Optimal design for TGF beta RI kinase inhibitor

Sophie Glatt, Kayode Ogungbenro and Iva Gueorguieva

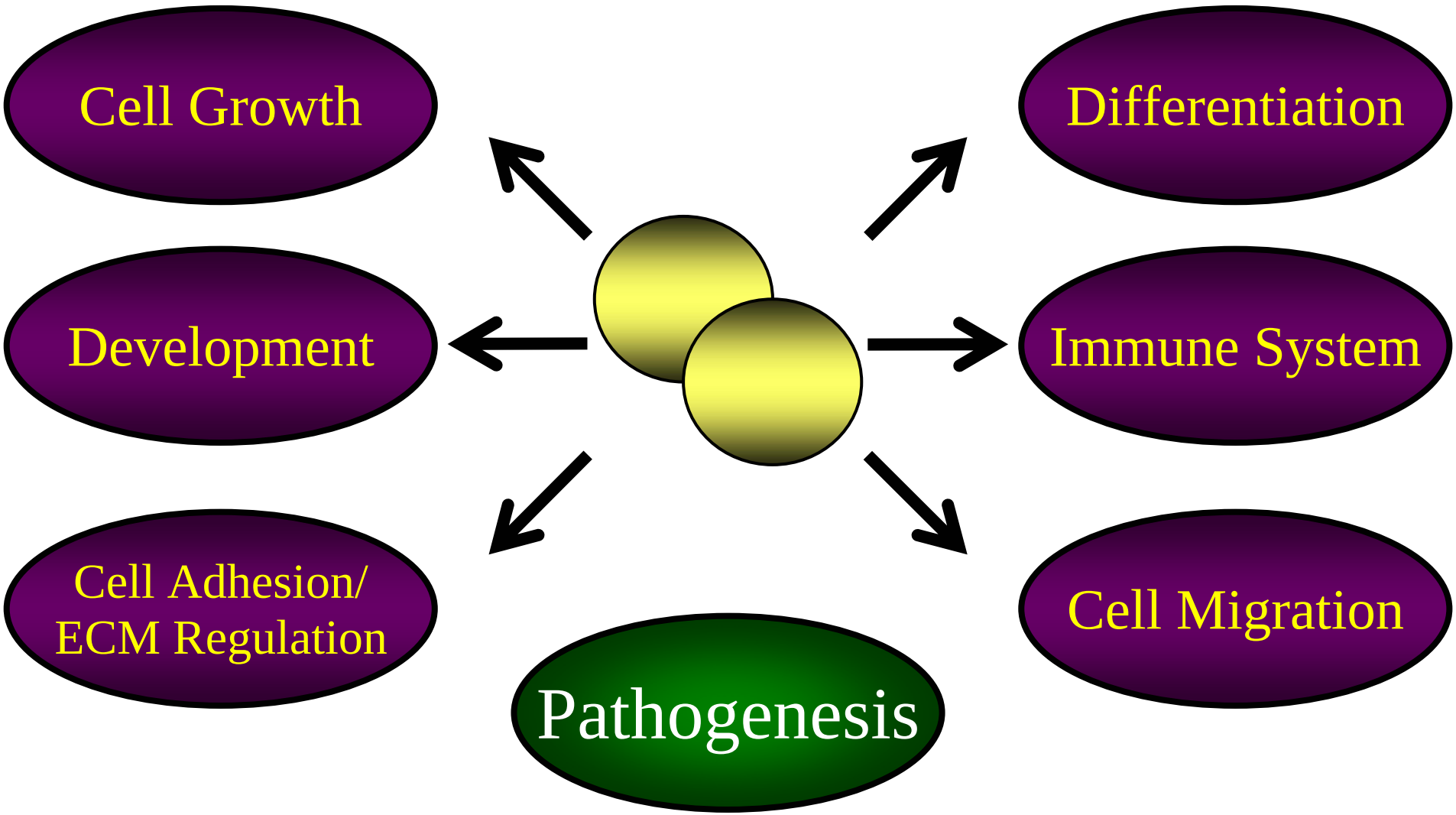
MANCHESTER 1824

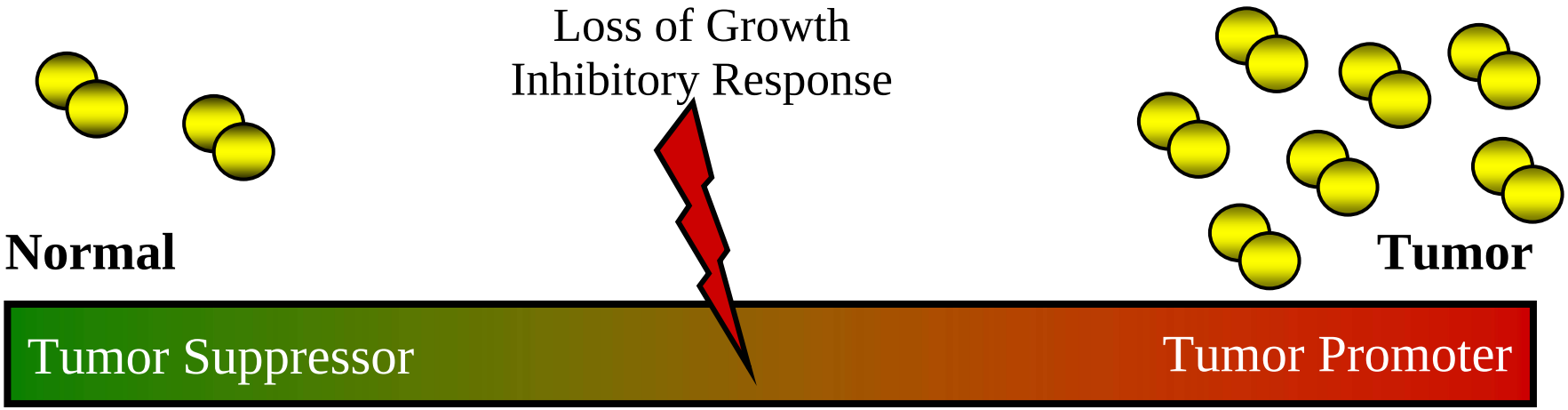
Lilly

Answers That Matter.

Outline

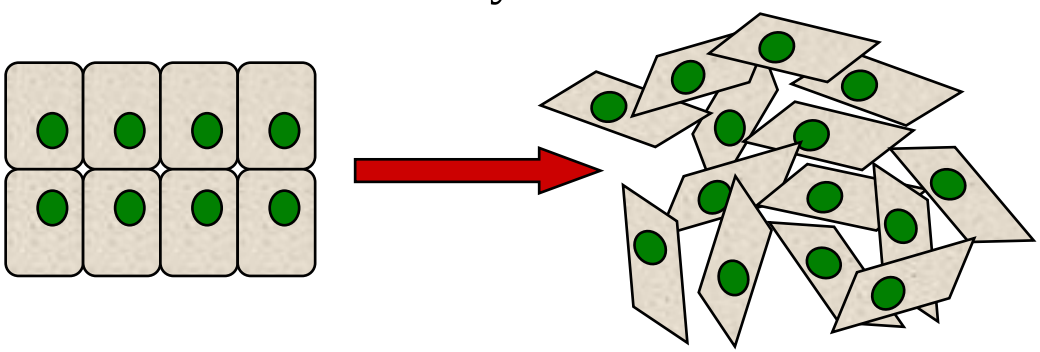
- Background
- Strategy
- TGFb PK/PD model in rats
- Multivariate optimal design
- TGFb PK/PD model & design in human
- Challenges in optimal design from practical point of view


Cell Growth
Differentiation
Development
Immune System
Cell Adhesion/
ECM Regulation
Cell Migration
Pathogenesis



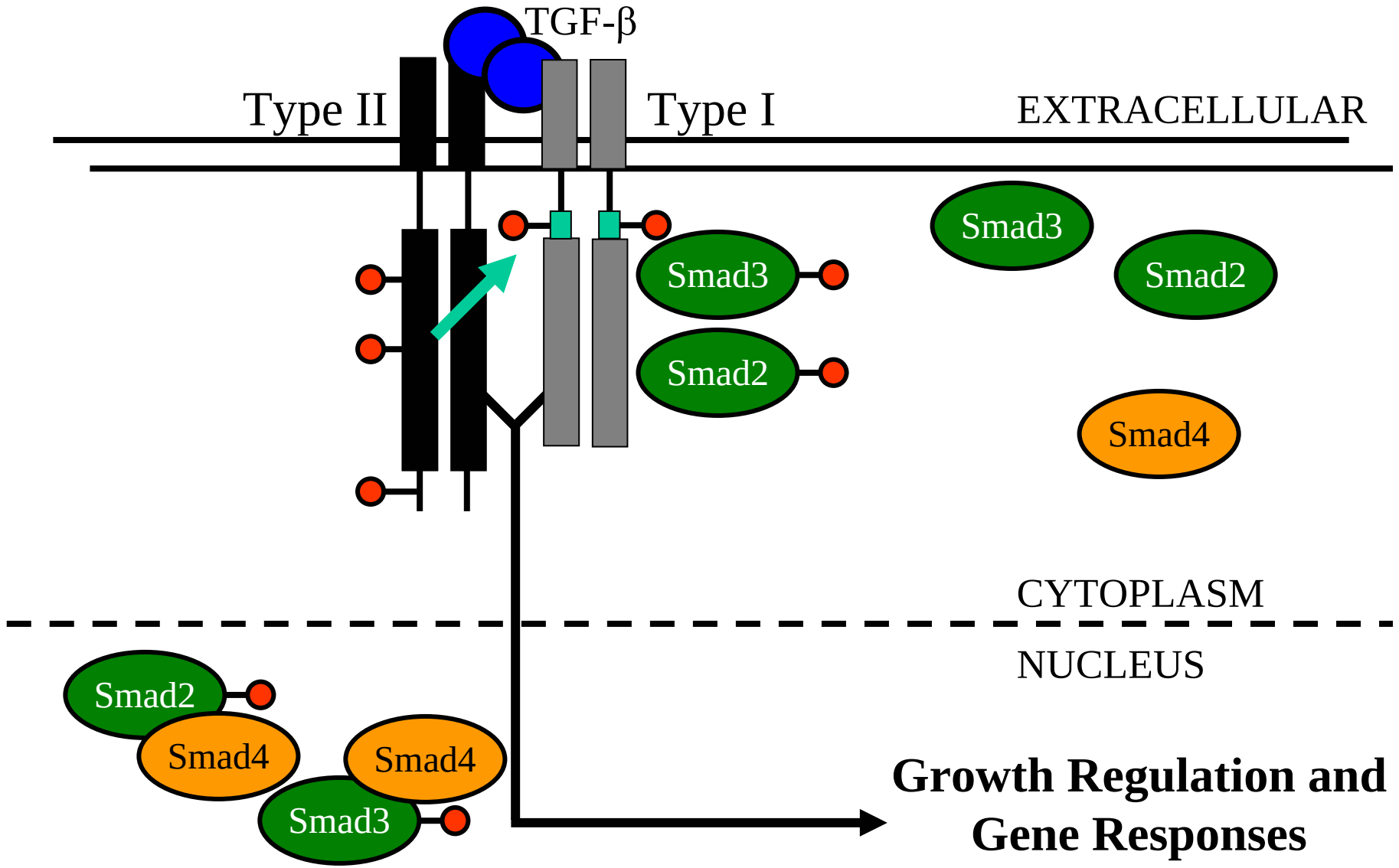
Tumor Cell

- Epithelial-to-mesenchymal transition
- Increased cell motility and invasiveness



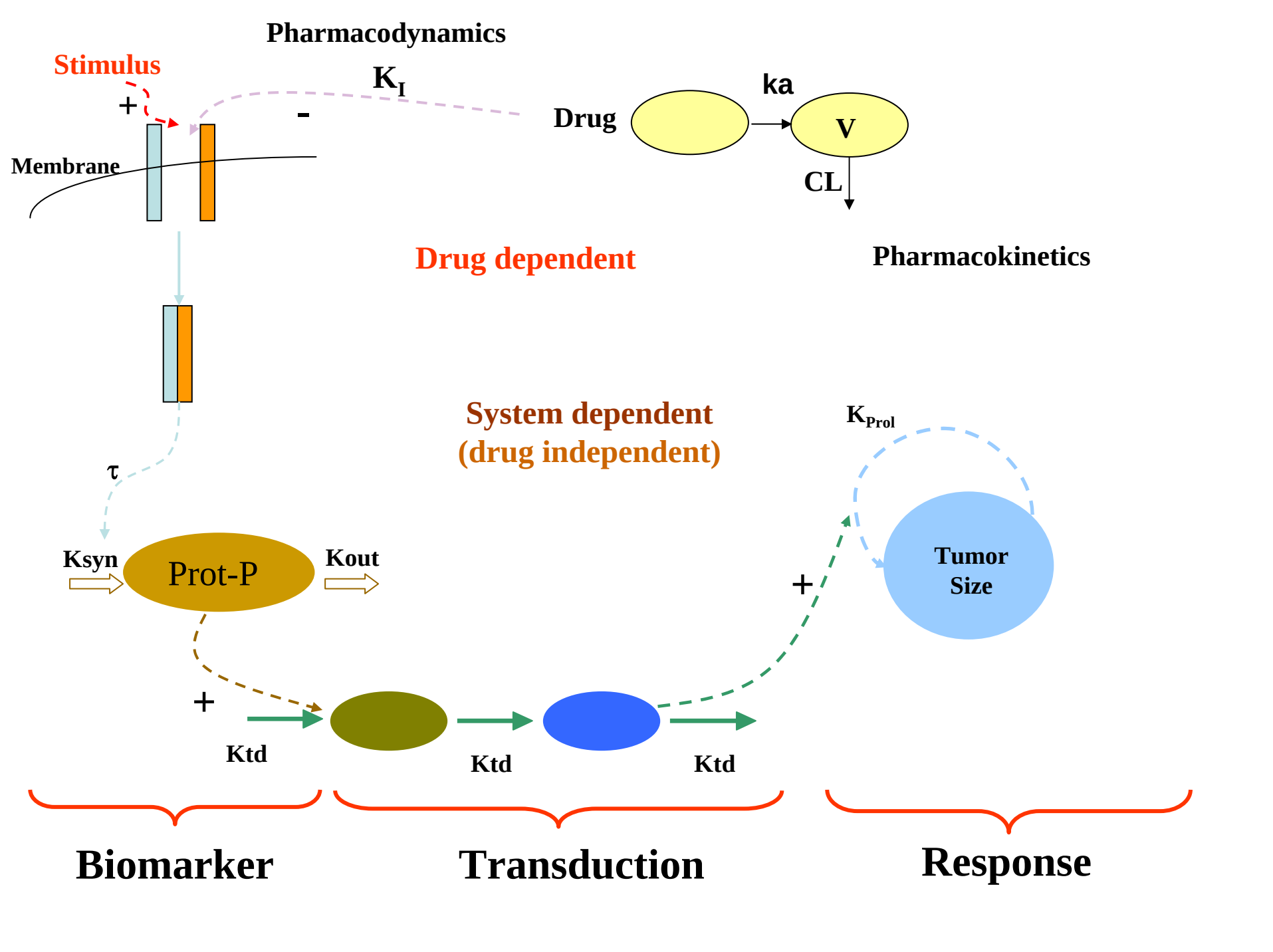
Tumor Microenvironment

- Extracellular matrix remodeling
- Activated stromal cells
- Protease activation
- Angiogenesis
- Immunosuppression

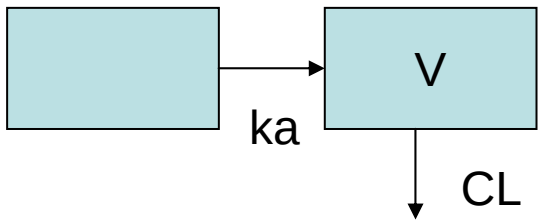

TGF-β
Type II
Type I
EXTRACELLULAR
Smad3
Smad2
Smad3
Smad2
Smad4
CYTOPLASM
NUCLEUS
Smad2
Smad4
Smad4
Smad3
Growth Regulation and
Gene Responses

Understand PK and determine PKPD relationship in animals:
Assist appropriate dose range selection

- Develop PK/PD model in animals using Smad phosphorylation (biomarker)
    - In rats, mouse
- Perform allometric scaling to predict human PK
- Variability of biomarker has been incorporated to assess response variability


Pharmacodynamics
Stimulus
+
K_I
-
Membrane
Drug
ka
V
CL
Drug dependent
Pharmacokinetics
System dependent
(drug independent)
K_{Prol}
τ
Ksyn
Prot-P
Kout
+
Tumor
Size
+
Ktd
Ktd
Ktd
Biomarker
Transduction
Response

Rat Pharmacokinetics



$$y_{ij} = f(\theta_i, t_{ij}) + \varepsilon_{ij}$$

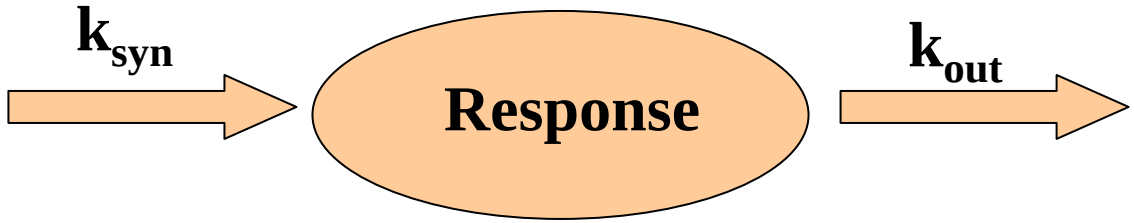
$$\theta_i = \theta + b_i \qquad \theta_i = \theta exp(b_i) \qquad b_i \sim N(0, \Omega)$$

$$\xi_i = [t_{i1}, ..., t_{in}]$$

	Parameters	Estimates	95% CI
Disposition			
	V (L)	1.09	[0.76 ; 1.42]
	CL (L/h)	0.339	[0.23 ; 0.45]
Absorption	KA (h^{-1}) fixed	8.00	
	F (%)	0.65	[0.49 ; 0.81]
Interanimal variability	ω^2_{CL}	0.48 (CV=69.6%)	[0.245 ; 0.723]
	ω^2_{V}	0.64 (CV=80.1%)	[0.335 ; 0.947]
residual error: additive part	µmol/L	64.20	[0.33 ; 0.95]

Indirect Response Models

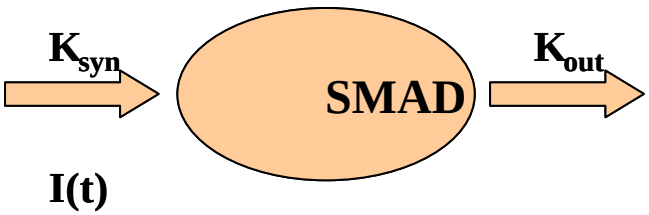
- Baseline response is maintained by factors controlling response synthesis and degradation



k_{syn} is a 0 order rate constant
k_{out} is a 1st order rate constant

$$\frac{dR}{dt} = k_{syn} - k_{out} * R$$

Summary of PD parameters corresponding to biomarker model (mice)



$$I(t) = 1 - \frac{I_{\max} \times C^{\gamma}}{C^{\gamma} + IC_{50}{}^{\gamma}}$$

$$k_{syn} = k_{out} \times pSMAD(\%)$$

$$pSMAD = 100(fixed)$$

Parameter	Population mean Estimate (%SEE) MX1	Population mean Estimate (%SEE) Calu6
K_{out} (h^{-1})	1.3 (15.8)	2.2 (6.9)
I_{MAX}	1*	1*
IC_{50} (μM)	0.7 (11.2)	0.8 (7.6)
n	2.5 (17.4)	1*
Additive Residual error (SEE %)	10.6% (28.6)	18.4% (11.9)

SEE Standard error of the estimate
* Fixed

Calu6: Lung cancer cell line;
MXI: Brest cancer cell line.

t1/2_kout(MX1)=32 min

t1/2_kout(Calu6)=18.6 min

Summary of PD parameters corresponding to biomarker model (rats)

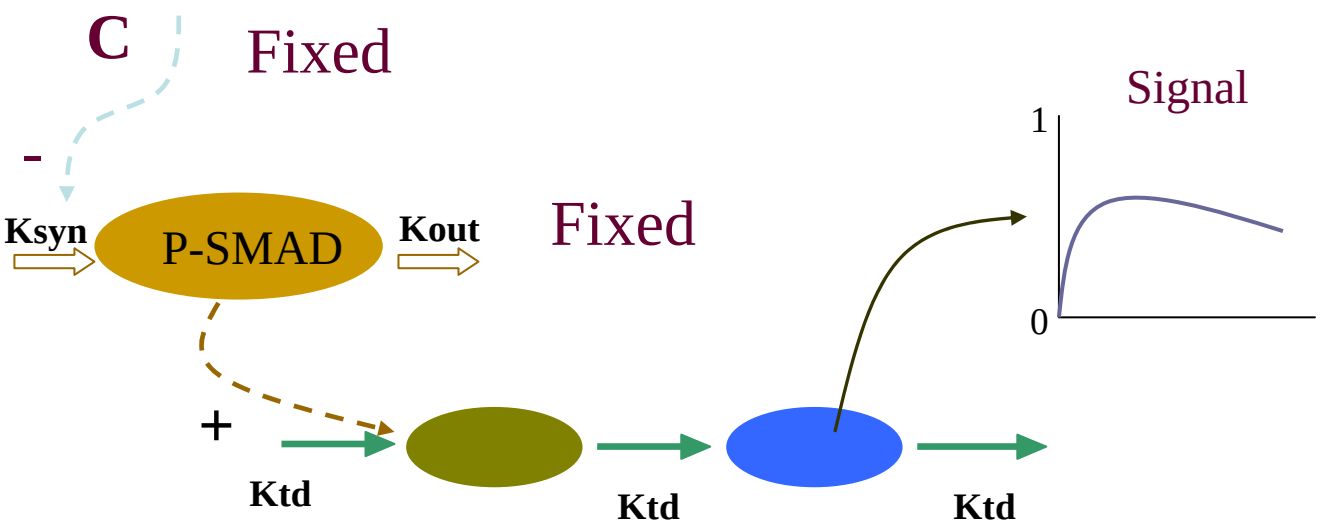
Parameter	Population mean Estimate (%SEE) Tumor	Population mean Estimate (%SEE) PBMC
K_{out} (h^{-1})	36.7 (7.3)	47.4 (1.8)
I_{MAX}	0.86 (3.4)	0.95 (1.1)
IC_{50} (μM)	0.72 (25.7)	1.96 (13.1)
Proportional Residual error (SEE %)	62.1% (19.9)	70.2% (25.2)

SEE Standard error on the estimate

PBMC: peripheral blood mononuclear cell

Semi-mechanistic model for tumor growth delay

$$\frac{dTS}{dt} = \frac{K_{grw1} \times TS}{\left[1 + \left(\frac{K_{grw1}}{K_{grw0}} \times TS\right)^{\gamma}\right]^{1/\gamma}} \times (1 - I(t))$$

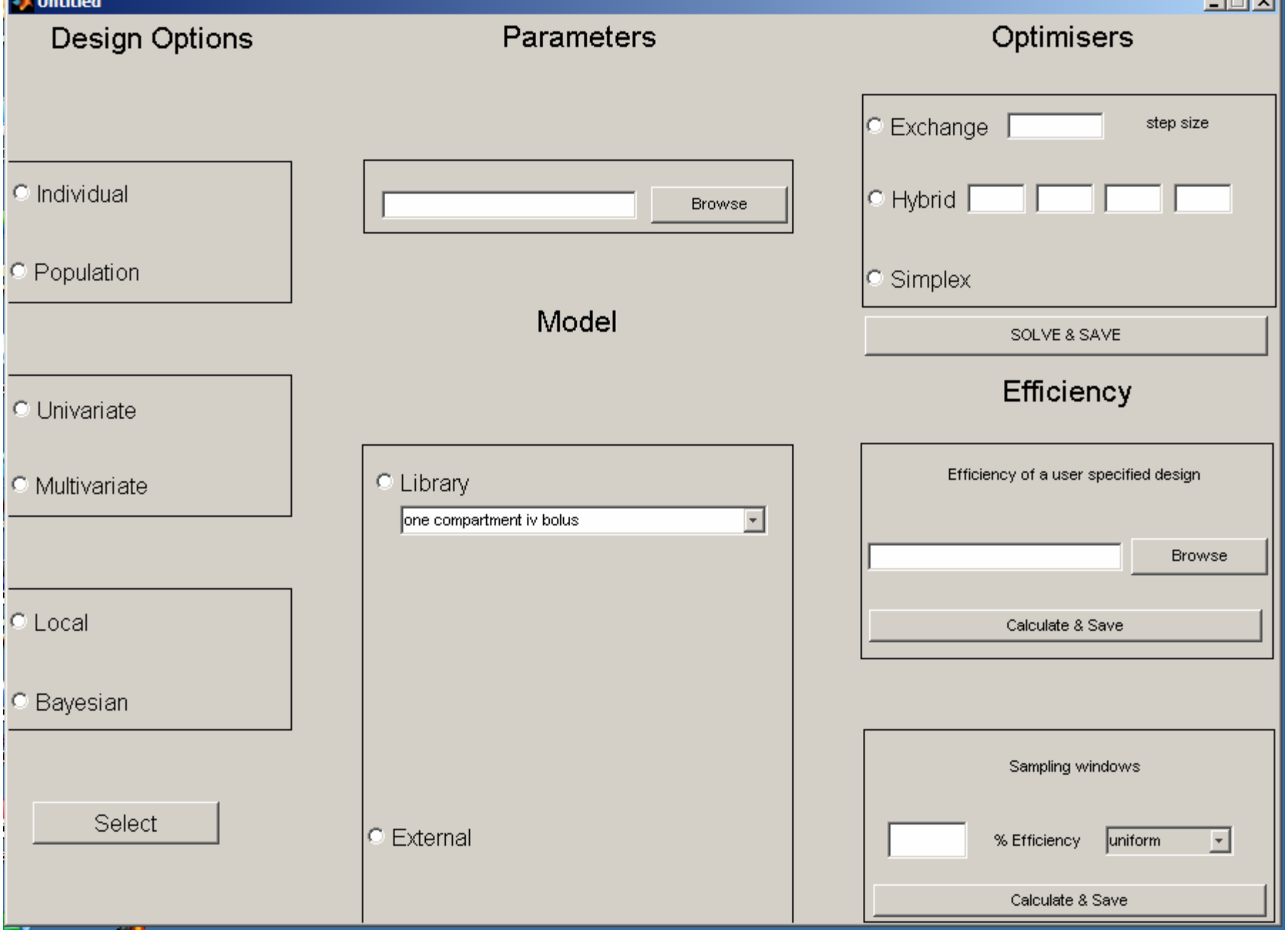


Simeoni, Cancer Res., 2006

Retrospective optimal design in rats

TGF-beta inhibitor pharmacokinetic/pharmacodynamic parameters in rats

	Parameter name	Individual RAT	Population RAT mean [%SEE]
Pharmacokinetic	ka [h^{-1}]	10	8
	V [L]	0.85	0.9 [15.5]
	CL [L/h]	0.29	0.34 [16.6]
	F [%]	65.3	65 [0.1]
	ω^2_{CL}	----	0.48 [2.5]
	ω^2_{V}	----	0.64 [24.3]
	Additive residual error $\sigma_{PK\_ADD}{}^2$	64.2	64 [32.9]
Pharmacodynamic	k_{out}	36.7	36.7 [7.3]
	I_{max}	0.86	0.86 [3.4]
	IC50	0.72	0.72 [25.7]
	Proportional residual error $\sigma_{PD\_PROP}{}^2$ [%]	62	62[19.9]



Popdes software: Gueorguieva, et al., Computer Method Prog Biomed, 2006 (in preparation)

Rat design constraints

- Individual rat
  - PK model $y_j = f(\theta, t_j) + \varepsilon_j$
    - Three sampling times (j=3)
    - Time bounds (0-24h)
  - PK/PD model $y_{mj} = f_m(\theta, t_j) + \varepsilon_{mj}$
    - Six sampling times chosen
    - Number of responses (M=2)
    - Response covariance matrix $\Sigma = \begin{pmatrix} 1 & 0.15 \\ 0.15 & 1 \end{pmatrix}$
    - Time bounds (0-24h)

Rat design constraints

- Population rat
  - PK model $y_{ij} = f(\theta_i, t_{ij}) + \varepsilon_{ij}$
    - Three sampling times (j=3)
    - Time bounds (0-24h)
  - PK/PD model $y_{imj} = f_m(\theta_i, t_{ij}) + \varepsilon_{imj}$
    - Six sampling times chosen
    - Number of responses (M=2)
    - Response covariance matrix $\Sigma = \begin{pmatrix} 1 & 0.15 \\ 0.15 & 1 \end{pmatrix}$
    - Time bounds (0-24h)

Optimal design for rat individual and rat population TGFb model

Optimiser	Optimal sampling times (h)									
Individual PK	0.1	0.5	3.46							
Individual PK/PD	0.0	0.0	0.5	0.5	3.5	24.0				
Population PK	0.1	1.0	7.1							
Population PK/PD	0.0	0.5	1.75	7.5	18.75	24				
	CVSE[a] [%]									
	ka	**CL**	**V**	ω^2_{CL}	ω^2_{V}	$\sigma_{PK\_2\_ADD}$	Imax	IC50	kout	$\sigma_{PD\_2\_PROP}$
Individual PK	0.43	0.32	0.16	--	--	40.83				
Individual PK/PD	0.30	0.31	0.12	--	--	28.9	20.6	244.6	35.7	126.9
Population PK	0.12	13.5	13.5	45.4	45.4	18.3				
Population PK/PD	0.10	12.4	12.4	33.2	36.0	9.13	1.66	18.8	4.24	11.75

* In all cases Exchange algorithm (Ogungbenro, 2006, Computer Method Prog Biomed) with 0.01 step size was used

Optimal design for individual and population TGFb model

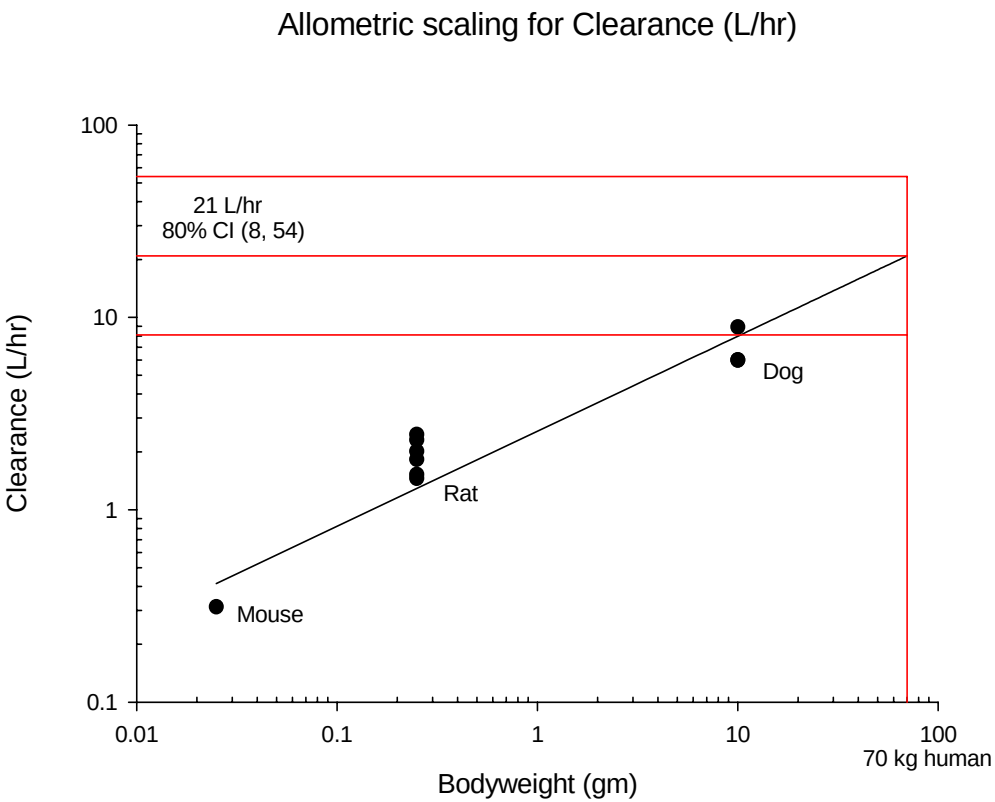
- Individual rat
  - PK
    - Early sampling with last time at 3.5h (due to additive model)
    - small CVSE on structural parameters; larger on additive error (40%);
  - PK/PD:
    - Last sampling at the upper bound (p-SMAD proportional error) and repeating the two early times;
    - Parameter CVSEs <40 with exception of IC50;
- Population rat
  - PK
    - Later last time point (7h)
    - CVSEs < or around 40%
  - PK/PD
    - No repeating time points with more even distribution in time (i.e. requiring samples before and after 12h);
    - Lower CVSEs (compared with individual PK/PD) < or around 30%.

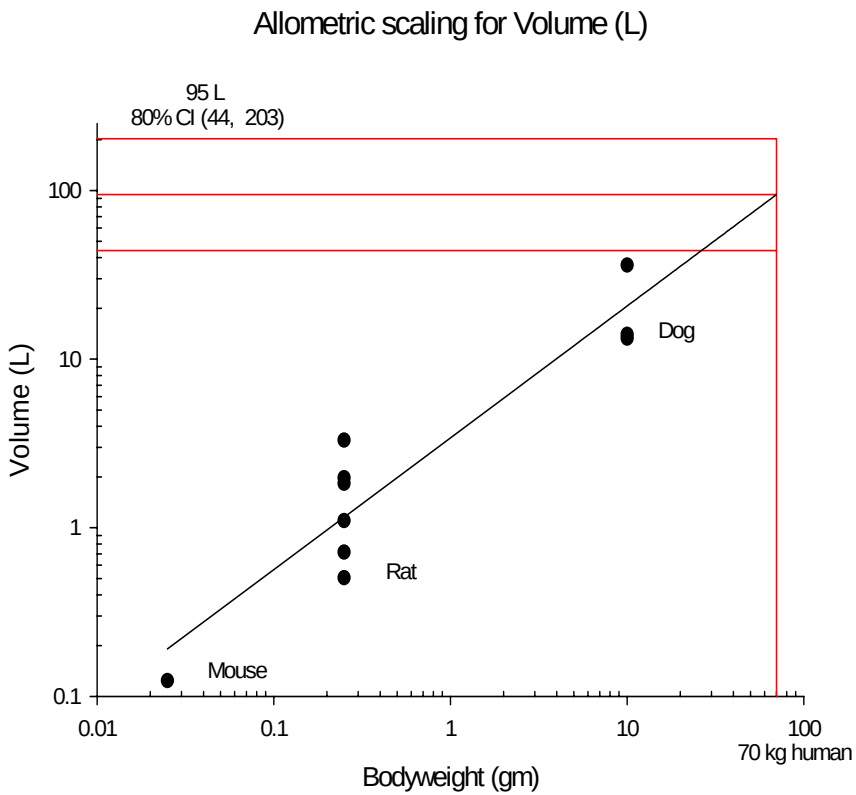
Interspecies allometry

- Using IV PK parameters in rat, mouse and dogs
- Included in the model was an allowance for estimating correlation between animals within a species
- Human clearance predicted to be 20.9 L/h (8.11-53.76).
- Volume of distribution predicted to be 94.57L (44.13-202.69).

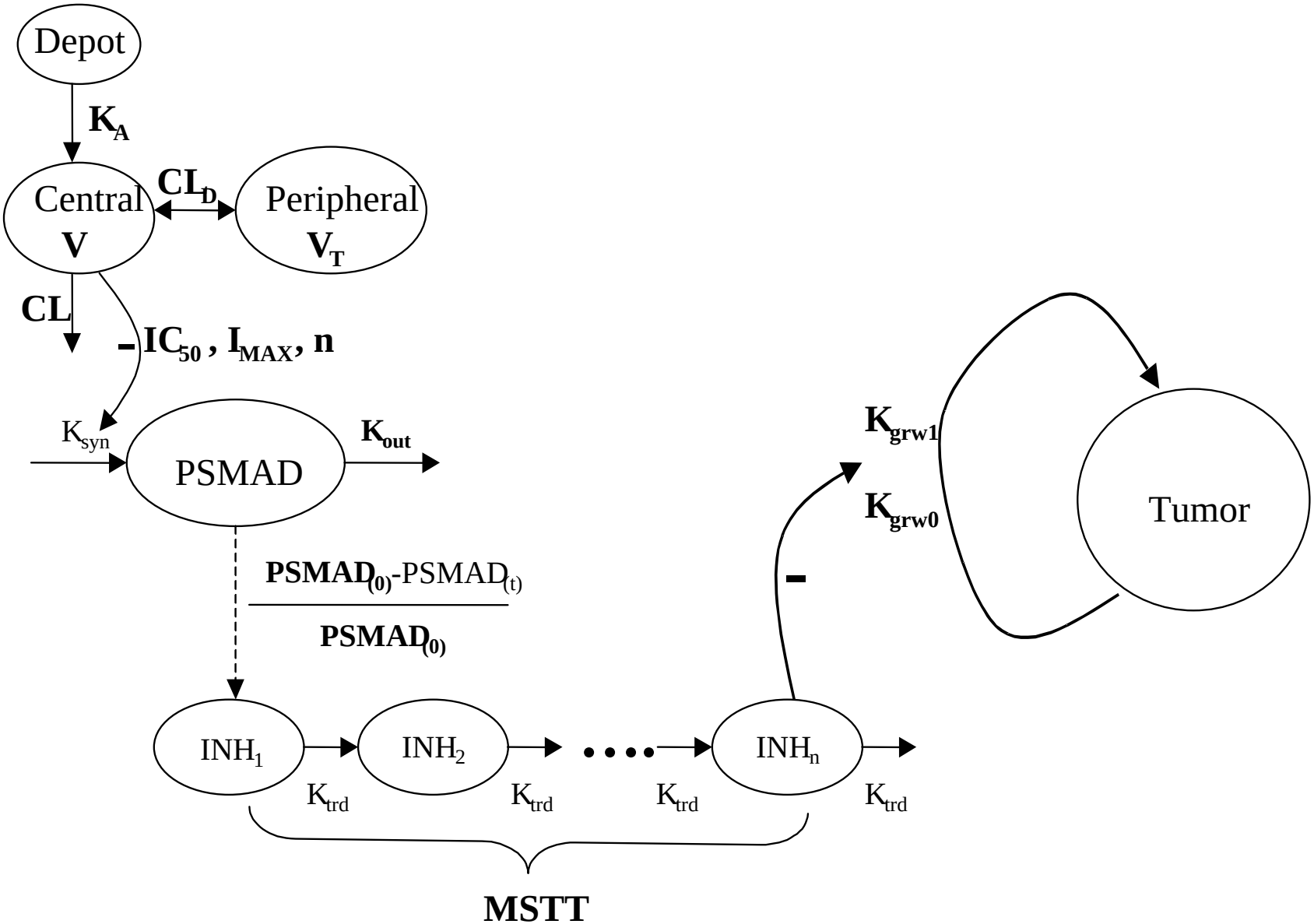
- Assumed bioavailability 50% (biopharmaceutics)

Allometric scaling





PK/PD model


Depot
K_A
Central
V
CL_D
Peripheral
V_T
CL
- IC_{50} , I_{MAX}, n
K_{syn}
PSMAD
K_{out}
$\frac{PSMAD_{(0)}-PSMAD_{(t)}}{PSMAD_{(0)}}$
-
K_{grw1}
K_{grw0}
Tumor
INH_1
INH_2
INH_n
K_{trd}
K_{trd}
K_{trd}
K_{trd}
MSTT

Design first in human studies

- Based on simulations

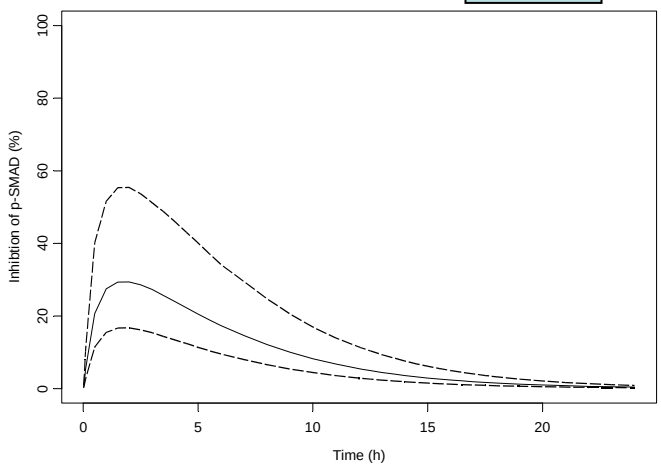
- Based on D-optimal design

Simulations in humans

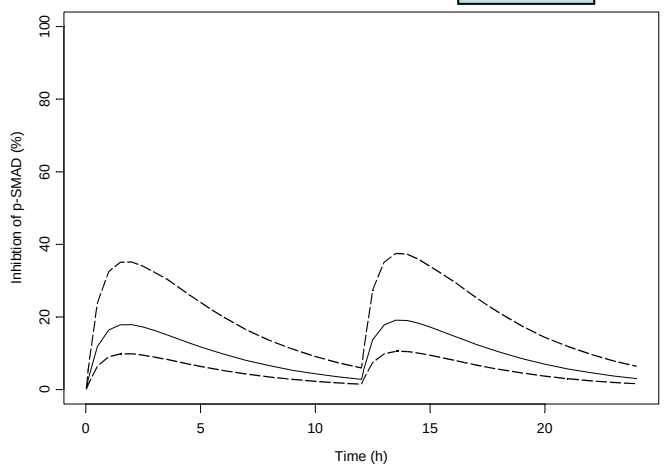
- Preclinical data suggest that
  - 30% inhibition of pSMAD over 24 hours and at least 50% inhibition at tmax (time at maximum inhibition) is required for tumor growth delay
- Simulation in humans were performed in order to achieve this level of inhibition
- Simulation used both cell lines, used allometric scaling for PK using mouse, rat and dog.
- Variability of the biomarker was incorporated in the simulations

From rat model : Simulated human PD and 90%CI profiles after QD and BID administrations

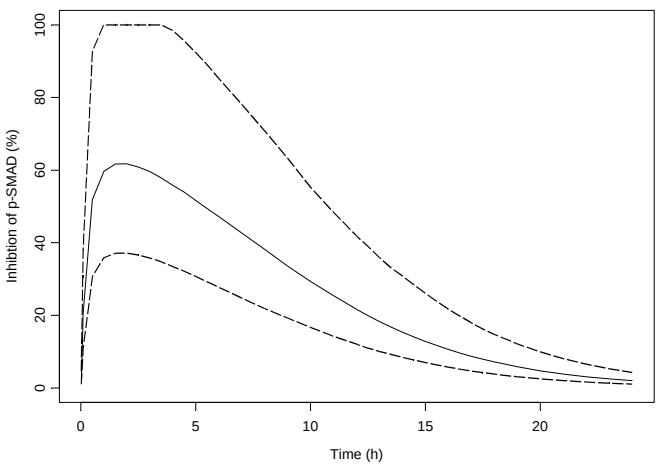
QD Amg



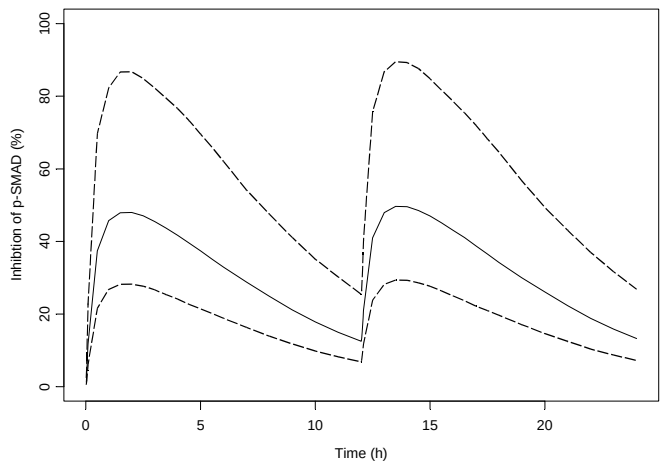
BID Amg



QD Bmg



BID Bmg



D-optimal design in human

Design	Optimal sampling times (h)							
Individual PK	0.0	0.75	24.0					
Individual PK/PD	0.0	0.0	0.8	0.8	24	24		
	CVSE[a] [%]							
	ka	CL	V	Imax	IC50	kout	$\sigma^2_{PK\_PROP}$	$\sigma^2_{PD\_PROP}$
Individual PK	43.2	24.5	30.4				44.8	
Individual PK/PD	48.7	17.4	21.0	7.2	96.9	12.3	31.7	42.6

* In all cases Exchange algorithm (Ogungbenro, 2006, Computer Method Prog Biomed) with 0.01 step size was used

Optimal design for individual human TGFb inhibitor model

- PK
  - Two early samples with last time at upper bound 24h (due to proportional error model)
  - reasonable CVSE on structural parameters (ka 43%); slightly larger on proportional error (45%);

- PK/PD:
  - Repetition of all three sampling times;
  - Parameter CVSEs close to or <40 with exception of IC50 (97%)

Assessing clinically relevant designs

A number of different designs were considered

Practical designs	Efficiency [%]
[0 1 3 6 8 16 24]	90.5
[0 2 6 8 16 24]	79.9
[0 1 3 6 12 24]	80.9

	CVSE [%]						
Ka	**CL**	**V**	**Imax**	**IC50**	**kout**	**$\sigma^2_{PK\_PROP}$**	**$\sigma^2_{PD\_PROP}$**
56.8	14.2	18.4	5.6	118.7	16.0	29.3	39.4
60.5	16.9	22.2	6.30	121.6	16.22	31.65	42.57
57.5	15.11	19.28	5.98	127.6	16.22	31.65	42.58

A variant of the first design is currently being implemented in the clinic

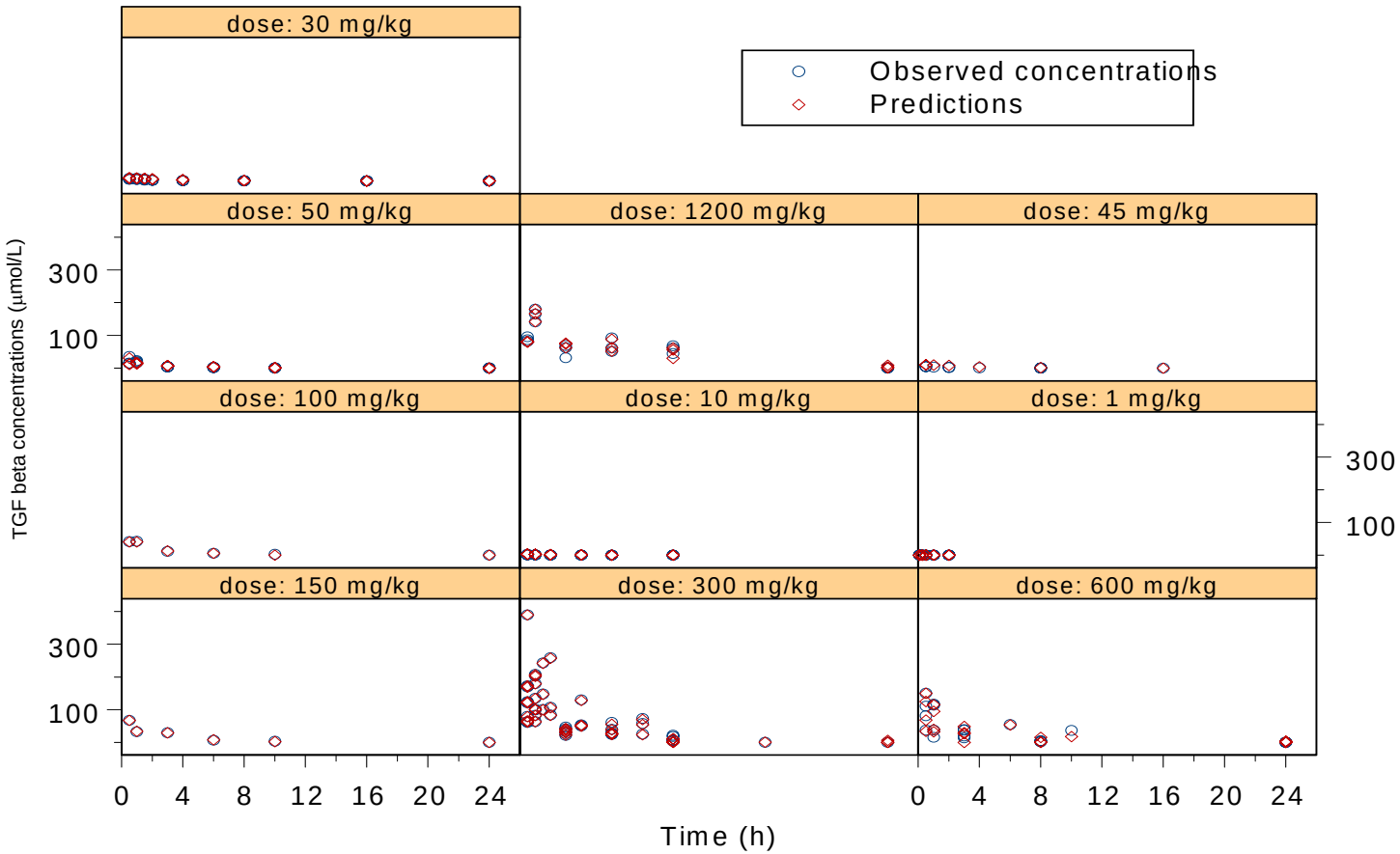
Challenges in optimal design

- Methodology
  - Responses measured on very different time scales (clinical outcome scales in Alzheimer's disease)
    - TGFb study designed as if PK and p-SMAD inhibition measured on the same time scale (0-24h); more realistic different time frames
  - sequential vs simultaneous design
  - Theorethical proof/disproof of Equivalence theorem in multirespose models

- ***Prospective*** rather than retrospective applications!

Back up slides

RAT observed versus individual predicted concentrations



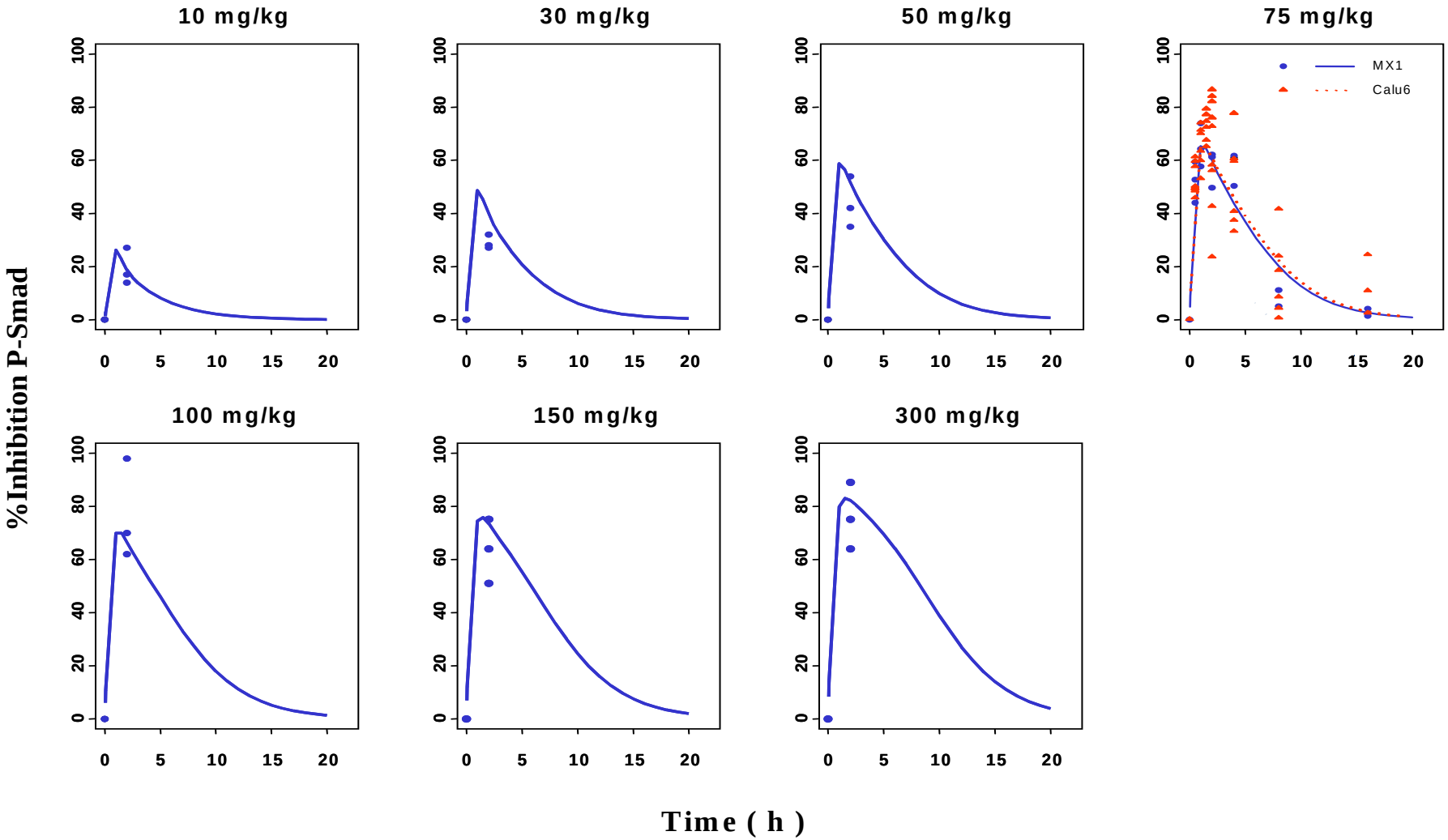
$$\frac{dA_1}{dt} = -kaA_1$$

$$\frac{dA_2}{dt} = kaA_1 - \frac{CL}{V_2}A_2$$

$$\frac{dA_3}{dt} = k_{syn}\left(1 - I_{\max}\frac{A_2/V_2}{A_2/V_2 + IC_{50}}\right) - A_3 k_{out}$$

$$\frac{\mathrm{dTS}}{\mathrm{dt}} = \frac{\mathrm{K_{grw1}} \times \mathrm{TS}}{\left[1 + \left(\frac{\mathrm{K_{grw1}}}{\mathrm{K_{grw0}}} \times TS\right)^{\gamma}\right]^{1/\gamma}} \times (1 - \mathrm{A_3})$$

Mouse PD profiles



Multivariate response design for an individual

$$y_{mj} = f_m(\theta, t_j) + \varepsilon_{mj}$$

$$\Sigma = \begin{pmatrix} \tau_{11} & \tau_{12} & \cdots & \tau_{1M} \\ \tau_{21} & \tau_{22} & \cdots & \tau_{2M} \\ \cdots & \cdots & \cdots & \cdots \\ \tau_{M1} & \tau_{M2} & \cdots & \tau_{MM} \end{pmatrix} = \left\{ \tau_{qm} \right\}_{1 \le q,m \le M}$$

$$F(\theta, \xi) = \sum_{q=1}^{M} \sum_{m=1}^{M} \left[\frac{\partial f_q(\theta, \xi)}{\partial \theta} \right] \tau^{qm} \left[\frac{\partial f_m(\theta, \xi)}{\partial \theta} \right]^T$$

$$\frac{\partial f_m(\theta, \xi)}{\partial \theta} = J_m(\theta, \xi) = \begin{bmatrix} \left[\frac{\partial f_m(\theta, t_1)}{\partial \theta_1} \cdot \frac{1}{\sqrt{(\sigma_{m1}^2 + \sigma_{m2}^2 f_m(\theta, t_1)^2)}} \right] & \cdots & \left[\frac{\partial f_m(\theta, t_n)}{\partial \theta_1} \cdot \frac{1}{\sqrt{(\sigma_{m1}^2 + \sigma_{m2}^2 f_m(\theta, t_n)^2)}} \right] \\ \vdots & \cdots & \vdots \\ \left[\frac{\partial f_m(\theta, t_1)}{\partial \theta_p} \cdot \frac{1}{\sqrt{(\sigma_{m1}^2 + \sigma_{m2}^2 f_m(\theta, t_1)^2)}} \right] & \cdots & \left[\frac{\partial f_m(\theta, t_n)}{\partial \theta_p} \cdot \frac{1}{\sqrt{(\sigma_{m1}^2 + \sigma_{m2}^2 f_m(\theta, t_n)^2)}} \right] \end{bmatrix}$$

$$\frac{\partial f_m(\theta, \xi)}{\partial \theta} = J_m(\theta, \xi) = \left\{ \frac{\partial f_m(\theta, t_j)}{\partial \theta_k} \cdot \frac{1}{\sqrt{(\sigma_{m1}^2 + \sigma_{m2}^2 f(\theta, t_j)^2)}} \right\}_{\substack{1 \le j \le n \\ 1 \le k \le p \\ 1 \le m \le M}}$$

Population multivariate response design

$$y_{imj} = f_m(\theta_i, t_{ij}) + \varepsilon_{imj}$$

$$Y_i = \begin{bmatrix} y_{11} & y_{12} & . & . & . & y_{1M} \\ y_{21} & y_{22} & . & . & . & y_{2M} \\ . & . & . & & & . \\ . & . & & . & & . \\ . & . & & & . & . \\ y_{n1} & y_{n1} & . & . & . & y_{nM} \end{bmatrix}$$

$$y_i = \mathrm{vec}(Y_i) = [y_{i1}^{'}, y_{i2}^{'}, ..., y_{iM}^{'}]^{'}$$

$$\varepsilon_i = \mathrm{vec}(\Gamma_i) = [\eta_{i1}^{'}, \varepsilon_{i2}^{'}, ..., \varepsilon_{iM}^{'}]^{'}$$

$$\varepsilon_i \sim MVN(0, R)$$

$$R = \begin{bmatrix} R_{11} & R_{12} & . & . & . & R_{1M} \\ R_{21} & R_{22} & . & . & . & R_{2M} \\ . & . & . & & & . \\ . & . & & . & & . \\ . & . & & & . & . \\ R_{M1} & R_{M2} & . & . & . & R_{MM} \end{bmatrix}$$

$$R_{qm}(j,l)\Big|_{j=l} = \left\{ \tau_{qm*} \sqrt{\left(\sigma_{q1}^2 + (\sigma_{q2}^2 * f_q(\theta, t_j)^2)\right) * \left(\sigma_{m1}^2 + (\sigma_{m2}^2 * f_m(\theta, t_j)^2)\right)} \right\}_{\substack{1 \le q,m \le M \\ 1 \le j,l \le n}}$$

$$R_{qm}(j,l)\Big|_{j \neq l} = \{0\}_{\substack{1 \le q,m \le M \\ 1 \le j,l \le n}}$$

$$\lambda = [\omega_1^2, ...\omega_p^2, \sigma_{11}^2, ..., \sigma_{1M}^2, \sigma_{21}^2, ..., \sigma_{2M}^2]$$

$$F(\Psi, \xi_i) = \left[-\frac{\partial^2 l(\Psi, y_i)}{\partial \Psi^T \partial \Psi} \right]$$

$$y_{im} = f_m(\theta, b_i, \xi_i) + \varepsilon_{im} \cong f_m(\theta, 0, \xi_i) + \left. \frac{\partial f_m^T(\theta, b_i, \xi_i)}{\partial b_i} \right|_{b_i = 0} b_i + \varepsilon_{im}$$

$$F(\Psi, \xi_i)_{ab} = \left\{ J_a^{\ T} V^{-1} J_b + \frac{1}{2} tr\left(\frac{\partial V}{\partial \Psi_a} V^{-1} \frac{\partial V}{\partial \Psi_b} V^{-1} \right) \right\}_{1 \le a,b \le (p*2+2*M)}$$

Predicted and observed tumor growth delay