M&S in Preclinical Development

Predicting thyroid hormones side effects in human from preclinical toxicity studies

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AstraZeneca

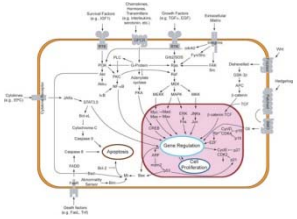
Modelling and Simulation Continuum at AZ

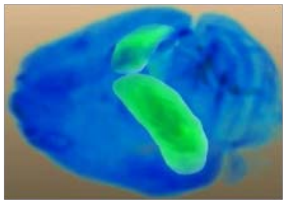
Target Selection → Discovery → Preclinical Development → Early Clinical Development → Late Clinical Development → LCM

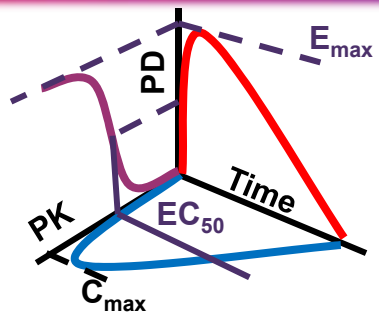
Biology *Network Target*

Pharmacology *Target Engagement Safety*

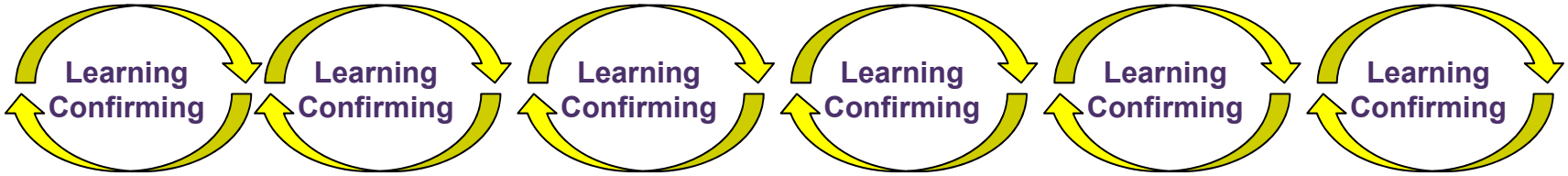
Disease *Efficacy Safety*





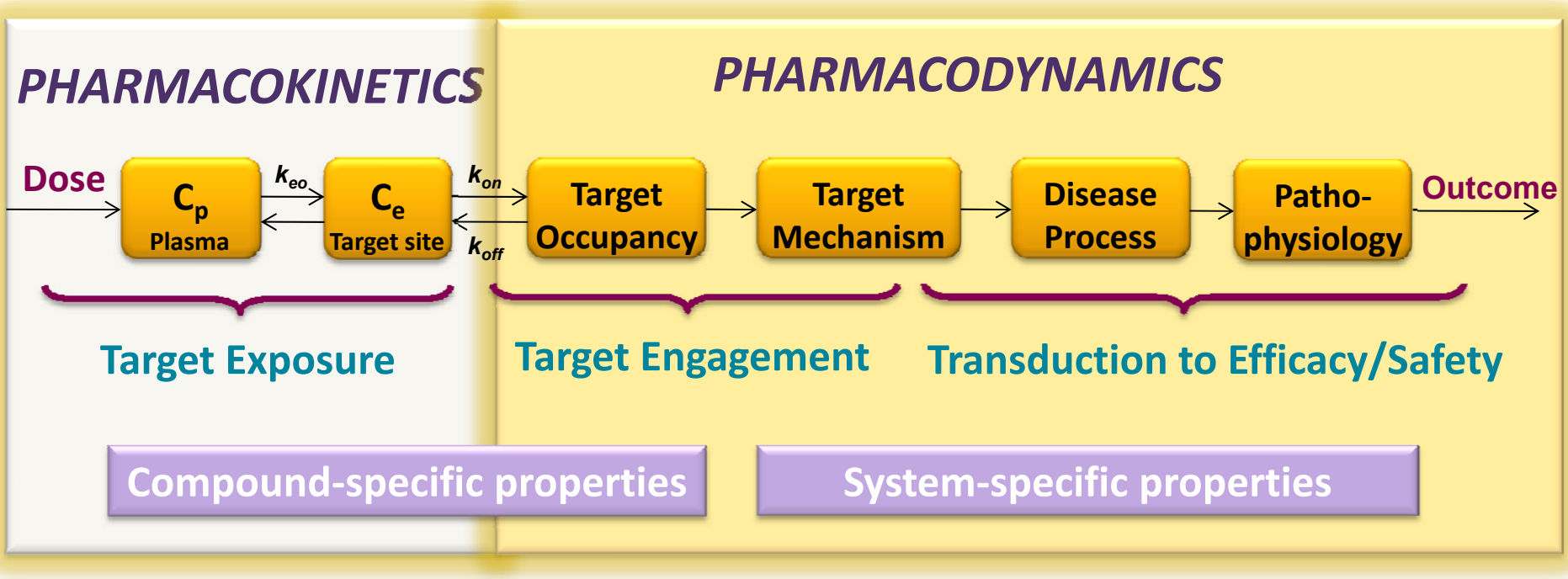


Right Target ***Tissue*** ***Exposure*** ***Dose*** ***Schedule*** ***Trial Design***



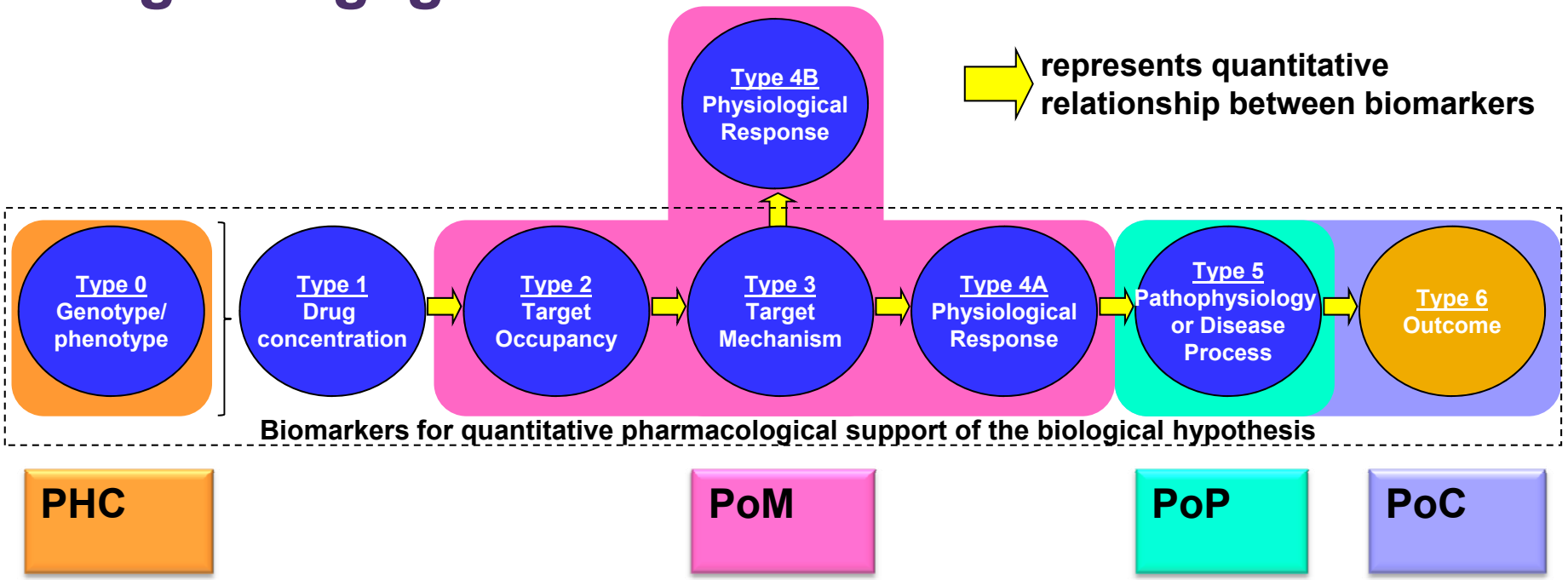
Predictive Sciences Modeling Network

Model Based Drug Discovery and Development
Pharmacokinetic-Pharmacodynamic Principles



Using a quantitative pharmacology approach to support decision making, by establishing a translational *exposure – target engagement – efficacy/safety model* in animals and humans and predicting the dose to man, optimal dosing schedule and clinical study design.

Biomarker Classification Map
Target Engagement and Clinical Outcome



PoM: degree, duration of target engagement sufficient for viable hypothesis test

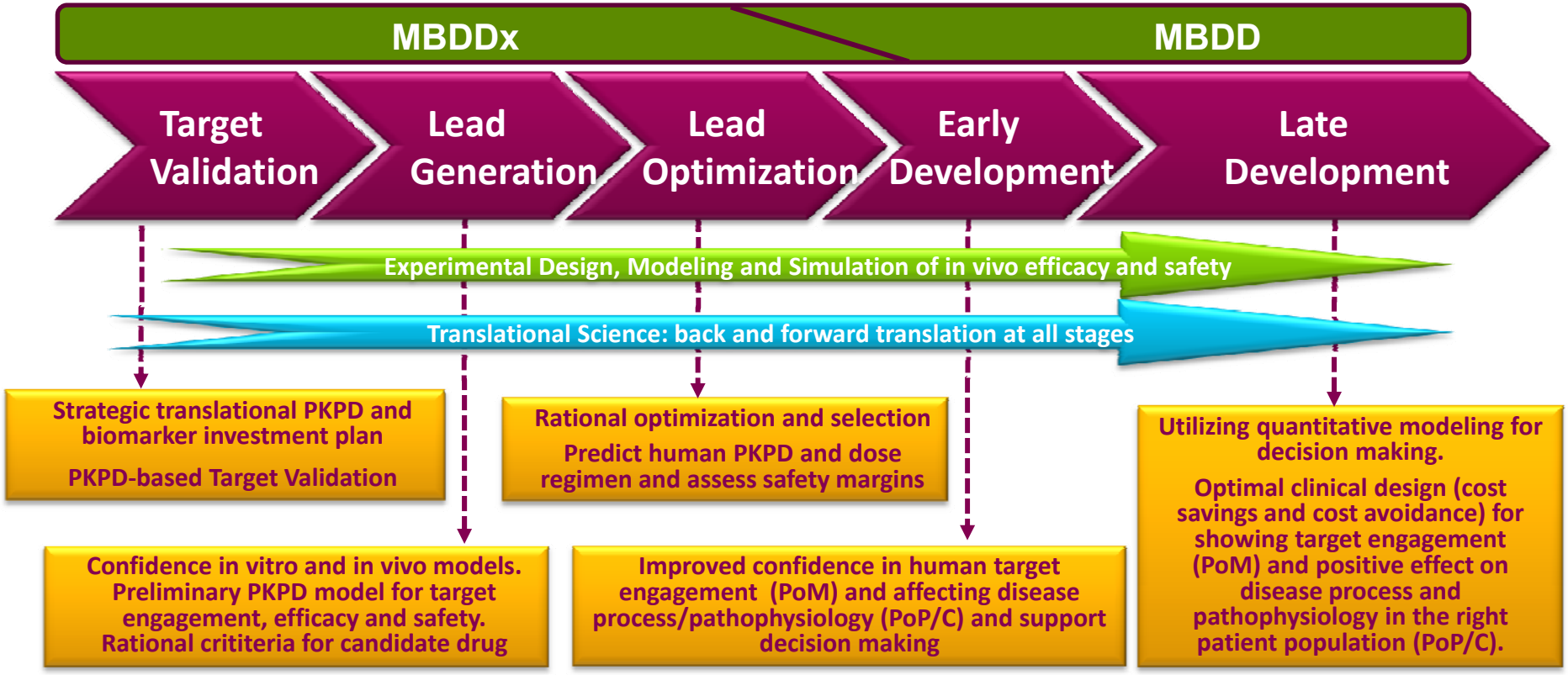
PoP: beneficial effect on targeted disease process or pathophysiology

PoC: beneficial effect on clinical outcome

Adapted from Danhof *et al* Pharmaceutical Research 22(9)1432. 2005

Model Based Drug Dx and Dv Strategy

Aspiration and Benefits of applying Quantitative Pharmacology Strategy along value chain



Case Study:

Mechanism-based Pharmacokinetic-Pharmacodynamic Feedback Model of Thyroid Hormones after Inhibition of Thyroperoxidase in the Dog: Cross-species Prediction of Thyroid Hormone Profiles in Rats and Humans.

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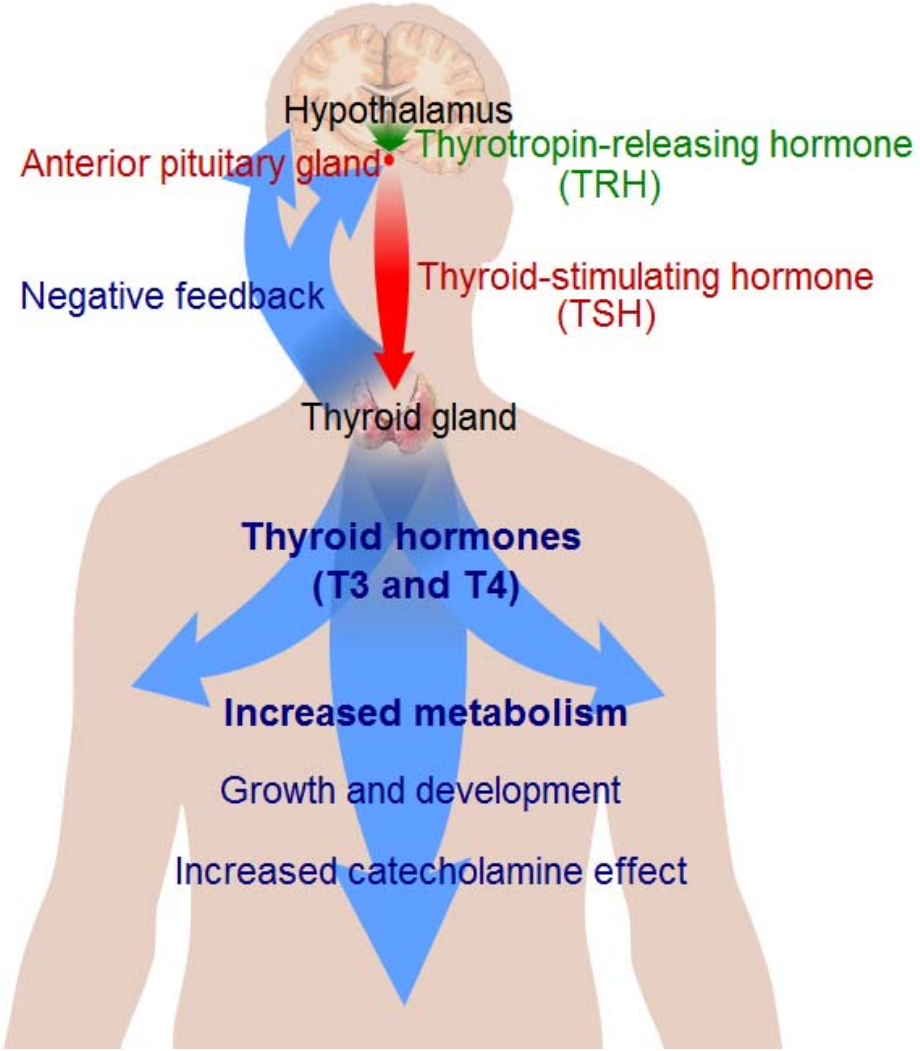
Impact of TPO inhibition on Thyroid Hormones

Thyroperoxidase (TPO) is a key enzyme involved in the synthesis of thyroxine (T4) and triiodothyronine (T3) thyroid hormones. The thyroid hormones T_4 and T_3 play important roles in metabolism, growth and development.

T4 (& T3) inhibit the synthesis of TSH. TRH stimulates the pituitary to produce TSH which stimulates synthesis and secretion of T_4 and T_3. – creating a negative regulatory feedback loop.

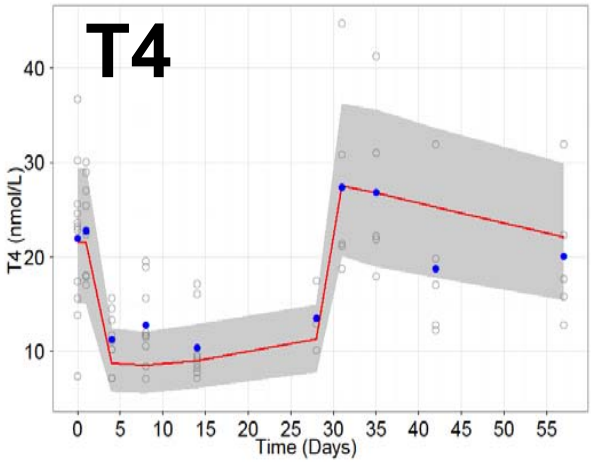
Aim: To create a model to describe how TPO inhibition would impact on the position of homeostasis using data from toxicity studies in dogs.

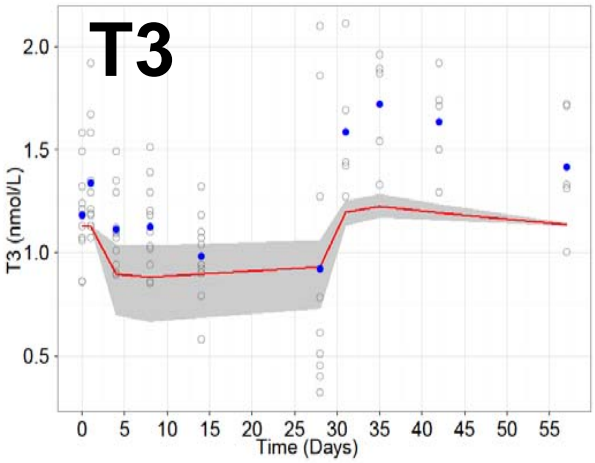


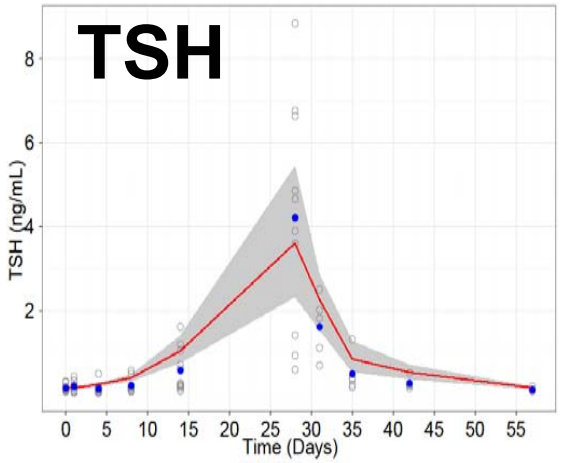
Model development AZD-1
1-month and 6-month dog safety study

Study	Dose groups (M/F) (µmol/kg)	PK and hormone sampling (day)
1 Month (28d)	0, 15, 90, 700	Day: -5, 1, 4, 8 ,14, 28
	0, 700	Day: 31 35, 42, 57
6 Month (27w)	0, 15, 60, 250	Week: -2, -1, 7, 13, 27
	0, 250	Week: 28, 31, 40

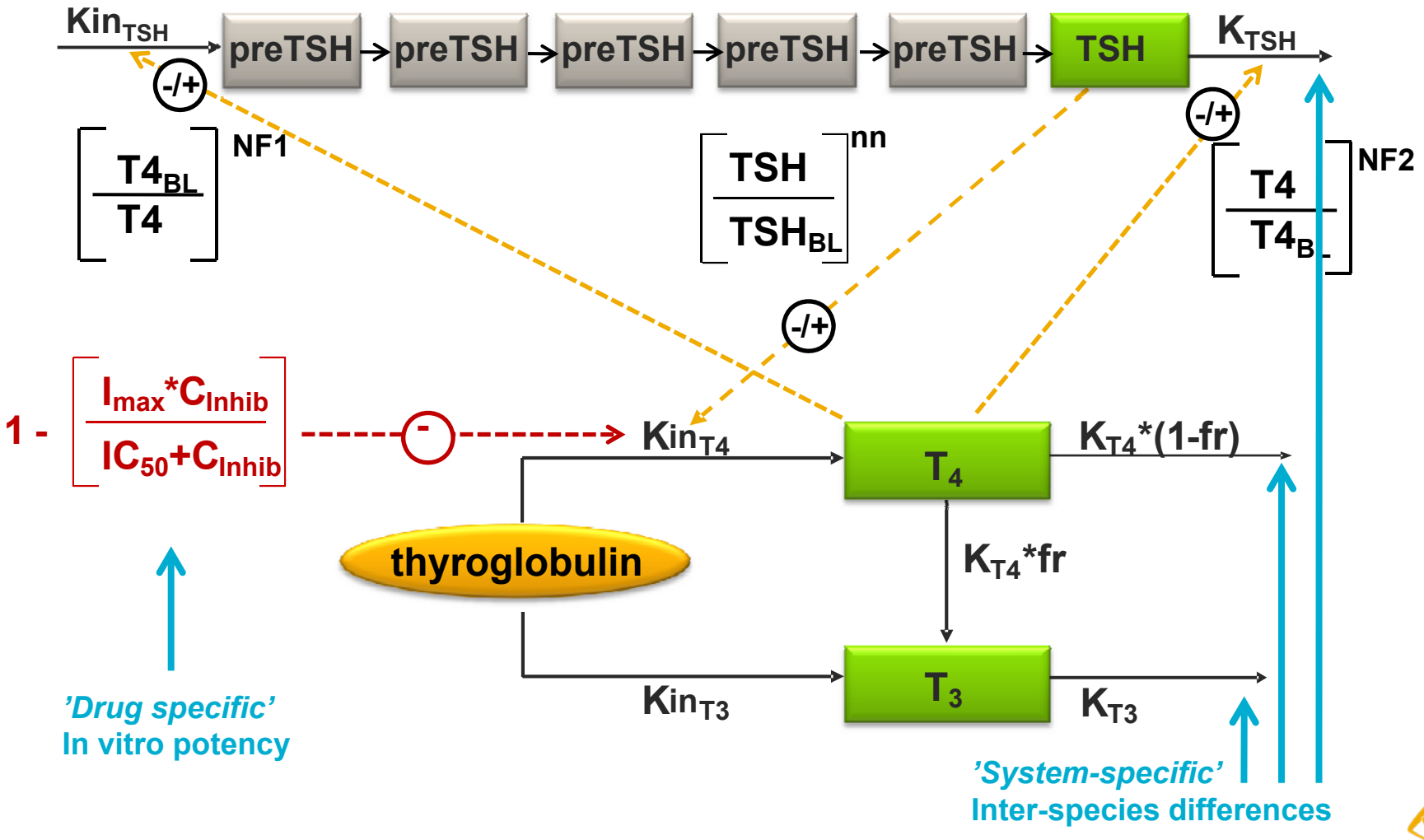
Simultaneous fitting of plasma levels of T_4, T_3 & TSH to characterize onset, intensity and return to baseline (including rebound)







PKPD model of thyroid hormone regulation
drug and system parameters



Validation & Interspecies Translation

Validation:

- Successful prediction of T4, T3 and TSH profiles in dogs after 1-month dosing of AZD-2 based on *in-vitro* IC_{50} for TPO inhibition and PK profile and model system parameter estimates from AZD-1 analysis.

Cross-species translation:

- Adjust rate-constants for known species differences in hormone half-lives & adjust in vivo IC50 for measured species differences in in vitro IC50 assays

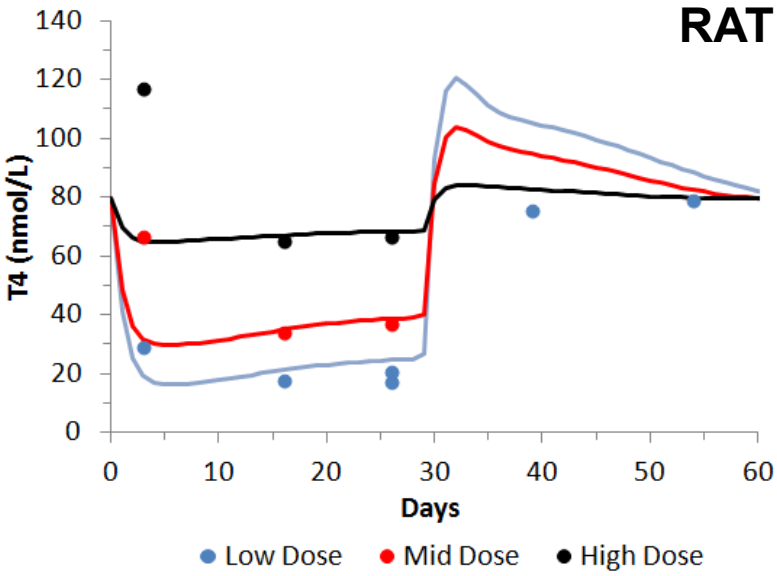
Species	T_4, half-life	T_3, half-life	% T_3 derived from peripheral conversion of T_4
Man	7 days [1]	1 day [1]	72 [2]
Rat	21 hrs [3]	6 hrs [3]	65 [4]
Dog	14-16 hrs [5]	5-6 hrs [5]	37 [6]

[1] Eisenberg et al., 2010: Thyroid, 20: 1215-1228
[2] Nicoloff et al., 1972: J. Clin. Investigations, 51: 473-483
[3] Bianchi et al., 1983: J. Clin. Endocrinology, 56: 1152-1163
[4] Taroura et al., 1991: Fd Chem. Tox., 29: 595-599
[5] Kinlaw et al., 1985: J. Clin. Investigations, 75: 1238-1241
[6] Maddison, J.E. & Page S.W., 'Small Animal Clinical Pharmacology; p499

Prediction of rat hormone levels
Revising safety screening cascade

Interspecies extrapolation

- Accurate prediction of thyroid hormone levels in 1-month rat safety study - both in terms of absolute levels and time to steady state



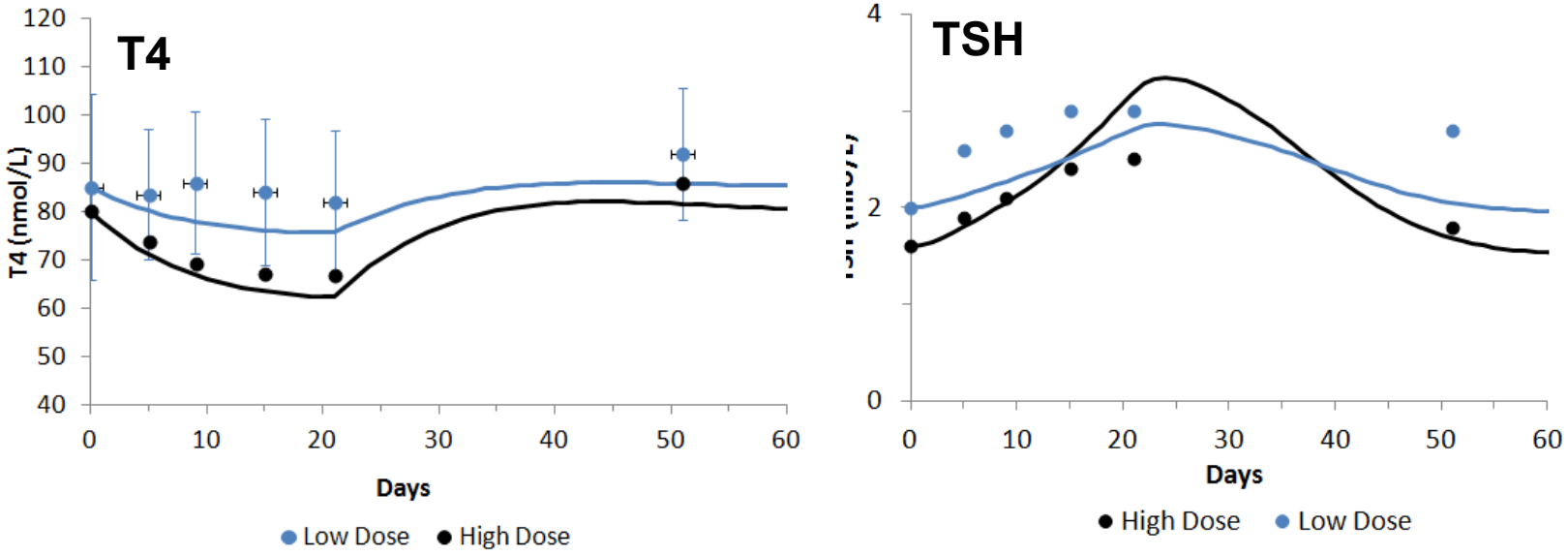
in-vitro/in-vivo correlation

- Cross-compound correlation established relating *in-vivo* IC_{50} to *in-vitro* IC_{50} based on series of 3-day rat safety studies

- Prediction of thyroid hormone levels in rat based on *in-vitro* TPO inhibition data -> reduced the need for *in vivo* safety screening of new drug candidates

Translation to man

Predicting T4 and TSH after 21 days MAD with AZD-1



Translation to man

– **Model predicts minor effects in human 21 day safety – consistent with small (non-significant) effects observed**

– **Builds confidence in ability to extrapolate pre-clinical safety results**

Concluding remarks

Key learnings

The proposed mechanism-based PKPD feedback model provides a scientific basis for the prediction of TPO inhibition mediated effects on plasma thyroid hormones levels in humans based on results obtained in vitro and animals studies..

Benefits to Discovery Pre-clinical safety studies can predict effects in man, which improves screening and selection of drug candidates. In vitro-vivo correlations reduce the in vivo safety screening needs (saving animals and $)

Benefits to Development Predicted timescale of anticipated T_4 effects allowed MAD for AZD-2 to proceed as planned without costly time delays. The model is currently used guiding dose selection and study design for Phase 2 studies by prediction the safety profile of AZD-2.

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