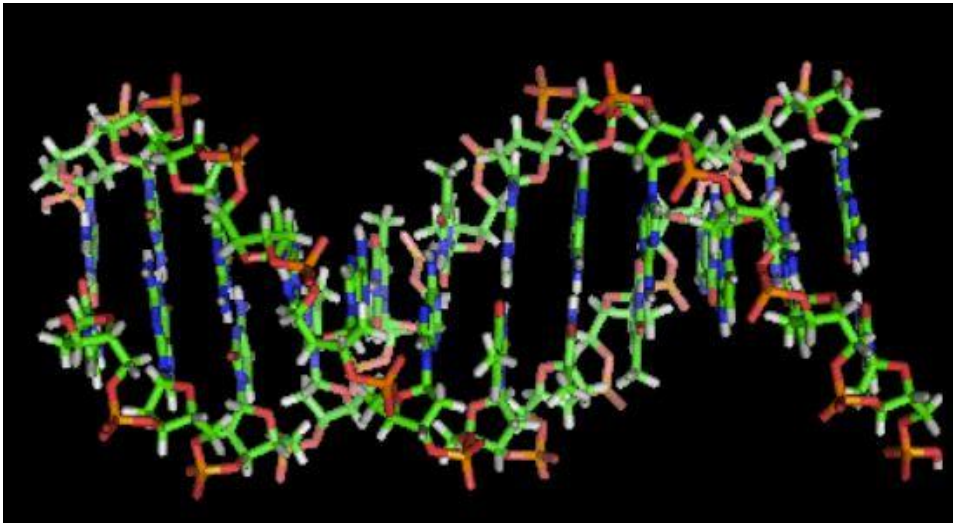
2. (Leuenberger): The same process is responsible for "inorganic life", i.e. for the formation of highly Ordered (e.g. Pyrite) crystals in nature: Chaos ➡ Order.

Pyrite Crystals as "Inorganic Life"?

The main difference is that inorganic chemistry has not the capability of storing so much information as DNAs!

3. (Schrödinger): Life = Information = Software = Genetic Code

This is the concept of a ***Virtual Patient*** based on the idea that each human cell is a microprocessor: **Number** of cells in the human body $\approx$**37.2 x 10^{12}** without Microbiom!

4. (Schrödinger / Prigogine): The human being is a living (super) computer! The latest NVIDIA GPU technology of the Ampere A100 GPU has arrived at UF (NVIDIA SuperPod). UF is the first university in the world to get to work with this technology.
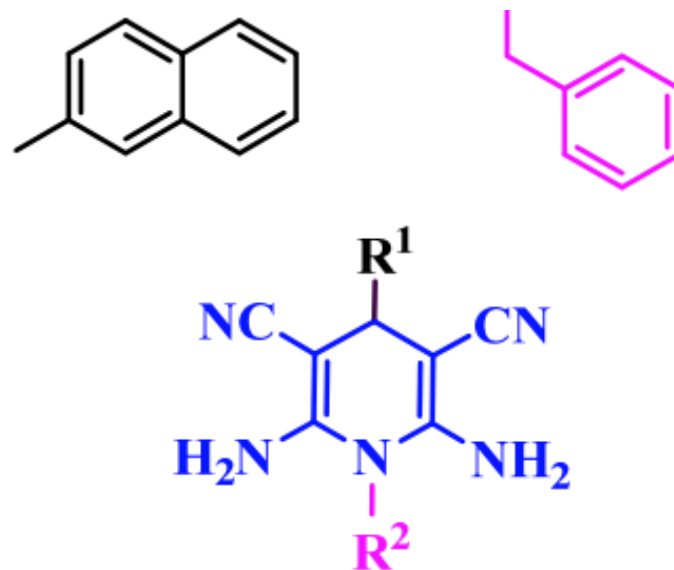
Publ: Design, Synthesis, and Biological Evaluation of Novel **Dihydropyridine** and Pyridine **Analogs** as Potent Human Tissue Nonspecific Alkaline Phosphatase Inhibitors with **Anticancer Activity**: ROS and DNA Damage-Induced **Apoptosis** (Ref: Molecules 2022, 27, 6235). **Optimal compound = 4d.**
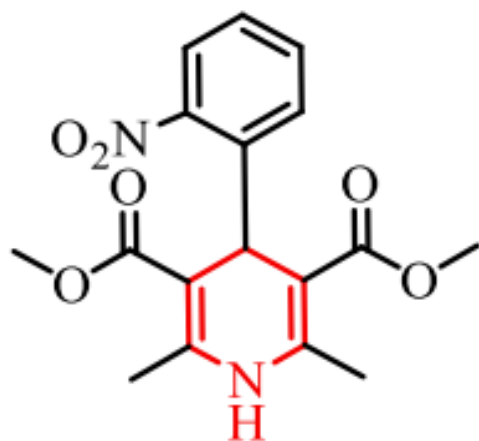

Nifedipine

4d

VIRTUAL PATIENT

Our human computer operating system is e. g. sensitive to Syrosingopine, a Reserpine deriv. to treat hypertension. Reserpine also is used as long-acting tranquilizer for horses, cattle, dogs, cats.
Reserpine is an interesting single API scaffold for fine-tuning our computer operating system!   Metformin is used to treat Diabetic type 2 patient as a Single API!
The Combination is an effective Anticancer Agent!*
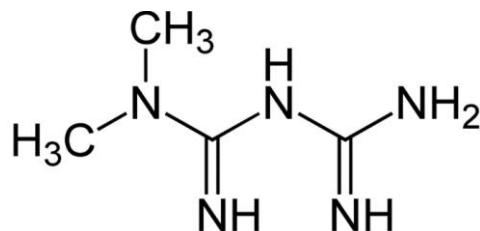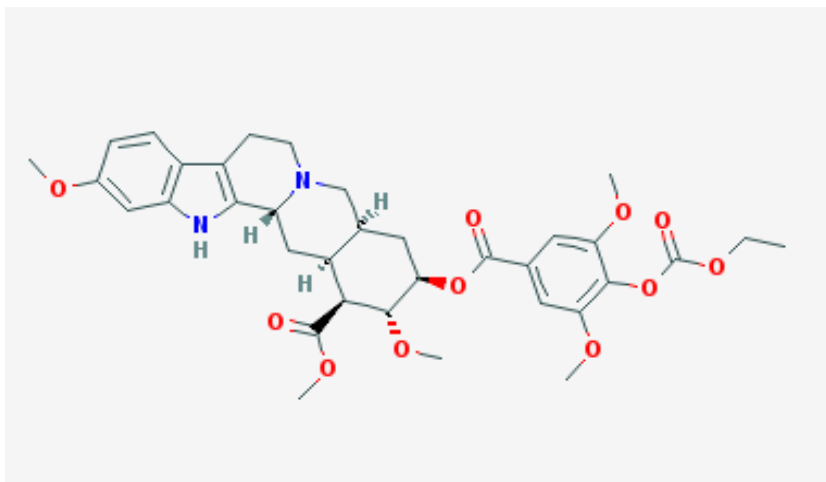
**Instead of designing a single API let us test Combinations!**

DIGITAL TWIN = VIRTUAL PATIENT

VIRTUAL PATIENT = SUPERCOMPUTER:

- Thus, the *Computer Operating System* of the VIRTUAL PATIENT is sensitive to *single drugs* (APIs), to *toxins,* to *brutal toxins* inducing multiple organ failures, to *food* (such as Grapefruit *interacting with drugs*), to *parasites* such as *worms*, *to the combination of drugs*, to *bugs* and to *viruses*.

- If the hardware of VIRTUAL PATIENT (Supercomputer) is damaged failing to work, it is questionable, whether the *system can be rebooted as a computer* or *reanimated as a human being* in an emergency room.

- What are our conclusions: ➡ Should we continue our normal expensive search for new single APIs or look for new research avenue

# Research Topic: Improved translational/animal replacement models

Improved (more predictive?) translational models/assays
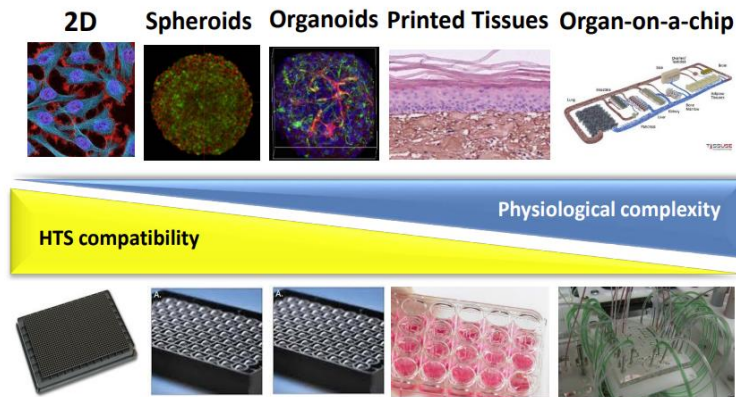
FDA Modernization Act 2.0 act authorizes the use of certain alternatives to animal testing, including cell-based assays and computer models, to obtain an exemption from the

Food and Drug Administration to investigate the safety and effectiveness of a drug.

EMA - Regulatory acceptance of 3R (replacement, reduction, refinement) testing approaches.

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16
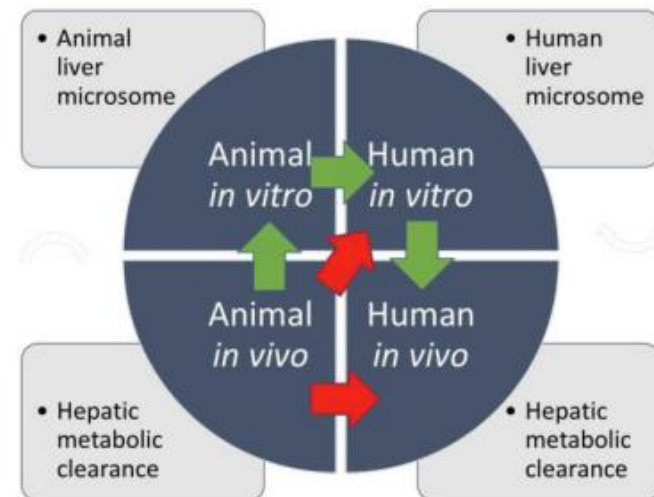
AI & Digital (Twin) Revolution:

F-CAD by CINCAP at SHIONOGI is the first DIGITAL TWIN* of the SOP "Tablet Design, Dev., Manufacture & Testing*".
The DIGITAL TWIN Industry has a bright future: $183B Annual revenue by 2031
(Reference: www.gartner.com/eng/documents/4011590).
Fig. 4: Digital Twin of a Turbine ➡

"GE: No unscheduled downtime"
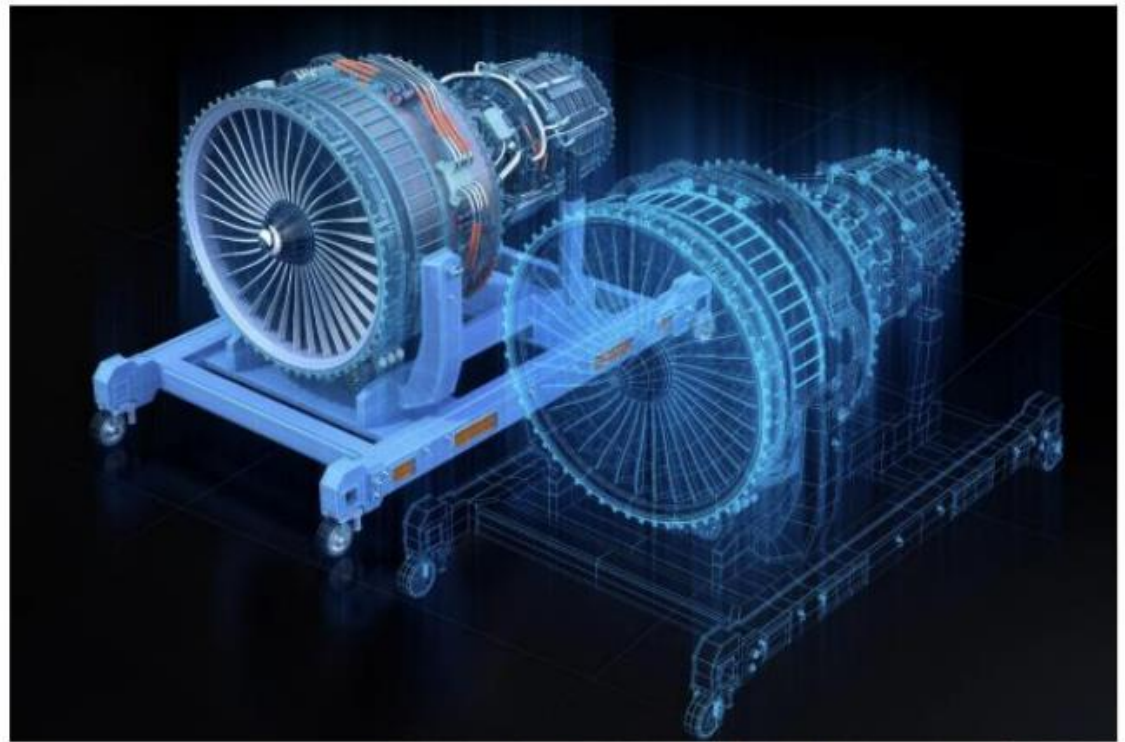
https://www.ingenjor40.se/module/cyber-physical-systems-and-digital-twins/

* D. Maneerojpakdee et al. An attempt to adopt the workflow of the automotive and aircraft industry for the design of drug delivery vehicles , Pharm. Tech. Japan, 33,11 (2017) 145-156.

VIRTUAL PATIENT

Can we use the VIRTUAL PATIENT to test Virtual Drugs & Drug Formulations?

- **Computer assisted drug design can be used to create a Virtual Drug.**
- However, **F**ormulation **C**omputer **A**ided **D**esign (**F-CAD**) is not yet part of the standard workflow.
- This is surprising, since **computer aided design of vehicles** is the **standard procedure** of the automotive and aircraft industry for reducing time to market.
- Dr. Go Kimura, my former PhD student, introduced successfully **F-CAD** **of CINCAP** at the company **Shionogi** in Japan for optimizing **drug delivery vehicles.**
- **PhD thesis at** http://edoc.unibas.ch/diss/DissB_9886

In-silico test of the dissolution profile

In-silico design of n formulations: design space exploration according to ICH Q 8 (R2)
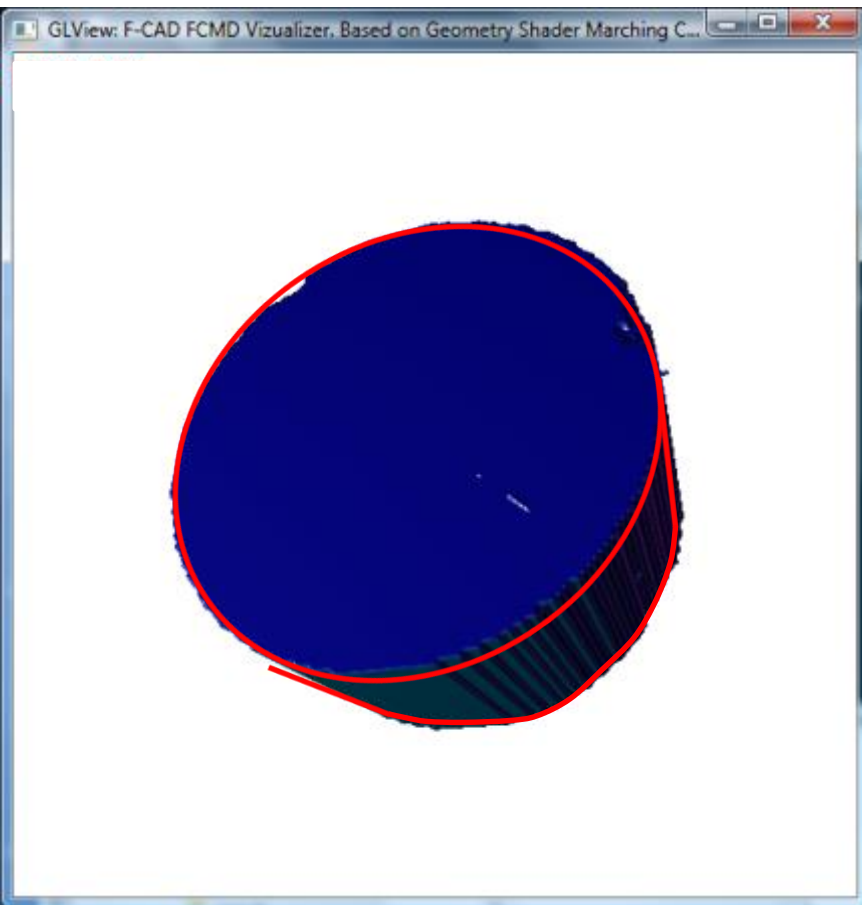
- Calculation of dissolution

AI & Digital (Twin) Revolution:

Plasma concentrations of theophylline related directly to the appearance of adverse reactions. Bronchodilation is the therapeutic effect of this drug
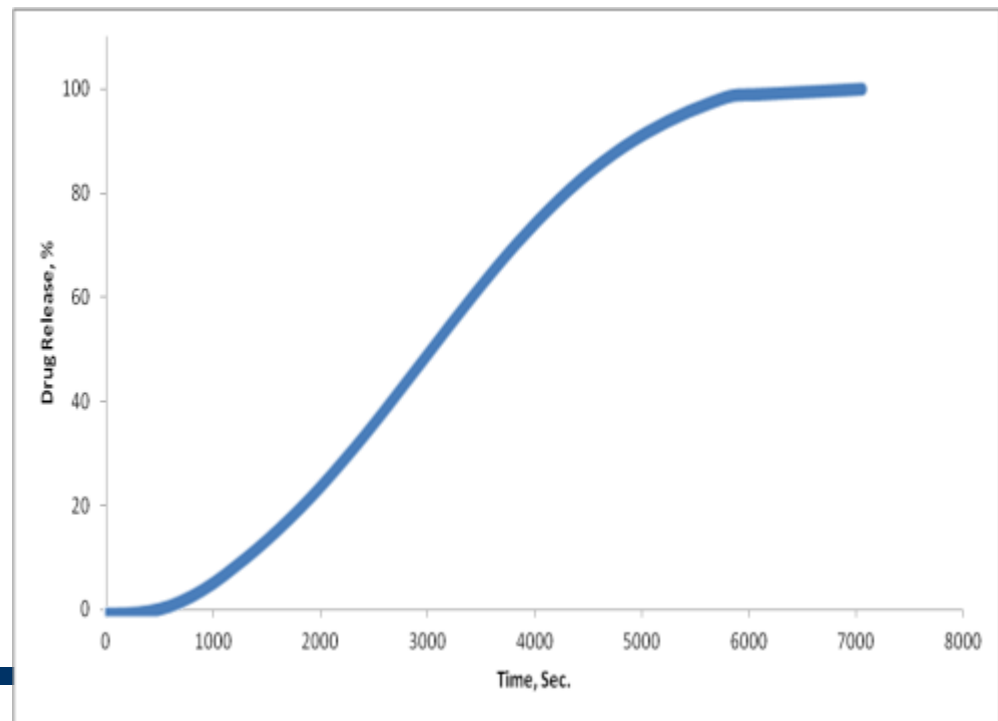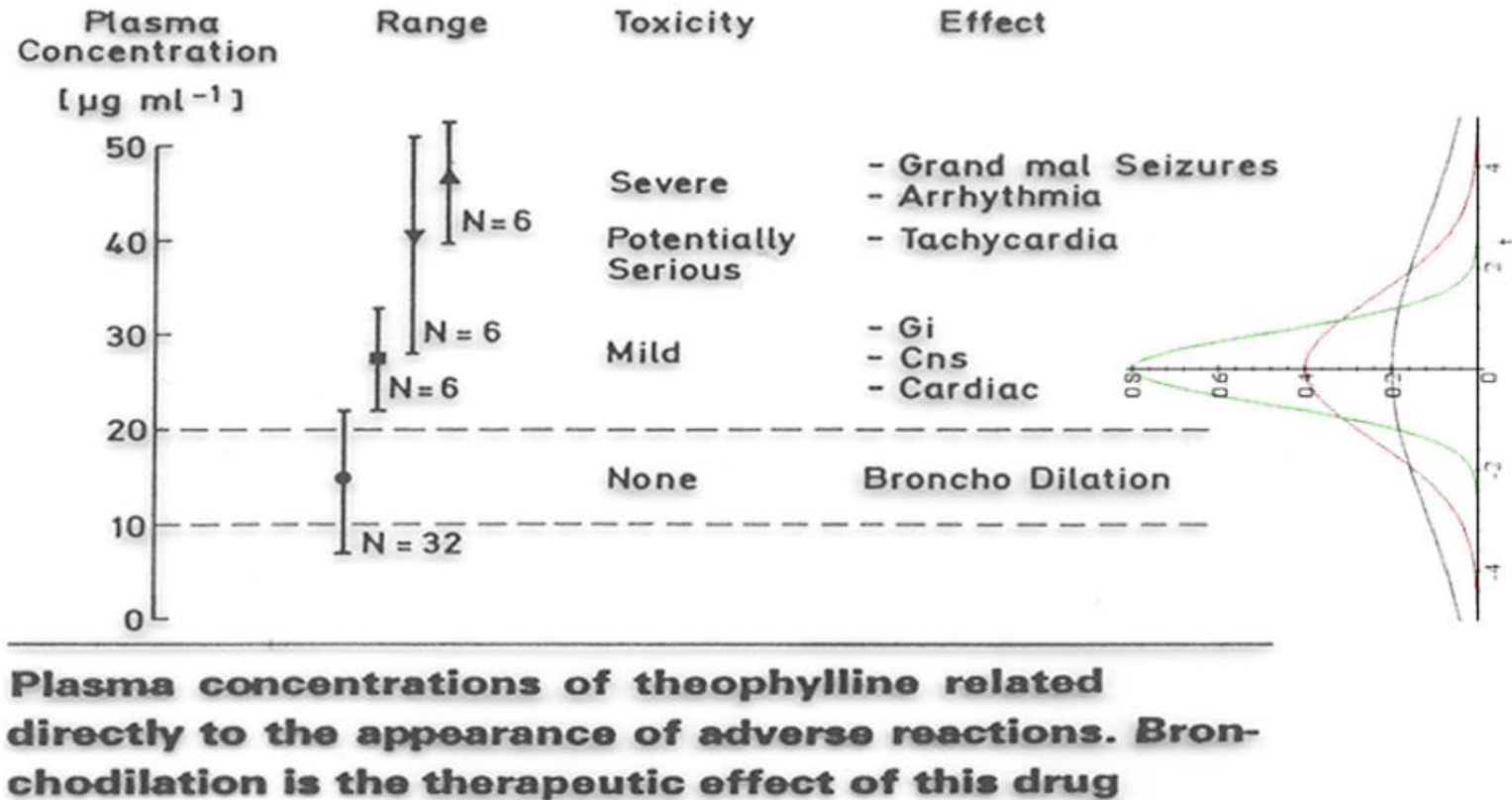
Fig. 3: A six-sigma quality formulation is needed already for Clinical Phase I & II, especially in case of a Narrow Therapeutic Window of the API . This goal can be achieved thanks to the DIGITAL TWIN.*

Nifedipine Formulations:

- For calibration purposes regarding the type of the in-vitro method it is necessary to manufacture in the real world at least one VIRTUAL F-CAD formulation in the design space.
- Thus, F-CAD can be used for virtual manufacturing!

The good News: F-CAD by CINCAP
- or an equivalent software should be applied, or if not available, and for the validation of the F-CAD results
- simply use design of experiments (DOE) for exploring the formulation design space leading to Virtual Manufacturing Equations for fast R. & C.R. Nifedipine Formulations.

Nifedipine Formulations (DOE) Central Composite Design:

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Table 2   Coded and uncoded (ratios [% w/w]) variables in a 3–level full factorial design of stage 1: Preliminary study on the effect of tableting speed concerning the harmonization of the equipment between the R&D and production department

No.	Coded Variable		Uncoded Variable	
	$A = x_1$	$B = x_2$	Ratio Nifedipine / PVP K-30 (mg)	Ratio MCC burst / MCC PH 102 (mg)
1	-1	-1	30:170	10:190
2	0	-1	60:140	10:190
3	+1	-1	90:110	10:190
4	-1	0	30:170	100:100
5	0	0	60:140	100:100
6	+1	0	90:110	100:100
7	-1	+1	30:170	190:10
8	0	+1	60:140	190:10
9	+1	+1	90:110	190:10

Nifedipine tablet formulations: Effect of composition on hardness & disintegration

- D. Maneerojpakdee et al. An attempt to adopt the workflow of the automotive and aircraft industry for the design of drug delivery vehicles , Pharm. Tech. Japan, 33,11 (2017) 145-156.

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Table A 1d   The tablet weight, thickness, diameter, hardness and disintegration time of NI tablets at 10,800 TPH, each value represents the mean±SD (n=3). Runs according to Table 2

No.	Weight (mg)	Thickness (mm)	Diameter (mm)	Hardness (N)	Disintegration time (sec)
1	400.5±2.2	4.83±0.02	10.07±0.01	110±6	1446±60
2	401.1±2.1	4.83±0.01	10.07±0.00	85±5	1197±47
3	400.4±0.8	4.74±0.01	10.06±0.00	100±4	922±11
4	402.8±0.9	4.86±0.01	10.07±0.01	92±3	1068±23
5	401.1±2.8	4.85±0.02	10.08±0.01	70±2	531±56
6	401.3±1.0	4.82±0.01	10.11±0.01	32±2	135±32
7	401.9±1.9	4.88±0.01	10.88±0.00	71±1	906±67
8	401.3±2.0	4.89±0.01	10.09±0.01	43±3	367±37
9	400.4±1.6	4.83±0.01	10.11±0.00	31±1	72±4

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