Development and validation of Dermal PBPK model towards Virtual Bioequivalence Assessment

Sebastian Polak

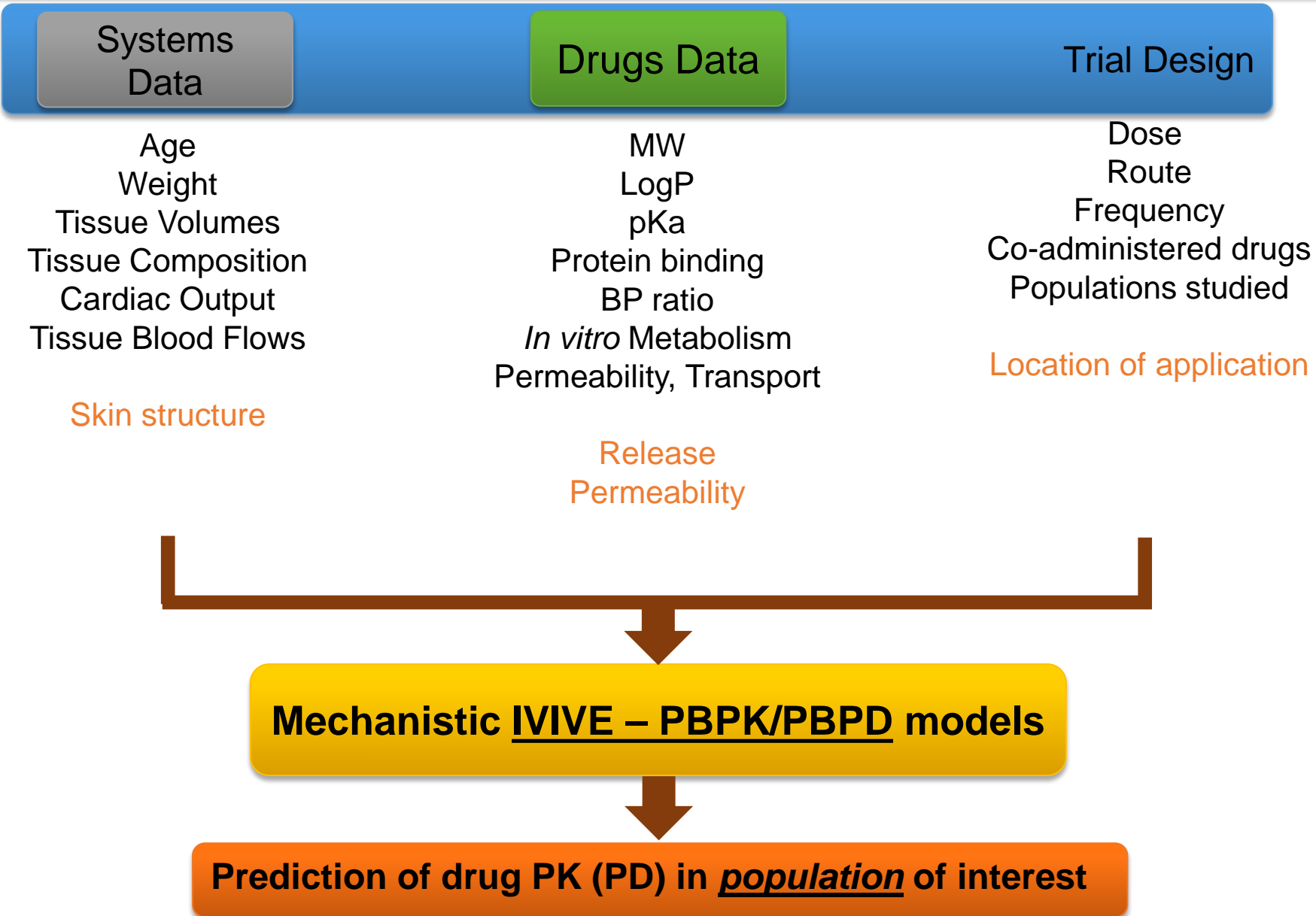**Senior Principal Scientist and Certara's Practice Lead for Cardiac Safety**
&
Associate Professor
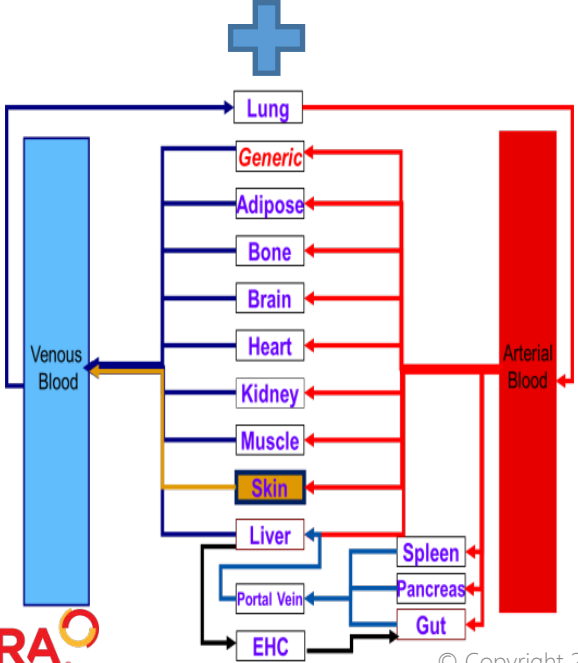**Jagiellonian University Medical College, Krakow, Poland**
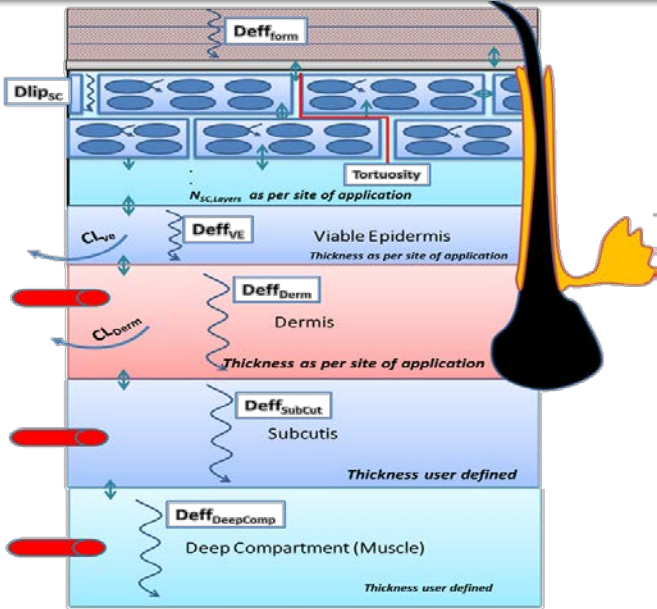
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- **BE challenges for complex and locally acting drug products**

  - costly and time consuming

  - challenging for the PD endpoints

- **New paradigm potentially useful**

  - include mechanistic in silico models

  - therefore allows for the virtual scenarios testing

  - bridging the clinical knowledge gap or reduce the clinical testing burden

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Advantage of mechanistic PBPK modelling

Systems Data	Drugs Data	Trial Design
Age	MW	Dose
Weight	LogP	Route
Tissue Volumes	pKa	Frequency
Tissue Composition	Protein binding	Co-administered drugs
Cardiac Output	BP ratio	Populations studied
Tissue Blood Flows	*In vitro* Metabolism	
	Permeability, Transport	
Skin structure		Location of application
	Release	
	Permeability	

Mechanistic <u>IVIVE – PBPK/PBPD</u> models

Prediction of drug PK (PD) in _population_ of interest
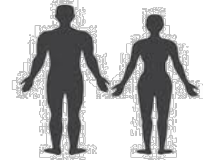
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We do have tools and methods

Paediatric Population
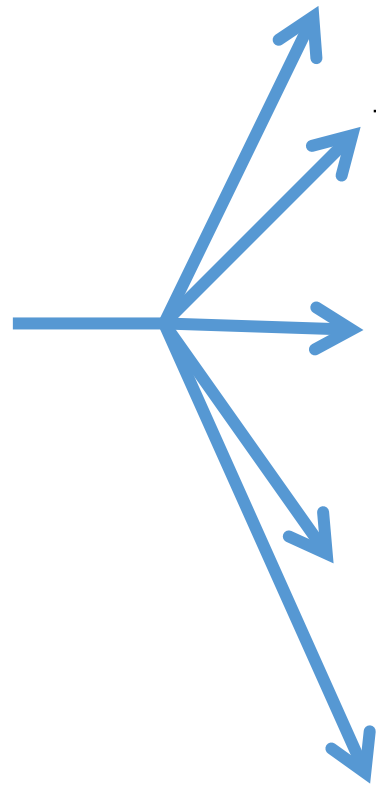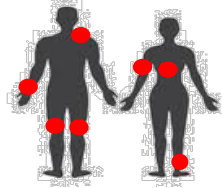
Healthy NEurCaucasian

Elderly Subjects

Ethnic Population

Diseased Population

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Inter- and intra-individual variability

Different locations

1. Forehead
2. Face (cheek)
3. Volar Forearm
4. Dorsal Forearm
5. Upper Arm
6. Lower Leg
7. Thigh
8. Back

- **Various structural elements**
  1. Skin surface
  2. Stratum corneum
  3. Viable epidermis
  4. Dermis
  5. Hair

- **Various parameters**
  1. Skin temperature
  2. Skin surface pH

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- Various structural elements

  1. Skin surface
  2. Stratum corneum
  3. Viable epidermis
  4. Dermis
  5. Hair

- Various parameters

  1. Number of layers
  2. Corneocyte pH
  3. Corneocyte size
  4. Fraction of p/w/l
  5. Tortuosity
  6. Lipids fluidity/th

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Formulations

DRUG/FORMULATION SPECIFIC PARAMETERS

- Partitioning

- Diffusion

- Binding

FORMULATION SPECIFIC PARAMETERS

- Formulation type (solution, emulsion, suspension, patch)…

- … and all necessary information to characterize them

- Evaporation

CHARACTERIZED BY THE IN VITRO DATA

- Supported with the QSAR/empirical models when necessary

- Allows accounting for the excipients

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Performance verification/validation

		1	2	3	4	5	6	7	8	9	10	11
	Compound											
Formulation type	solution		x		x	x				x	x	x
	emulsion					x		x (with particles)	x (paediatric)	x		
	paste										x	
	patch	x	x			x	x		x (adult)			x
Formulation reported	matrix patch	x				x	x				x	
	reservoir and other patches			x					x			
	gel				x	x				x		x
	cream		Not clear		x			x	x	x	x	
	ointment									x	x	
Place of application	forehead											
	inner forearm				x				x	x	x	
	outer forearm								x			
	upper arm	x					x		x			
	face				x			x		x	x	
	lower leg								x	x		
	upper leg						x		x		x	x
	back	x	x	x			x				x	x
Exposure data	plasma	x	x	x	x	x	x		x	x	x	x
	dermal flux and IVPT						x	x				x
	SC					x				x		
	subcutis					x						
	muscle					x					x	
	synovium fluid				x	x					x	
	synovium tissue					x					x	
	cerebrospinal fluid						x					
Chemical character	acid				x	x				x	x	
	ampholyte	x						x				
	base		x	x			x		x			x
	zwitterion											

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Conclusions

IVIVE in the Virtual Bioequivalence area

- USEFUL AND ALREADY AVAILABLE TOOL

- TRUST AND VALIDATION – absolutely necessary already reach and still growing

- POPULATION ANALYSIS – very important and already achievable

- PD ENDPOINTS – can be included to the validation and further analysis

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Thank you