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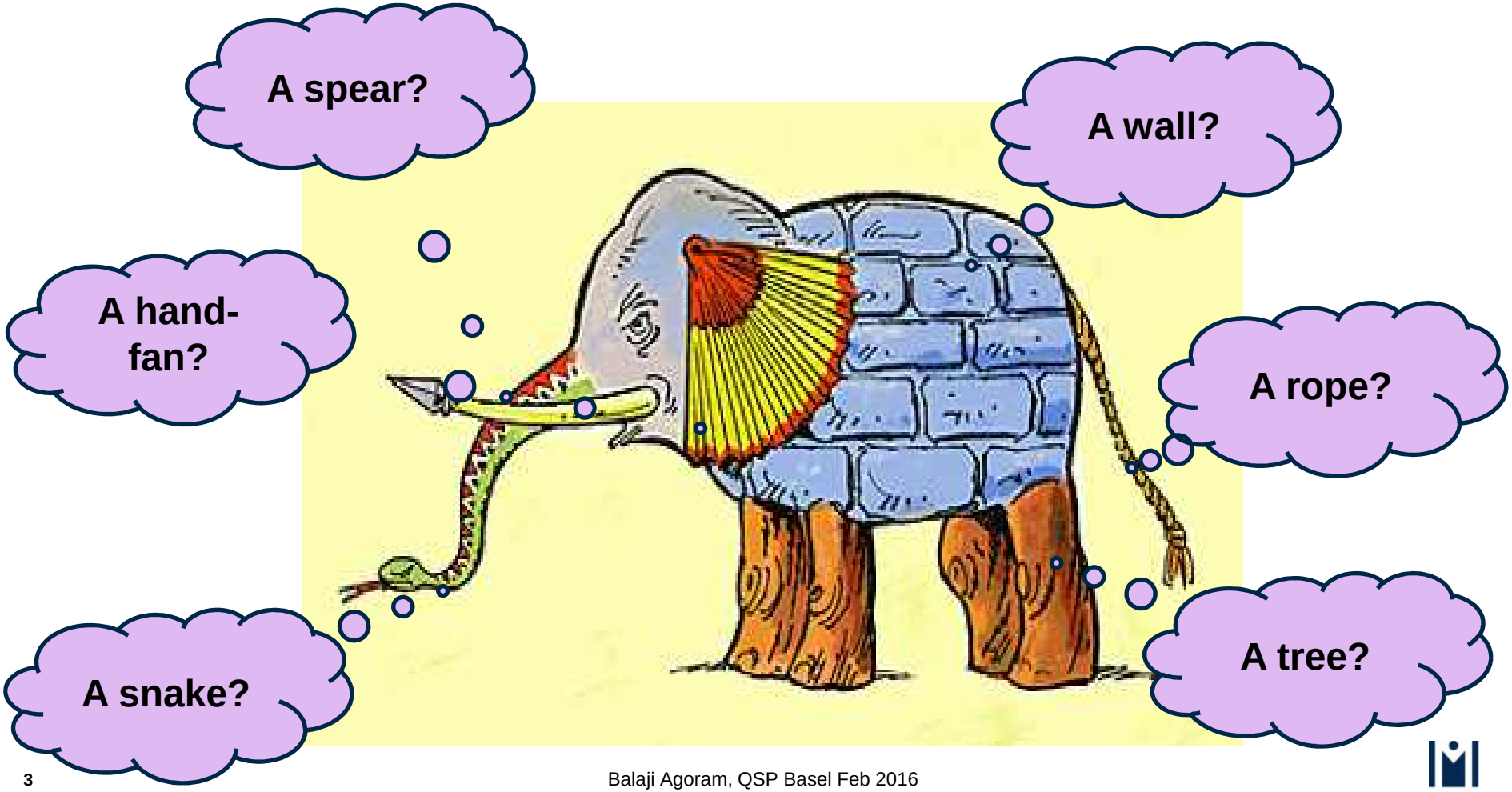
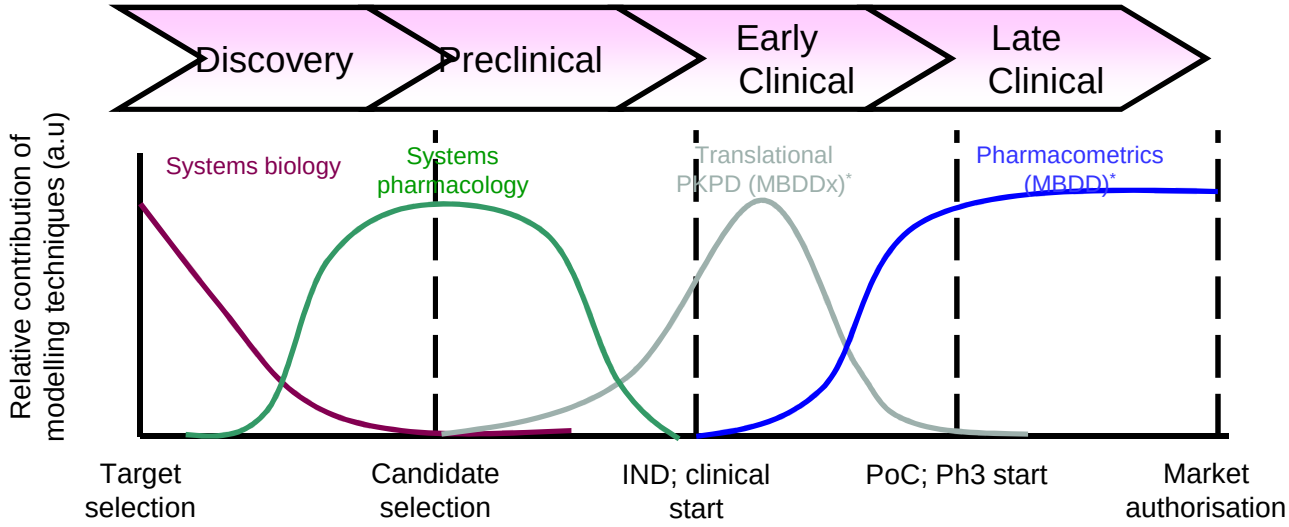
Success factors in the implementation of systems pharmacology models during R&D

Balaji Agoram, Ph.D
Director, Clinical Pharmacology
MedImmune, Mtn View, CA

It was six men of Indostan
To learning much inclined,
Who went to see the Elephant
(Though all of them were blind),
That each by observation
Might satisfy his mind


A spear?
A wall?
A hand-fan?
A rope?
A snake?
A tree?

How are these models used within typical industry?



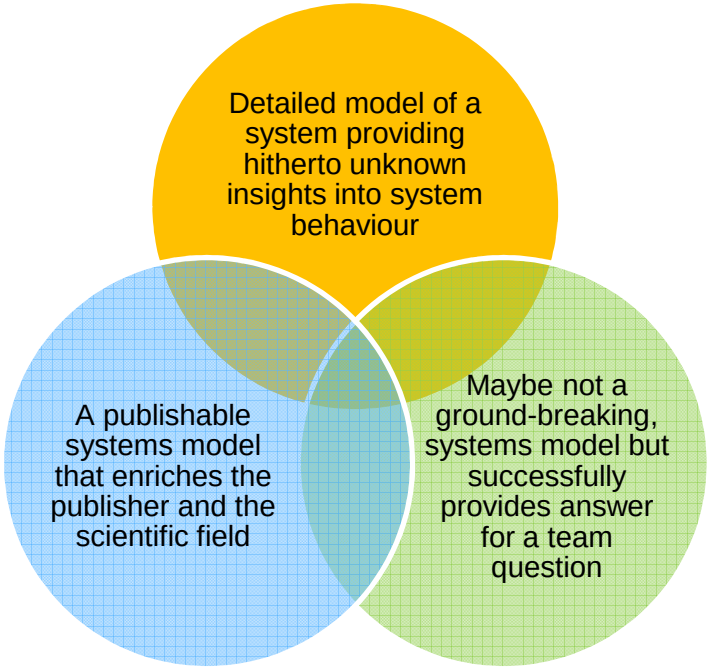
While standard PKPD models are *de rigeur* in pharma/biotech today, systems models is perceived to be an unmet research need*

*See Identifying CDER's Science and Research Needs Report July 2011

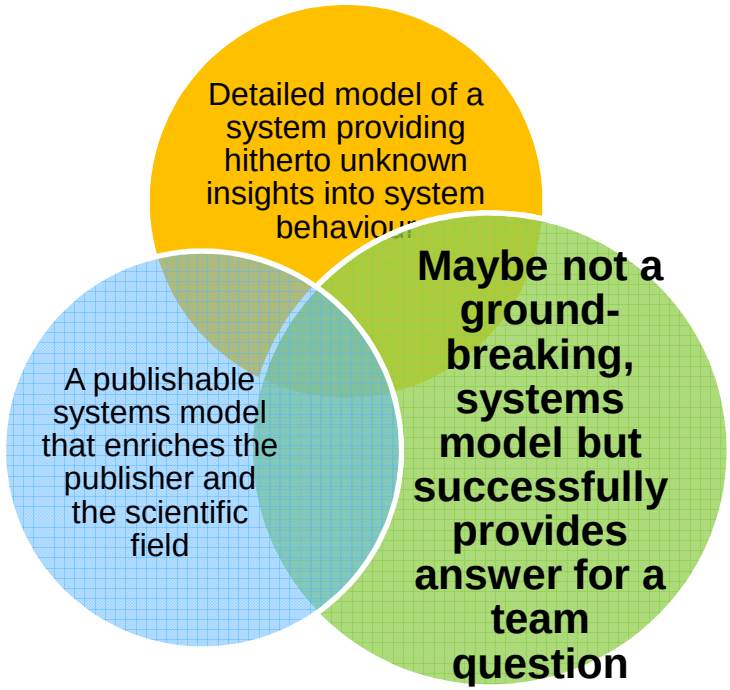
*MBDD= Model-based drug development

*MBDDx=Model-based drug discovery

Successful QSP effort could be defined in many ways



For the purposes of this presentation, success is…

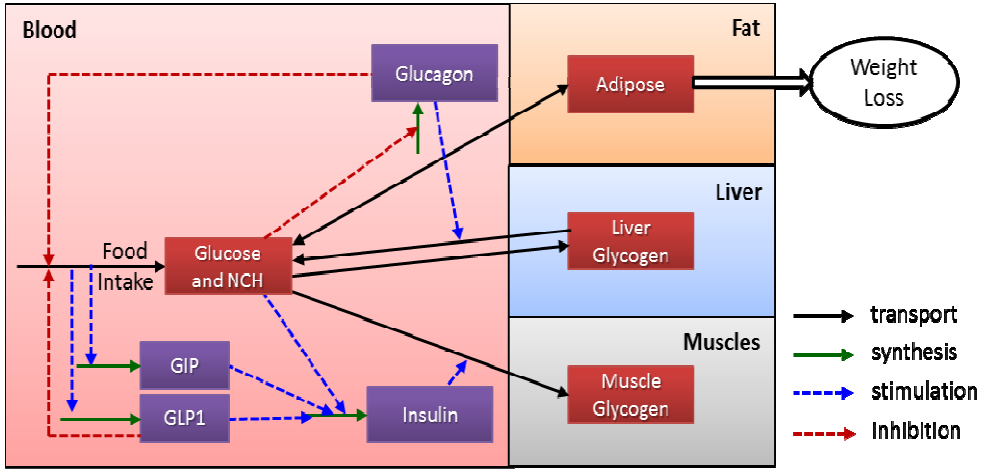


Successful QSP implementation consists of three successful steps

“Asking the right question is half the answer” – (must be a proverb somewhere)

Specific and verifiable	Quantifiable, resulting in a tractable problem Roadmap can be created to check answer is reached Model results can be verified with reasonable investment (preferable)
Supported by data	Knowledge needs to exist regarding the problem at hand – preliminary exploratory analysis
Alternative methods are not easy	Cheaper animal models, in vitro testing, etc.

Identification of the optimal GLP1/glucagon balance in a dual agonist

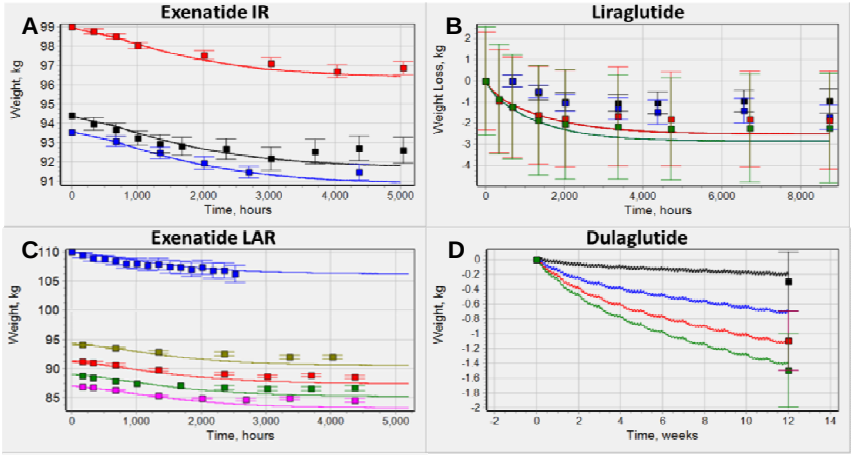


Agoram, et al. ADA 2015

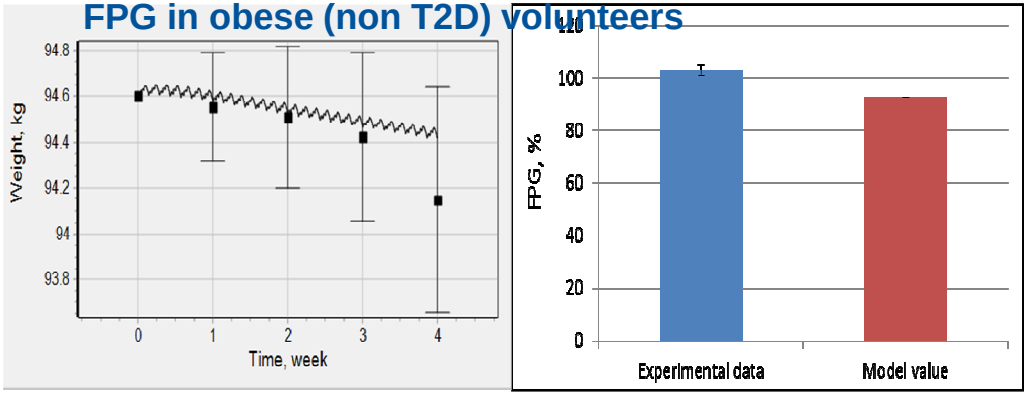
- We hypothesised that in order to guide the design of optimised multi-pharmacology incretin-like molecules, a detailed organ/organism level understanding of the action of the incretins on weight regulation and glucose control was necessary
- We developed a systems pharmacology model to enable this understanding using a modular approach and evaluated its performance using a range of literature-reported data

Example: Affinity goals for a GLP-1/glucagon dual agonist (2/2)

Model predicted weight loss and FPG after GLP-1 agonist treatment in T2D patients



Verification of dual agonist predictions: Simulated vs. observed effects of oxyntomodulin on weight and FPG in obese (non T2D) volunteers



Agoram, et al. ADA 2015

How does this example demonstrate success factors?

Specific and verifiable	Quantifiable, resulting in a tractable problem Roadmap can be created to check answer is reached Model results can be verified with reasonable investment (preferable)	√
Supported by data	Knowledge needs to exist regarding the problem at hand – preliminary exploratory analysis	√
Alternative methods are not easy	Cheaper animal models, in vitro testing, etc.	√

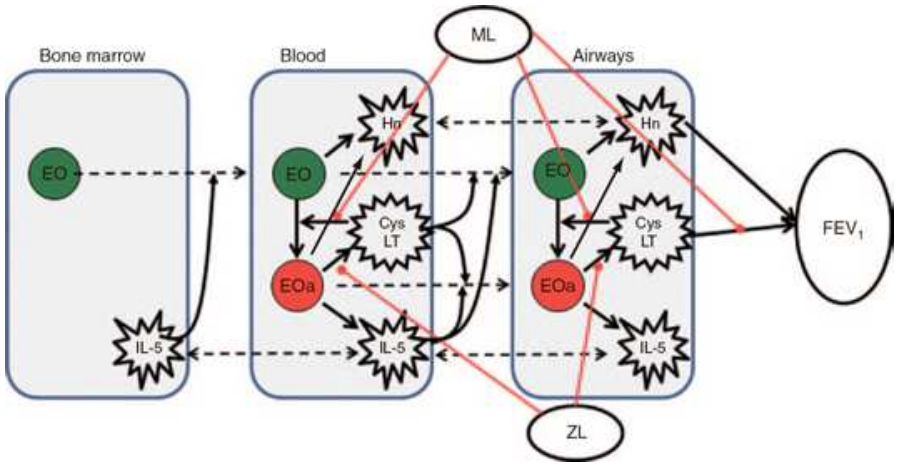
Managing simplicity vs complexity during model development…

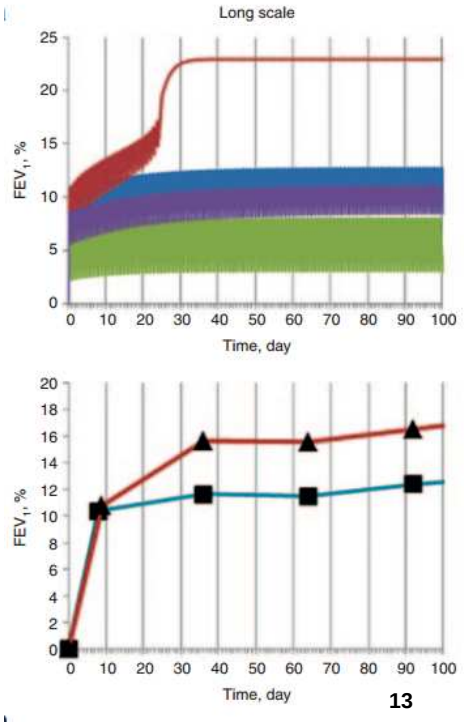
Start with the simplest possible model to test/generate hypothesis	Formal statement of hypothesis (see next presenter) Supported by project physician and biologist
Add complexity only if supported by data and if necessary	Sensitivity analysis
Check roadmap from question to answer	Ensure unnecessary additions are avoided

"Any darn fool can make something complex; it takes a genius to make something simple."
– Pete Seeger

"Everything should be made as simple as possible, but not simpler."
Albert Einstein

Systems model to understand action of 5Lipoxygenase-inhibitors





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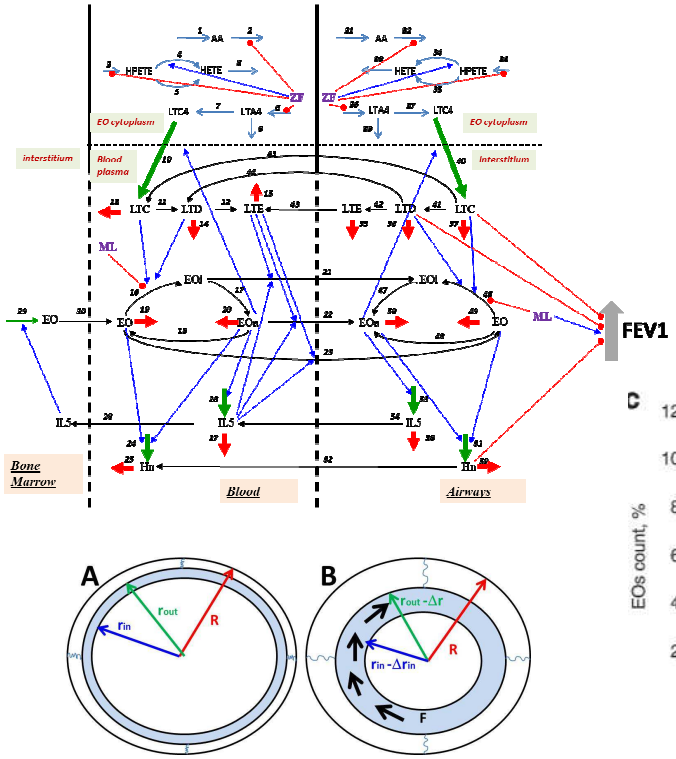
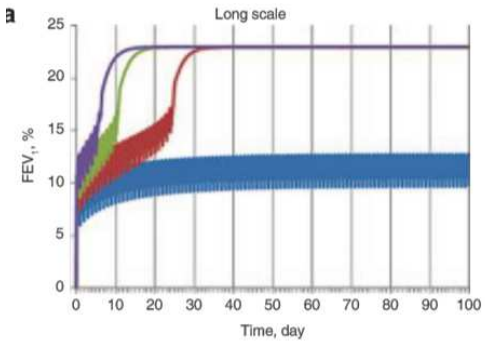
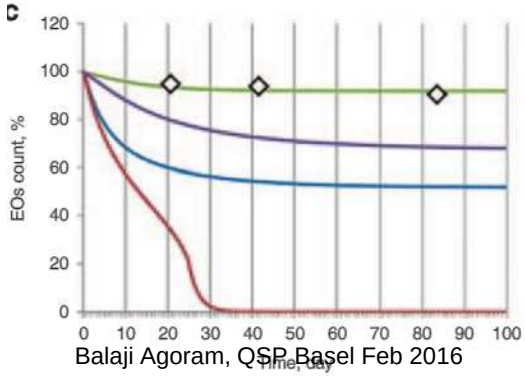
Did the model really need to be that complex?

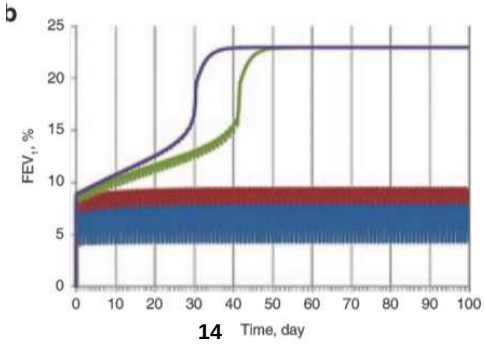


- Extra details on montelukast were added to the model for verification purposes
- Detailed biophysical model was added to link active cytokine levels to changes in FEV_1 through bronchus volume changes

Agoram, Demin, et al CPT:PSP 2013







Model communication should include tabled assumptions

Table 1 Description of available experimental data and facts

Assumption/fact	References
Eosinophils and mast cells are the key cells mainly responsible for bronchoconstrictors production	16,18,44
Cysteinyl leukotrienes C4, D4, and E4 (LTC4, LTD4 and LTE4), histamine, and prostaglandins D2 and F2 are key bronchoconstrictors responsible for excessive bronchoconstriction in asthmatic patients. Among leukotrienes, LTD4 is the strongest bronchoconstrictor	45
IL-5, granulocyte-macrophage colony-stimulating factor, and stem cell factor are main cytokines governing eosinophils and mast cells maturation	16,46
Binding of LTD4 and LTC4 to cysteinyl leukotriene receptors 1 and 2 (CysLT1R and CysLT2R) is able to transform inactive eosinophil to activated eosinophil	44
Only activated eosinophils are responsible for high production of IL-5 and LTC4	44
Life span of activated eosinophil is larger than that of inactivated eosinophil	47
Mast cells are able to produce histamine spontaneously. Mast cells of asthmatics produce more histamine than those of healthy subjects	16
Eosinophils are able to modulate histamine production in mast cells via excretion of eosinophil cationic protein (ECP). Increase in ECP results in degranulation of mast cells	16
The key chemoattractants driving eosinophils migration are LTE4 and IL-5	31,34,45,48
Increase in LTE4 concentration results in significant accumulation of eosinophils in airways from blood	18,34,45
Increase in IL-5 blood plasma level leads to elevation of eosinophils trafficking from blood plasma to airways	31,48
ASM contraction is governed by intracellular calcium level	45
Intracellular calcium level depends on concentration of bronchoconstrictors (LTD4, LTC4, and histamine)	49
Binding of LTD4 and LTC4 to CysLT1R and CysLT2R of ASM and binding of histamine to H_1 receptor results in increase in intracellular Ca^{2+} concentration	49,50

ASM, airway smooth muscle; IL-5, interleukin-5.

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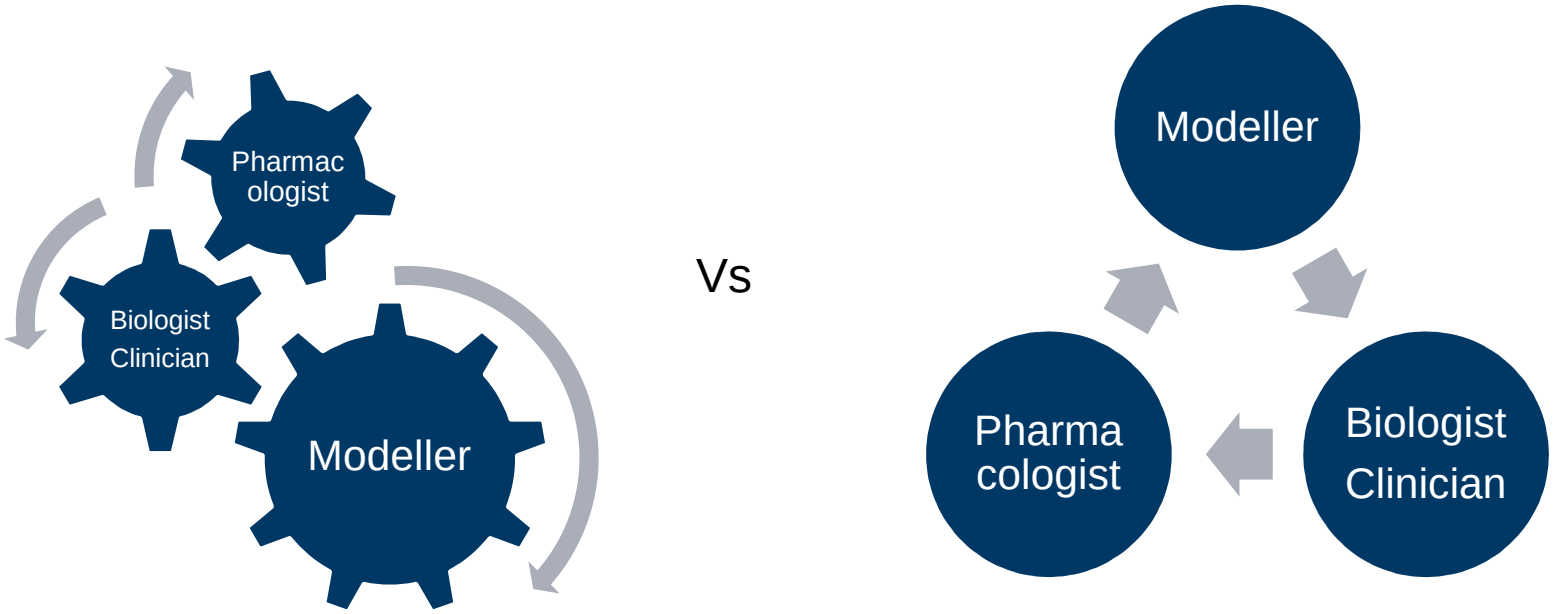
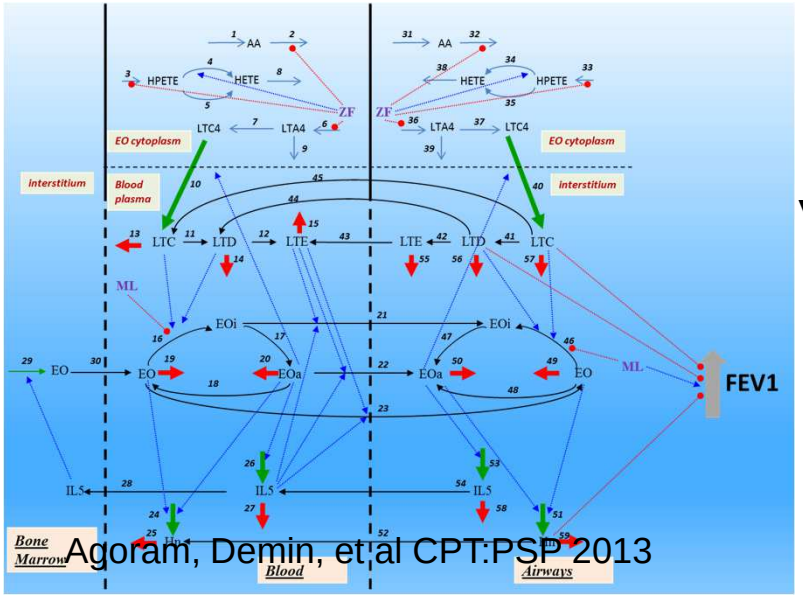
Systems model development is a community activity…



Communication of model should be succinct…



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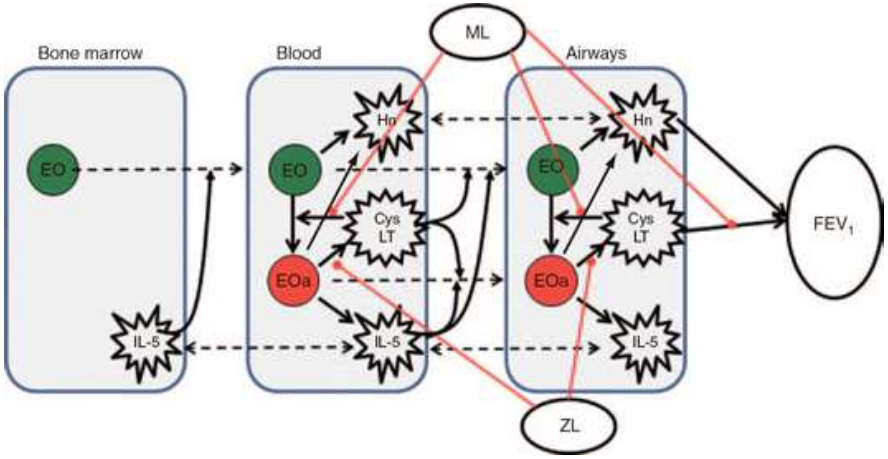
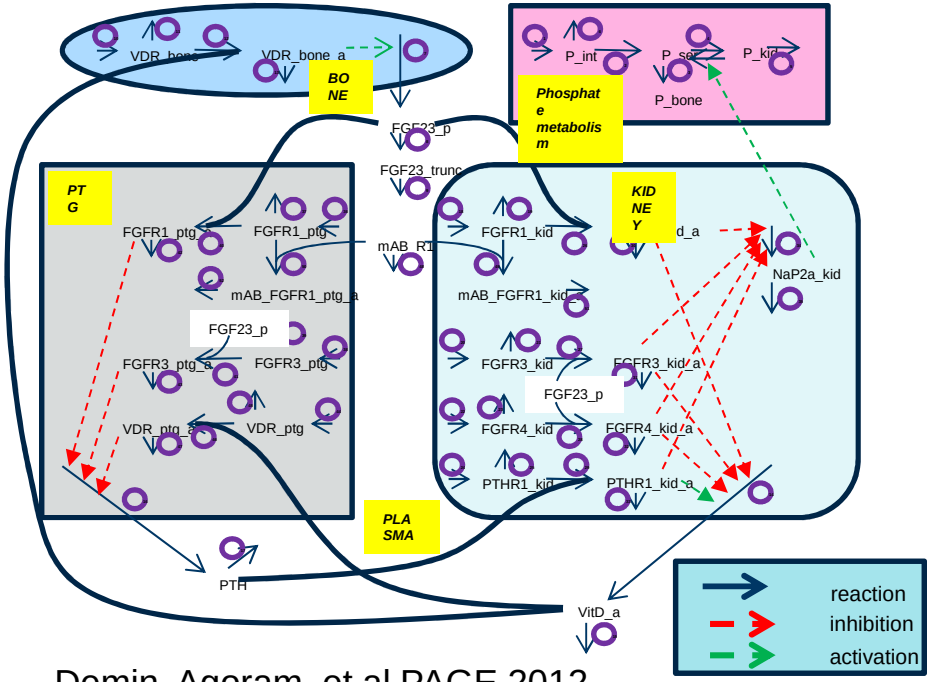
Vs

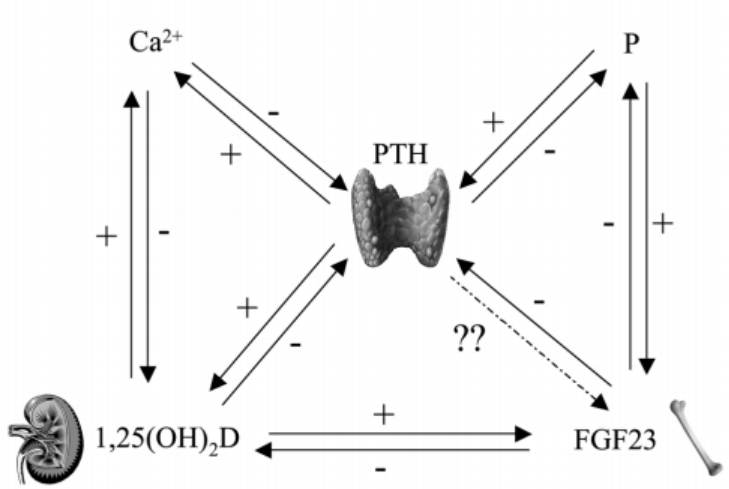


Communication of model should be succinct…



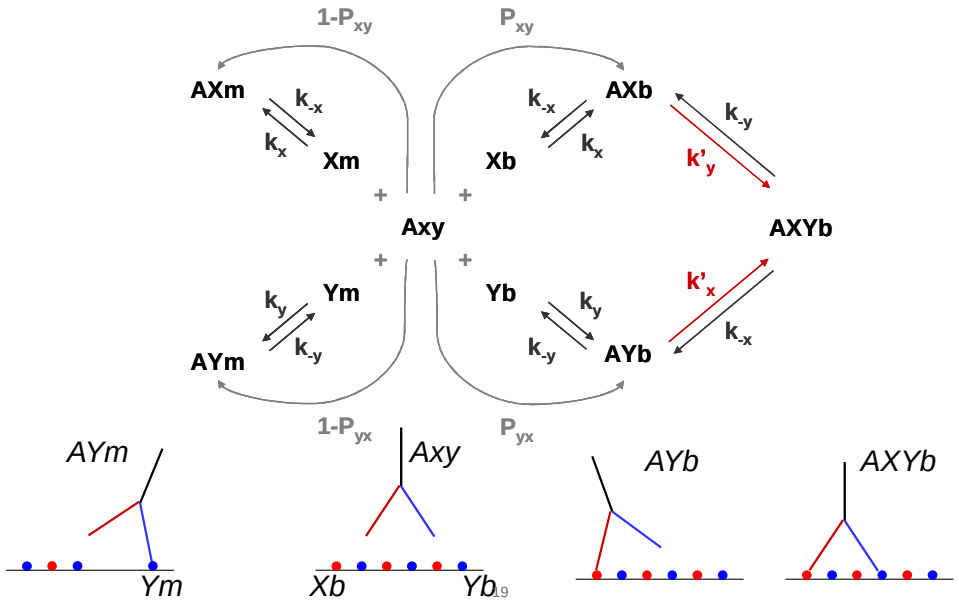
Demin, Agoram, et al PAGE 2012

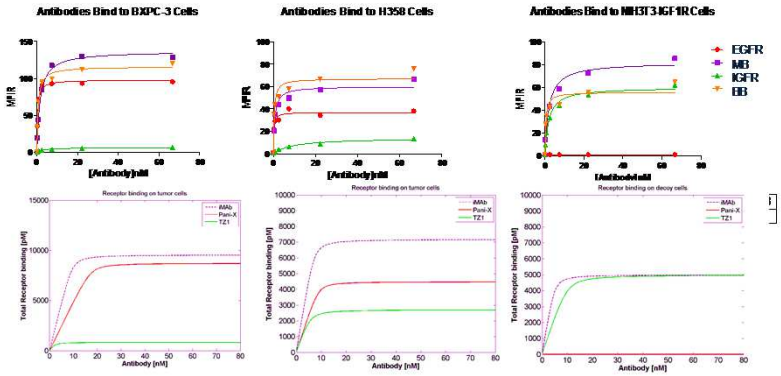
Vs



Ben-dov et al 2007

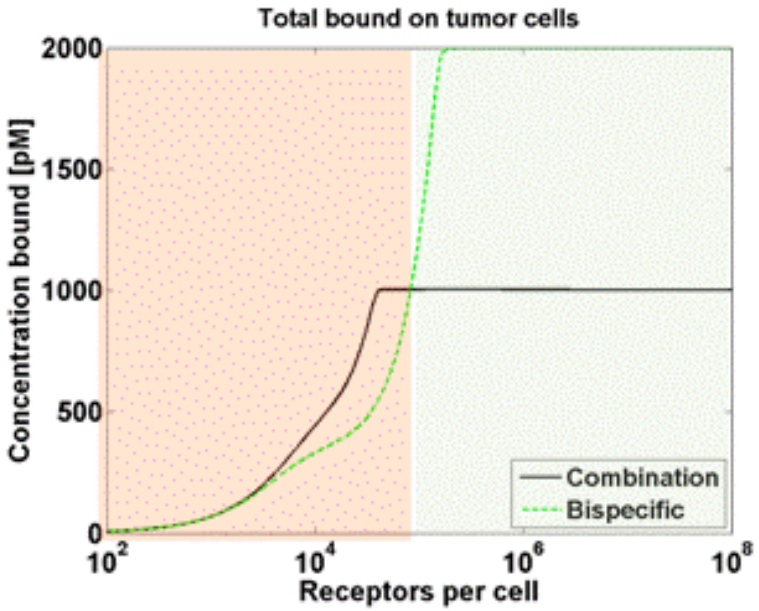
A simple model of bispecific binding was developed from basic principles





Van Steeg, Agoram, et al mAbs (2016)

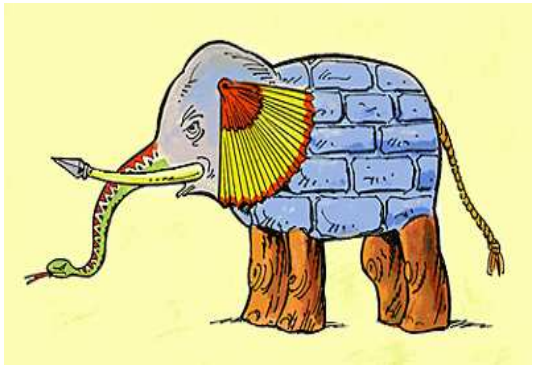
Binding =f(receptor density): Avidity hypothesis *is* true, albeit NOT universally



Van Steeg, Agoram, et al mAbs (2016)

- In the presence of decoy cells, at high receptor densities, bispecific is better than combination treatment, but not at low receptor densities
- N.B: All in vitro experiments were done at high receptor density

Communication of results to external audience…



- Need to convince that the individual submodels add up to an elephant, rather than say… a tapir
- Justification of the underlying structure is critical in systems modelling rather than data fitting
- Selection of data for individual submodels
  - Avoiding bias in data selection and relationships
- Unknown/unknown bias is always present in systems models
  - One among many plausible explanations

Development of systems models is different from that of PKPD models

- Three key elements to the development and implementation of a systems model:
  - Right question, continuous communication/teamwork, and clear communication of results
- The right question is one that is specific, verifiable, supported by data, and not easily answered through traditional methods
- Systems modelling is a community activity → continuous involvement of team members required
- Clear and succinct internal and external communication strategy required

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