



ADAPTIVE DESIGNS WORKSHOP: OPPORTUNITIES, CHALLENGES and SCOPE IN DRUG DEVELOPMENT

PHARMACOKINETIC AND PHARMACODYNAMIC MODELING TO CHOOSE THE DOSE FOR PHASE III

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TOPICS TO BE COVERED TODAY:



- **WHY IS DOSE vs RESPONSE RELEVANT TO ADAPTIVE CLINICAL TRIAL DESIGNS? (two simulation examples)**
- **DOSE vs RESPONSE THAT IS EASY (real example)**
- **DOSE vs RESPONSE THAT IS HARD!! (real example)**
- **SUMMARY**

USING DOSE-RESPONSE AS PRIOR KNOWLEDGE CAN CREATE MORE EFFICIENT ADAPTIVE DESIGNS BY:



Reducing the variance of estimated model parameters can reduce the sample sizes needed in an adaptive clinical trial

- **DEMONSTRATION EXAMPLE:**

- **A dose vs response relationship that has**
 - **Five progressively increasing doses**
 - **Group sizes of 100 subjects per dose**
 - **Response normally distributed with underlying standard error set to 10 units**
- **Calculation details: For each assumed shape of the Dose-Response, variances of mean response are derived explicitly based on the design matrices.**
- **Thanks to Amy Racine at Novartis for this example**

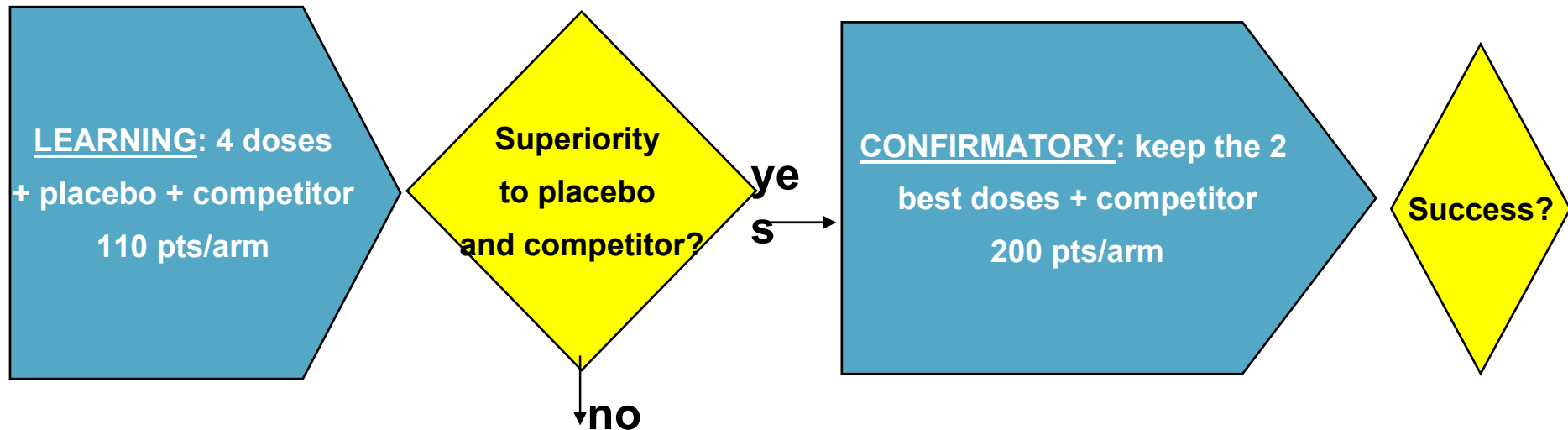
DOSE-RESPONSE KNOWLEDGE REDUCES THE VARIANCE WHICH REDUCES SAMPLE SIZE

DOSE vs RESPONSE MODEL	VARIANCE ESTIMATES				
	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5
No Dose* Response	1	1	1	1	1
Linear	0.60	0.30	0.20	0.30	0.60
Quadratic	0.89	0.37	0.49	0.37	0.89
Cubic	0.99	0.77	0.49	0.77	0.99

* = using ANOVA

LEARNING FROM THE DOSE-RESPONSE MODEL IN AN ADAPTIVE SEAMLESS CLINICAL TRIAL DESIGN:

- A simulation example:



- STO**
- One can compare Bayesian Model averaging (learning on the dose-response) to
 - No learning on the dose-response using only an adaptive, seamless clinical trial design where the focus is only on the response

DECISION RULES (YELLOW BOXES)



- **Continue trial at the interim:**
 - **For Adaptive Seamless Design**
 - **Dunnett's test for superiority to placebo + observed means superior to competitor**
 - **For Bayesian Model Averaging**
 - **Dunnett's test for superiority to placebo + Probability that the effect is different to Competitor at a dose $x > 0$ | interim data) ≥ 0.5**
- **Successful trial**
 - **when P (effect different to competitor at dose $x > 0$ | all data) ≥ 0.975**

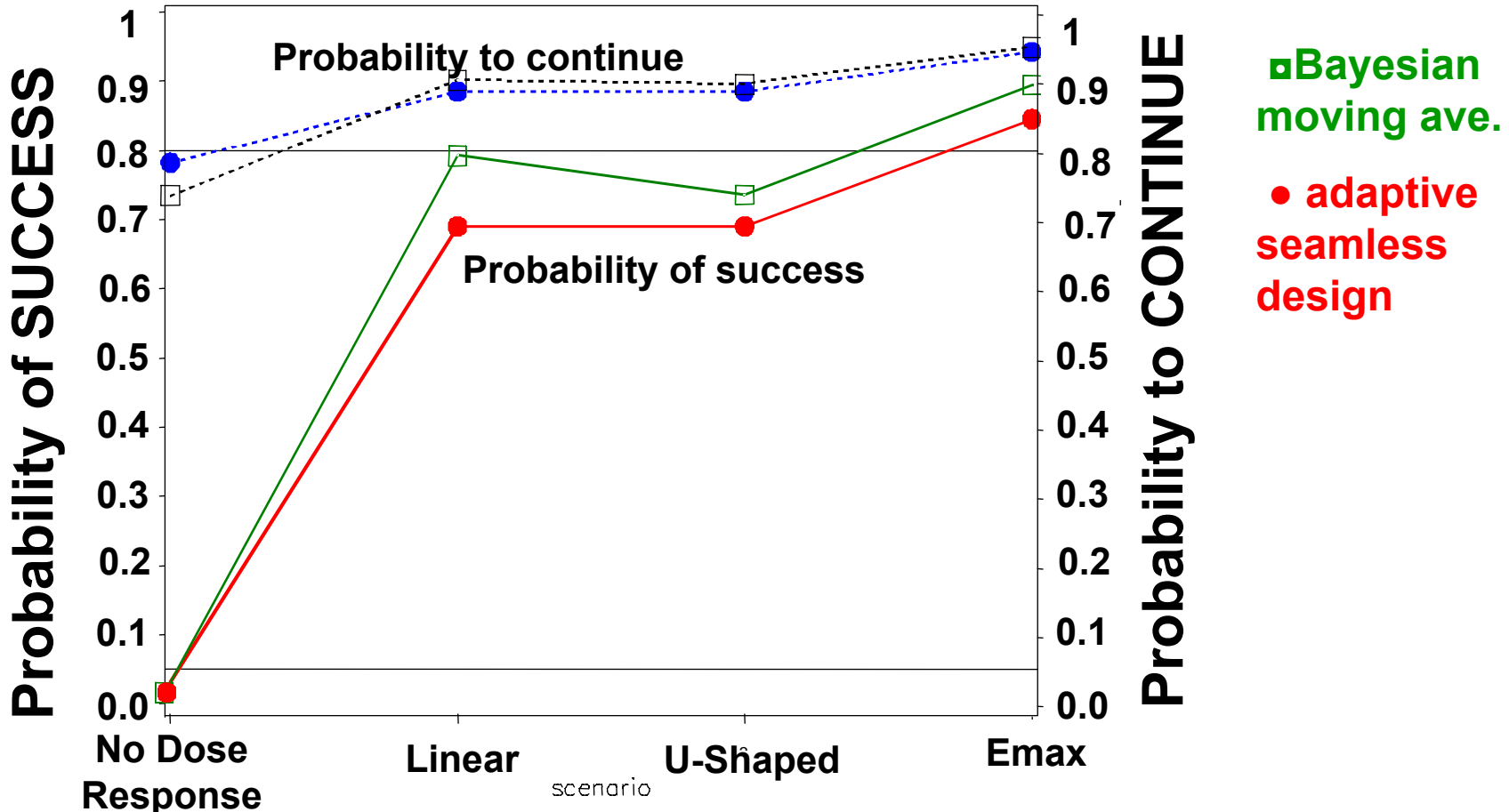
DOSE-RESPONSE SIMULATION SCENARIOS:



	clinical responses in different dose groups (0 is no response, 4 is maximal response)					
SCENARIOS	placebo	Dose 1	Dose 2	Dose 3	Dose 4	Competitor
No dose response	0	4	4	4	4	4
Linear dose response	0	1	2	3	4	2
U-shaped response	0	1	3	4	2	2
Emax dose response	0	1	2	4	4	2

Between patient standard deviation of 8 units

LEARNING ON DOSE-RESPONSE IMPROVES EFFICIENCY



CONCLUSIONS FROM THESE DOSE VS RESPONSE SIMULATION STUDIES:



- **Prior knowledge of a dose-response model can induce a significant gain in sample size / power**
- **Learning on and from the dose response curve improves dose finding decisions in subsequent adaptive seamless designs**
- **Savings and benefits occur not only in terms of sample sizes, but also in terms of probability to stop for futility**
- **Not shown;**
 - **Dose vs response data is needed to properly evaluate the competitor responses to test drug treatment**
 - **Dose vs response is needed to optimize dose spacing**
- **Thanks to Novartis Biostatistics and Modeling & Simulation colleagues for the analysis: Amy Racine, Billy Amzal,**

Marina Savelieva Praz, Beat Neuenschwander

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- **WHY IS DOSE vs RESPONSE RELEVANT TO ADAPTIVE CLINICAL TRIAL DESIGNS**

- **DOSE vs RESPONSE THAT IS EASY**

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- **SUMMARY**

BUILDING A DRUG AND DISEASE MODEL OF LDL CHOLESTEROL LOWERING,

JW Mandema, D. Herman, W. Wang, et al. AAPS Journal 2005:7(3)E513



Accumulated data from 25 trials (~9500 patients)

- **5 Pfizer sponsored trials for Lipitor**
- **7 AstraZeneca summary basis trials for Crestor**
- **9 Merck summary basis trials for Zetia**
- **4 Pfizer sponsored trials for an investigational non-statin**

POPULATION MIXED EFFECTS MODELING OF STATIN/NON-STATIN LDL LOWERING vs DOSE



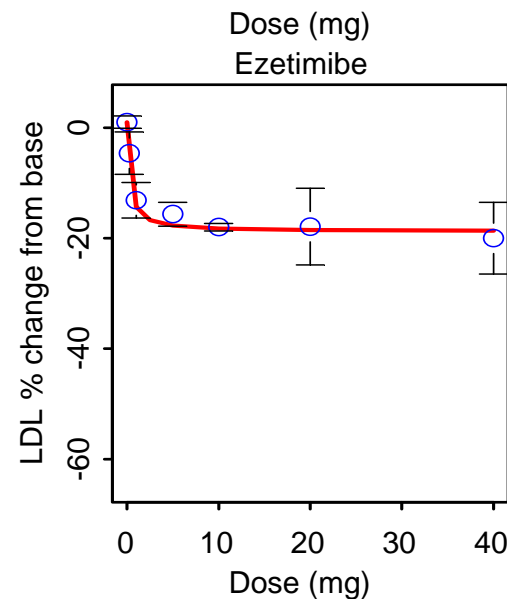
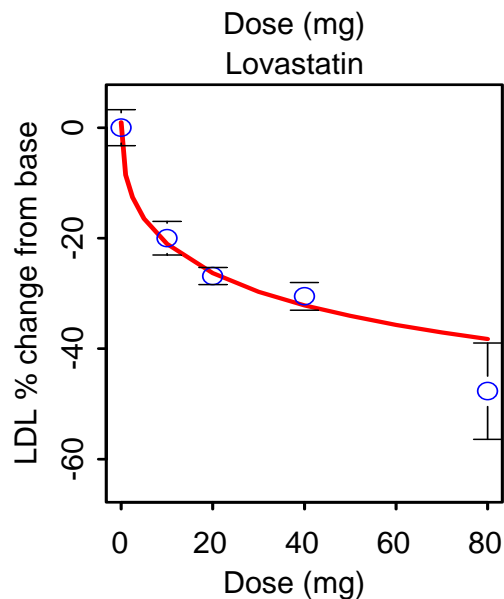
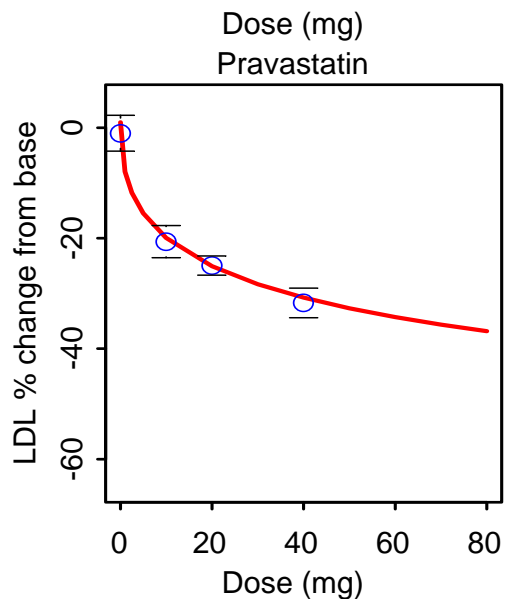
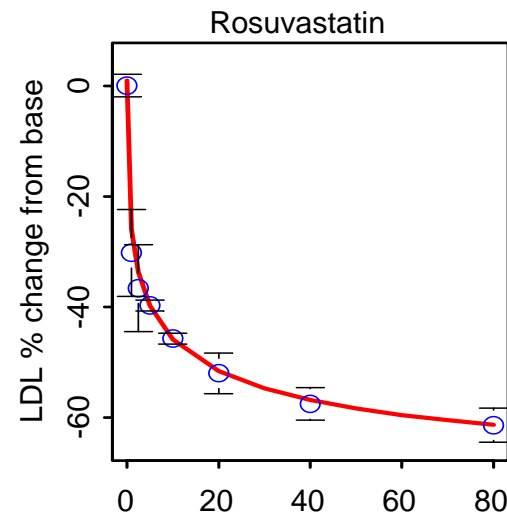
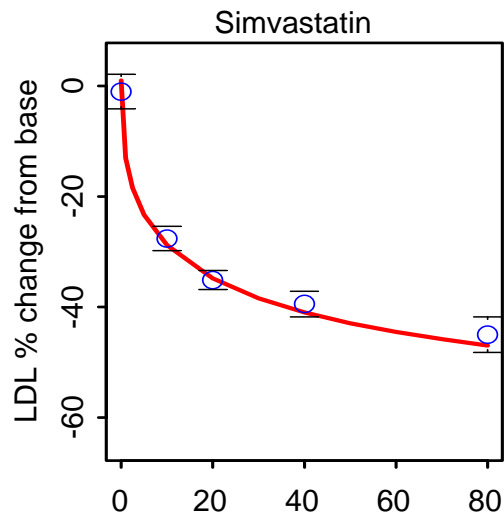
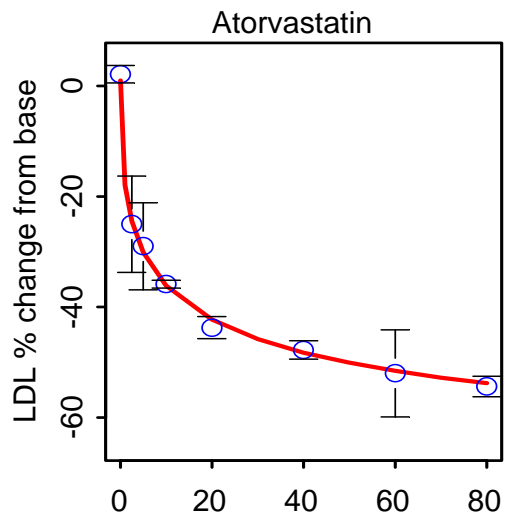
$$LDL \% \text{ change} = E_0 + E_{statin} + E_{non-statin} + \gamma \cdot E_{statin} \cdot E_{non-statin}$$

$$E_{drug} = \frac{Dose^n \cdot E_{max}}{Dose^n + ED_{50}^n}$$

Weighted (by variance) non-linear mixed effects regression to estimate model parameters

Model allows pooling of trials with different drugs, doses, patient types, durations, etc...

DOSE VS LDL LOWERING RESPONSE: POPULATION, MIXED EFFECTS RESPONSE META-ANALYSIS:



Modeling the Progression of Skin Scores in Scleroderma: Application (dose-response that is hard)

Nitin Kaila, Russ Wada, Sohail Ahmed, Dean Bottino, Tim Wright

October 11, 2006



SYSTEMIC SCLEROSIS: DESCRIPTION

Autoimmune disease

- Raynaud's phenomenon usually predates onset of fibrosis
- >95% of patients have autoantibodies
- Prevalence ~1/240 (70,000 in USA)
- Hallmark: skin and internal organ fibrosis

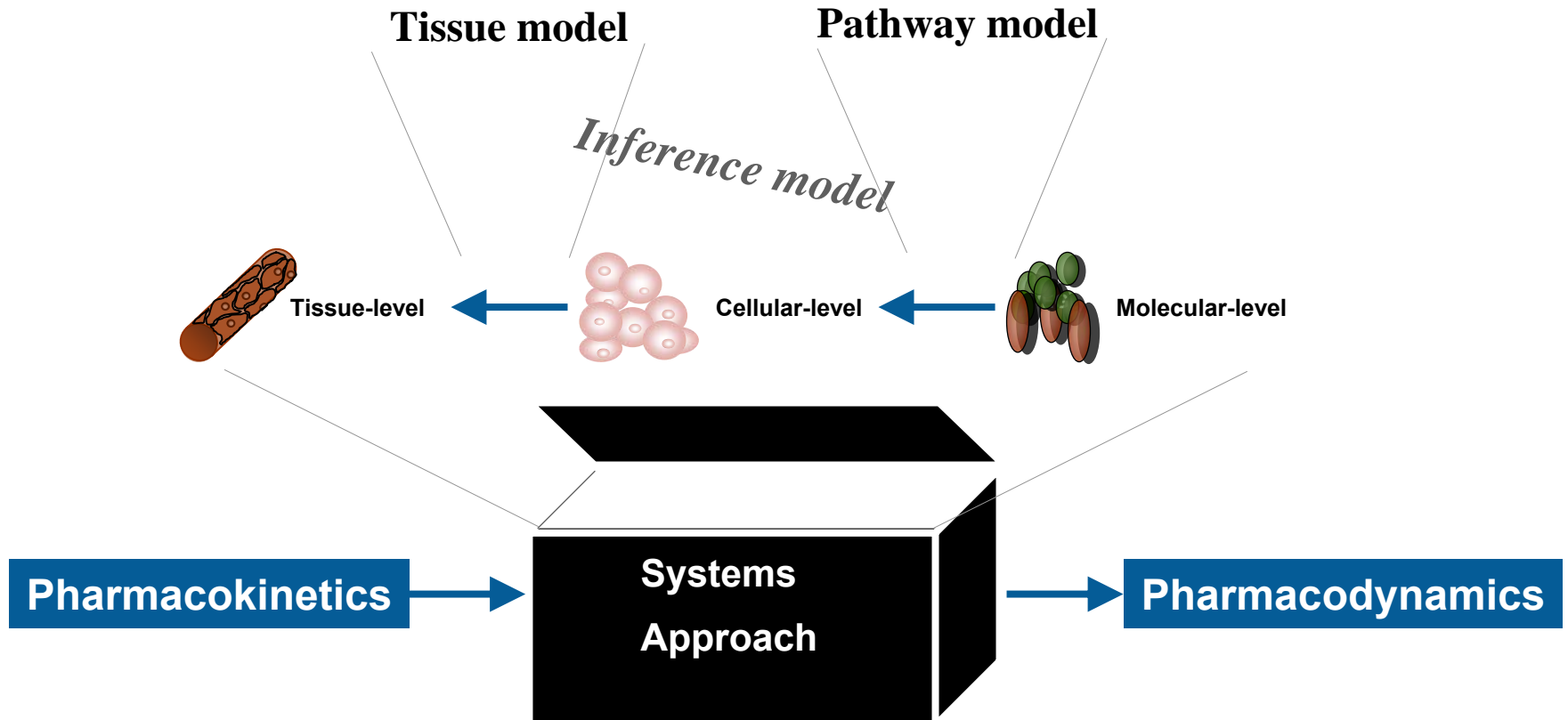


Two major disease subtypes

- Limited cutaneous – distal skin fibrosis, GI involvement
- Diffuse cutaneous – proximal and distal fibrosis, pulm. fibrosis, renal disease, GI involvement



INTEGRATED MODELING OF BIOLOGICAL AND PATHO- PHYSIOLOGICAL PROCESSES:



SCLERODERMA: FROM CELL AND MOLECULAR MECHANISMS TO DISEASE MODELS

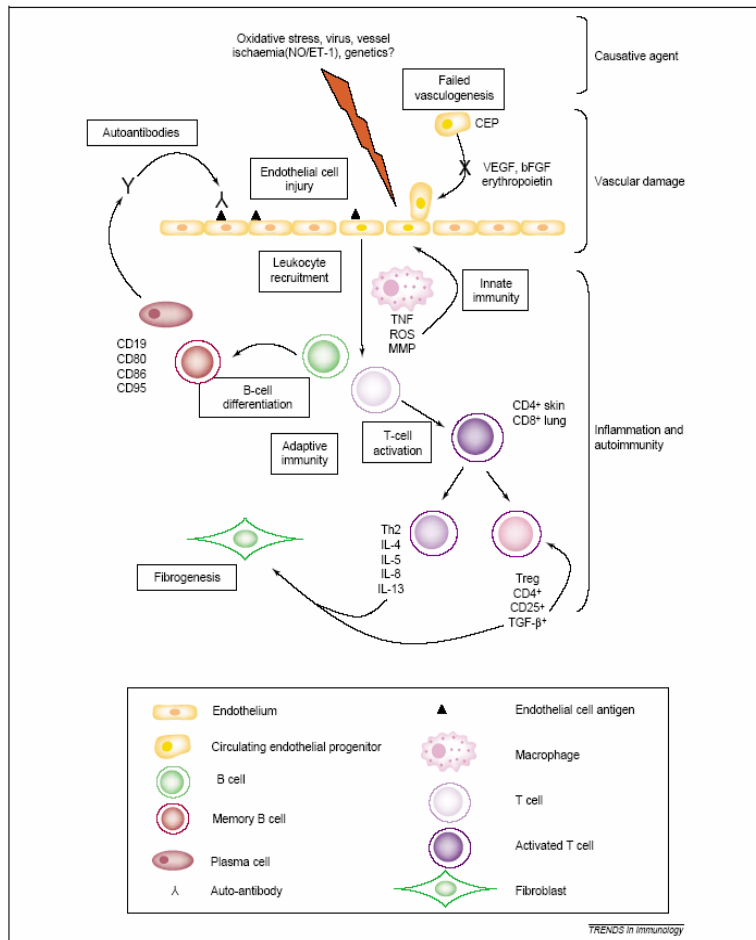


Origin of Auto-immunity

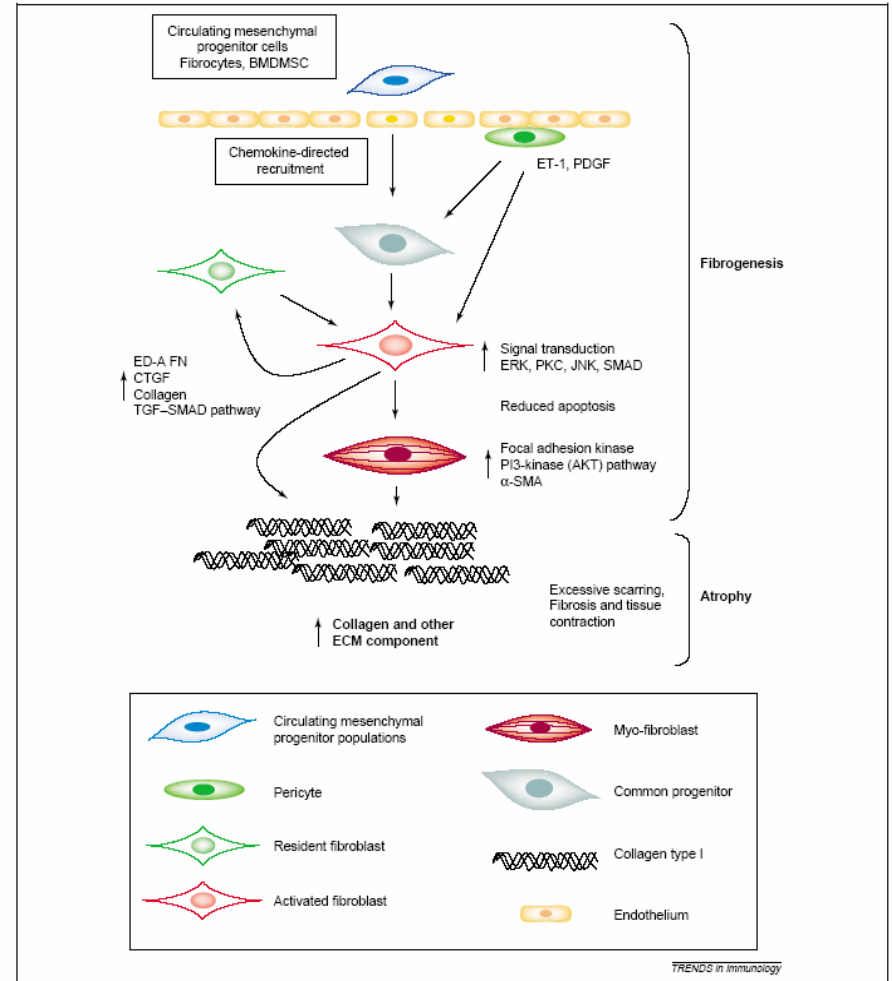
Review

TRENDS in Immunology Vol.26 No.11 November 2005

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Fibroblasts and Fibrogenesis



SKIN THICKNESS IN DIFFUSE SCLERODERMA HAS THREE PHASES: ACUTE WORSENING, PLATEAU, THEN SPONTANEOUS IMPROVEMENT.

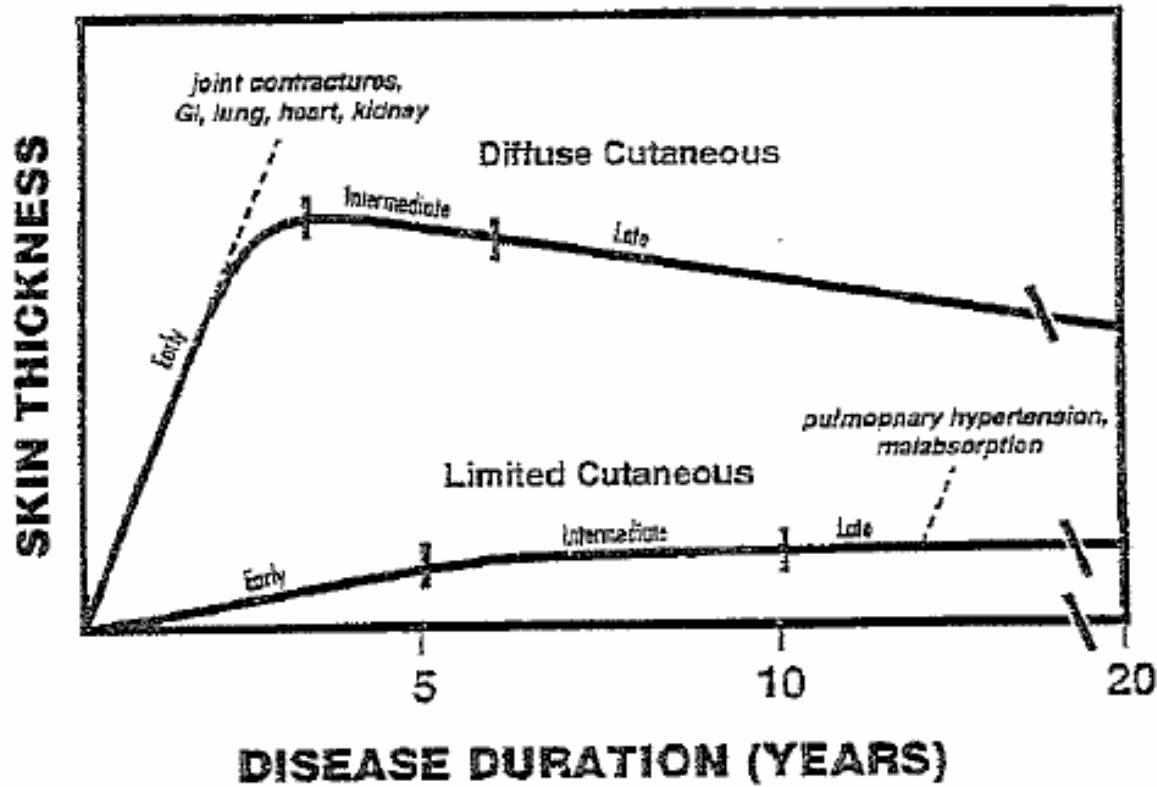
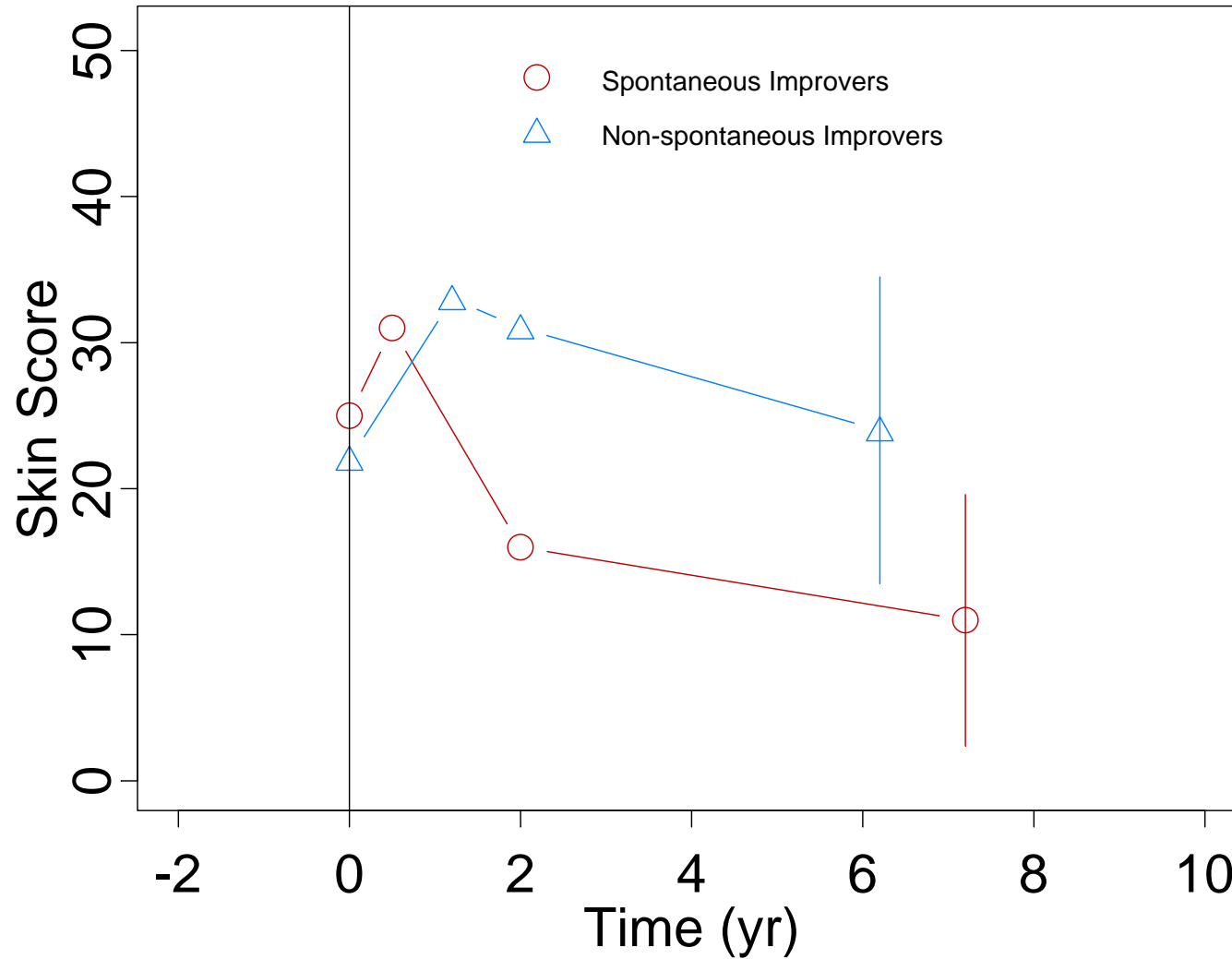
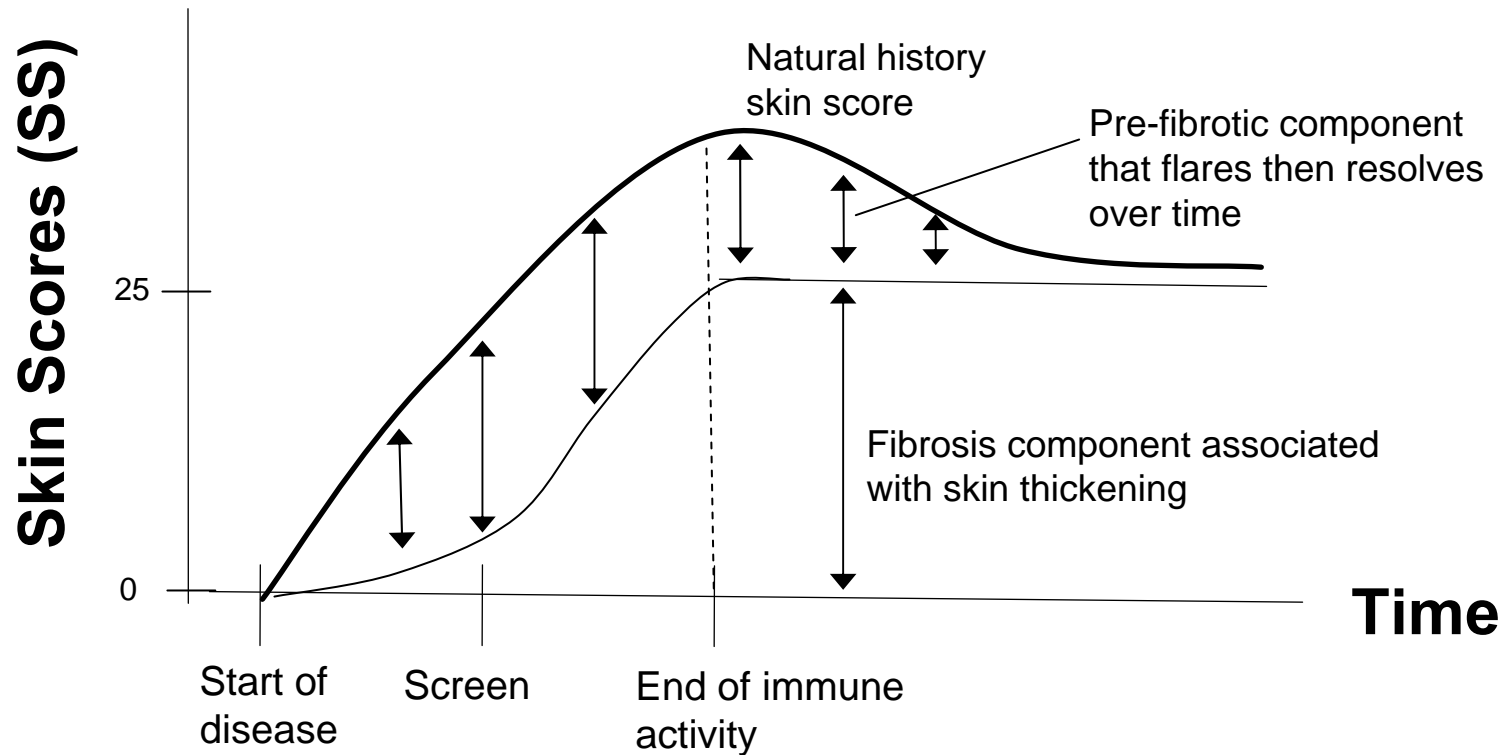


Fig. 1. Diagrammatic representation of the stages of diffuse and limited scleroderma over time, including the typical relationships between skin thickness and selected organ system involvements. (From Medsger TA Jr, Steen VD. Classification, prognosis In: Clements PJ, Furst DE, editors. Systemic sclerosis. Baltimore: Williams & Wilkins; 1996. p. 51-64; with permission.)

SKIN SCORE PROGRESSION DATA MODEL:

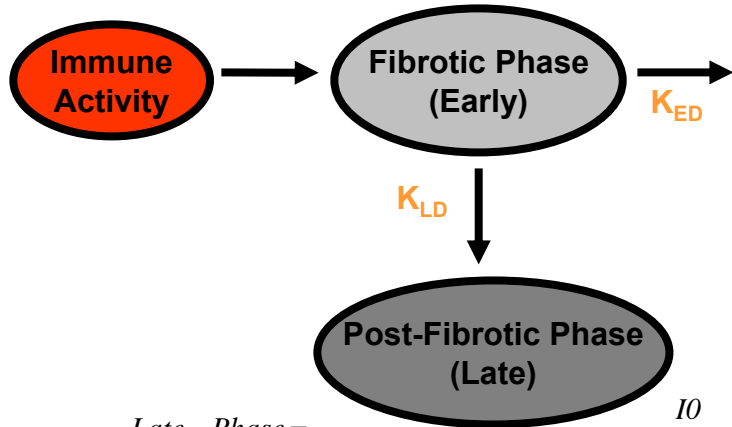


FIBROGENESIS (REVERSIBLE) IS SUCCEEDED BY FIBROSIS (IRREVERSIBLE), NEW TREATMENTS MAY AFFECT FIBROGENESIS IN DIFFUSE SCLERODERMA



EARLY / LATE FIBROSIS PHASE MODEL FOR PROGRESSION OF SKIN SCORES

Equation 1



$$\text{Early - Phase} = \begin{cases} 0 & \text{if } t \leq T_{start} \\ \frac{I0}{T_{end} - T_{start}} \left[1 - e^{-(k_{ED} + k_{LD}) \cdot t} \right] & \text{if } T_{start} < t \leq T_{end} \\ \frac{I0}{T_{end} - T_{start}} \left[(1 - e^{-(k_{ED} + k_{LD}) \cdot t}) - (1 - e^{-(k_{ED} + k_{LD}) \cdot T_{end}}) \right] & \text{if } t > T_{end} \end{cases}$$

Equation 2

$$\text{Late - Phase} = \begin{cases} 0 & \text{if } t \leq T_{start} \\ \frac{I0}{T_{end} - T_{start}} \cdot K_{ED} \cdot \left[(t - T_{start}) - \frac{1}{K_{ED} + K_{LD}} \cdot (1 - e^{-(k_{ED} + k_{LD}) \cdot (t - T_{start})}) \right] & \text{if } T_{start} < t \leq T_{end} \\ \frac{I0}{T_{end} - T_{start}} \left\{ K_{ED} \cdot \left[(t - T_{start}) - \frac{1}{K_{ED} + K_{LD}} \cdot (1 - e^{-(k_{ED} + k_{LD}) \cdot (t - T_{start})}) \right] - K_{LD} \cdot \left[(t - T_{end}) - \frac{1}{K_{ED} + K_{LD}} \cdot (1 - e^{-(k_{ED} + k_{LD}) \cdot (t - T_{end})}) \right] \right\} & \text{if } t > T_{end} \end{cases}$$

$I0$ = Immune activity (units)

T_{end} = Time to end of immune activity (yr.)

T_{start} = Time at start of immune activity (yr.)

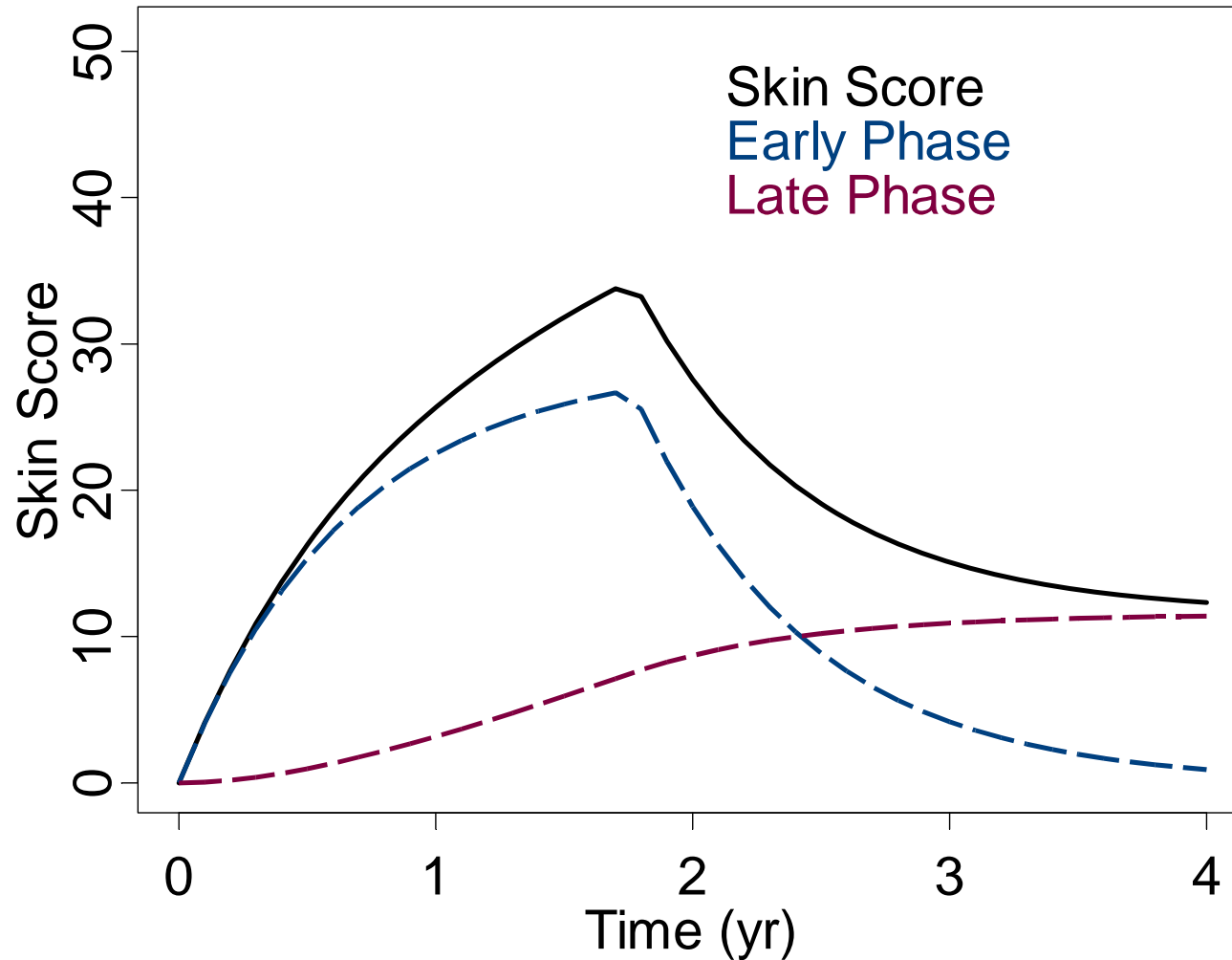
K_{ED} = Rate constant improving skin score (yr.⁻¹)

K_{LD} = Rate constant worsening skin score (yr.⁻¹)

$$\text{Skin - Score} = \begin{matrix} \text{Early - phase} \\ + \\ \text{Late - phase} \end{matrix}$$

Equation 3

REPRESENTATION OF SKIN SCORES WITH RESPECT TO THE EARLY / LATE FIBROSIS MODEL



SUMMARY:

- **The dose vs response relationship is fundamental to integrate into any approach that uses adaptive clinical trial design**
- **Prior knowledge of the dose vs response relationship can be used to design adaptive clinical trials that are more efficient by**
 - **Reducing treatment group sizes by having more accurate estimation of underlying variability**
 - **Choosing the correct spacing of doses**
 - **Allowing accurate analysis of comparator vs test compound**
- **Dose vs response is easy when measures of the disease and drug effect are established and treatments for diseases exist**
- **Dose vs response is hard in difficult, complex diseases where treatments do not exist**
- **Drug and disease models can be created to estimate the dose vs response relationship for innovative therapeutic approaches**

Implementing Bayesian model average



Model Space

1. Linear in dose
2. Piece-wise linear with one change point @ dose 1, 2 or 3 : to approximate umbrella or Emax
3. Linear in $\log(\text{Dose}+0.1)$
4. Second order Polynomial

Prior

Equal probability for all models in model space

Uninformative prior for model parameters given model