10th Annual Neurodegenerative Drug Development Summit

How Regulatory-Ready Biosimulation is Revolutionizing Neurodegenerative Disease Development

Piet van der Graaf

Senior Vice President Certara

Professor of Systems Pharmacology

Boston, 29th March 2022

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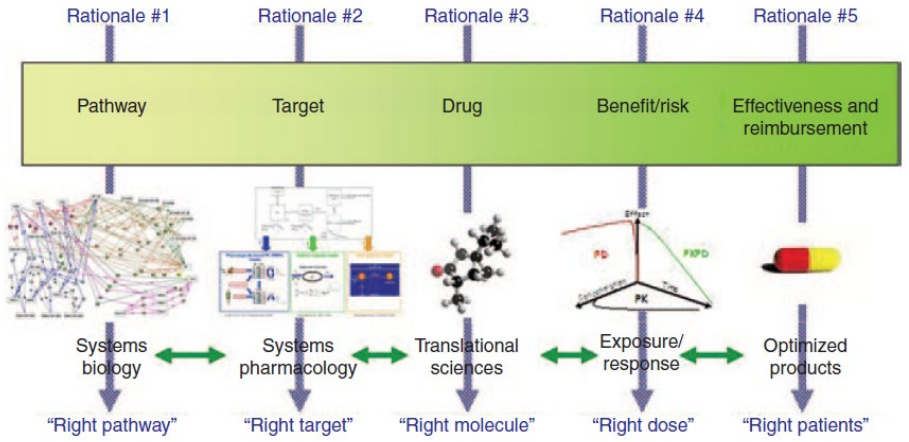
Agenda

- Definition of biosimulation and how global regulators are actively encouraging its use in drug development
- Use of biosimulation to inform, reduce and eliminate preclinical and clinical studies
- Biosimulation applications in neurodegenerative disease development (NDD)
- Case studies

What is Biosimulation (or Model-informed Drug Development)

- The application of quantitative computer models in drug development to facilitate the decision-making process and advance regulatory acceptance
- Biosimulation is centered on knowledge and inference generated from integrated models of compound, mechanism and disease level data
- There have been hundreds of regulatory applications
- It is increasingly used to inform, reduce and eliminate clinical trials
- Certara is the global leader in biosimulation with 2,000 biopharm, academic and regulatory partners
- Applied across all stages of R&D



doi:10.1038/clpt.2013.54

Biosimulation reduces development time and costs

PERSPECTIVE

Industrial Perspective on the Benefits Realized from the FDA's Model-Informed Drug Development Paired Meeting Pilot Program

- **International Consortium for Innovation and Quality in Pharmaceutical Development (IQ)**
- **19 Case studies (~2/3 pilot programs to date)**
- **Survey of 15 questions**

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Conclusion:

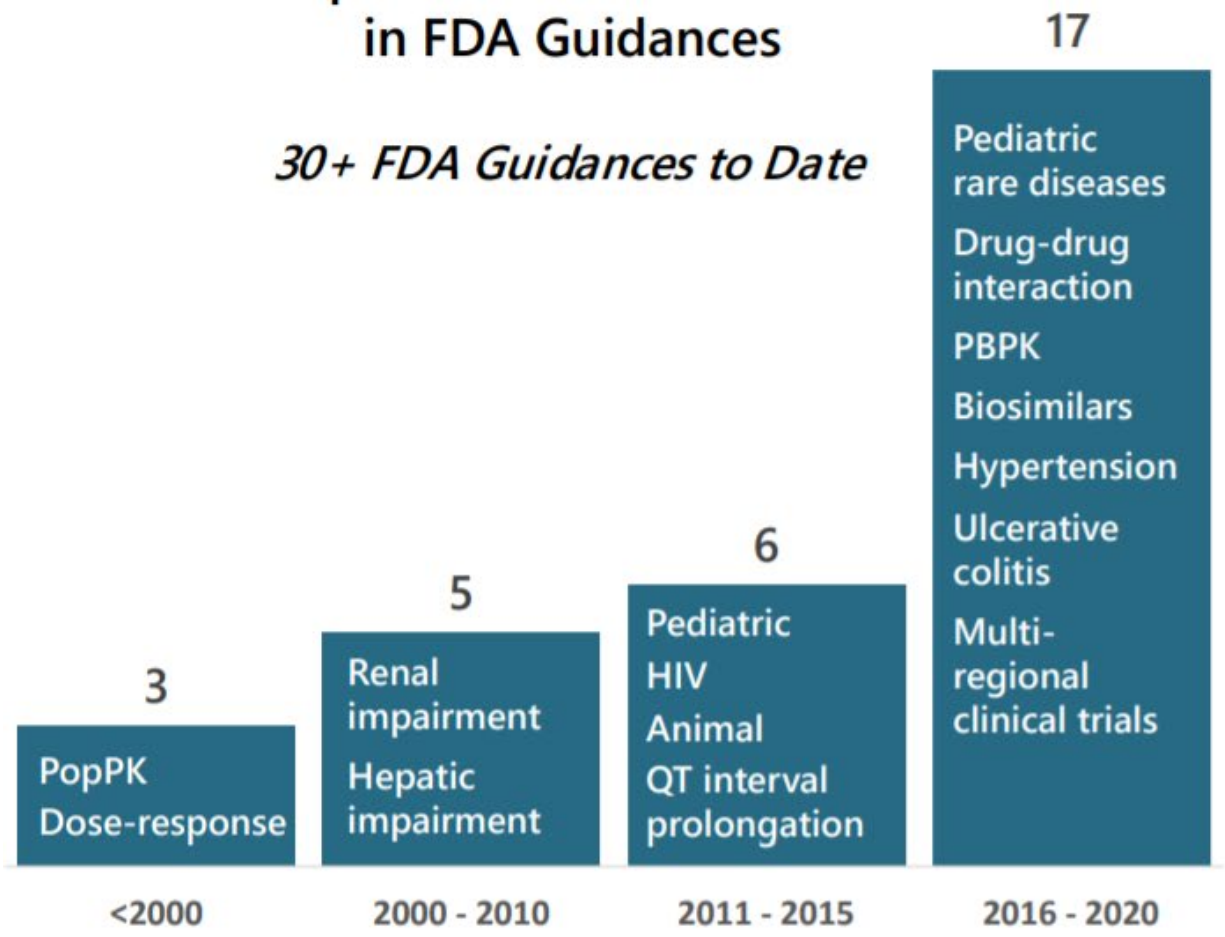
- *The examples from the survey, note significant estimated savings in time, **up to 2 years** for some programs. Additionally, there were substantial savings in resources, **up to $30-70 million** in development costs.*

- *Main mechanisms for time/cost savings:*
  - *Acceleration to go/no go through simulation*
  - *Obviating need for clinical study (i.e. PBPK)*
  - *Reduced group sizes*
  - *Approval based on single pivotal trial*
  - *Getting to right dose faster*
  - *Using less costly biomarkers to demonstrate efficacy through PKPD*

Active Regulatory Adoption and Encouragement

Incorporation of Biosimulation in FDA Guidances

30+ FDA Guidances to Date



2021 FDA Focus Areas of Regulatory Science

Model-informed product development aims to integrate information from diverse data sources to **help decrease uncertainty and lower failure rates, and to develop information that cannot or would not be generated experimentally.**

MIDD applications in the report include:

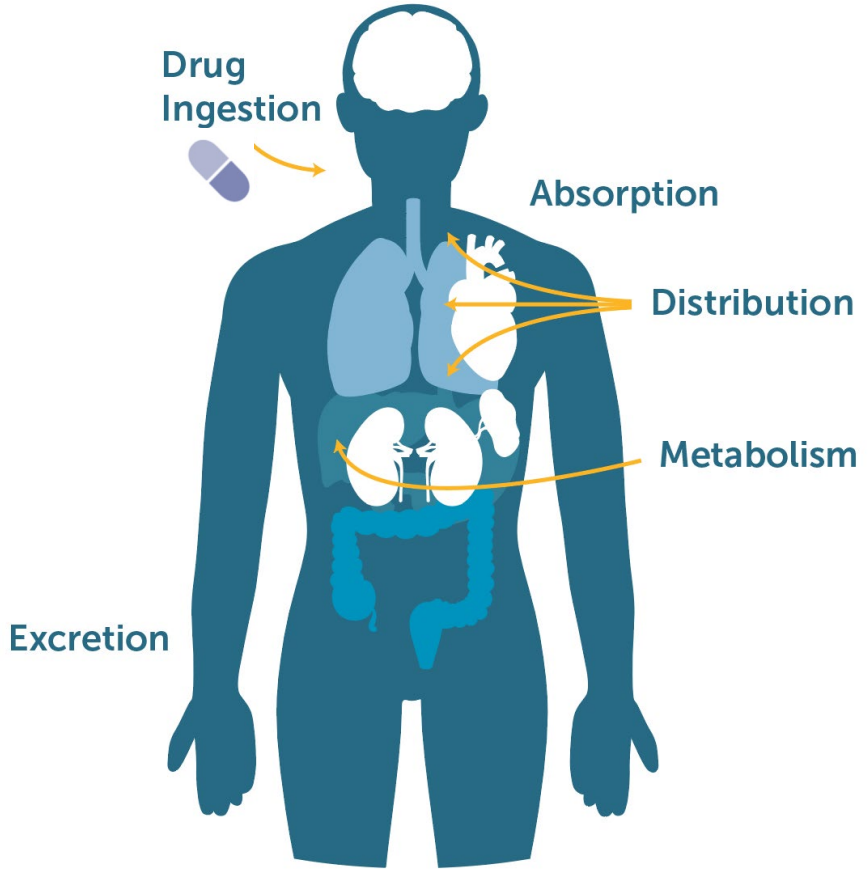
- Predicting clinical outcomes
- Informing trial designs
- Supporting evidence for efficacy
- Optimizing drug dosing
- Predicting product safety

Predictive Modeling - PK

Mechanistic biosimulation is used to quantitatively predict, without human or animal studies…

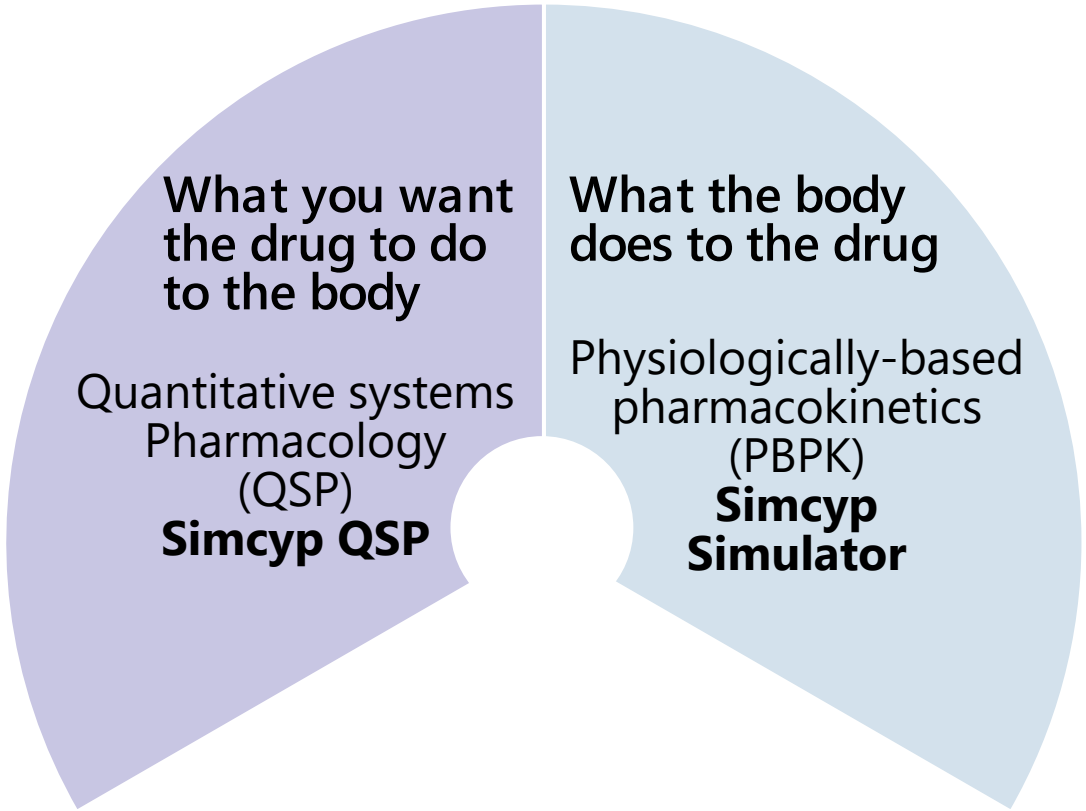
What the body does to the drug

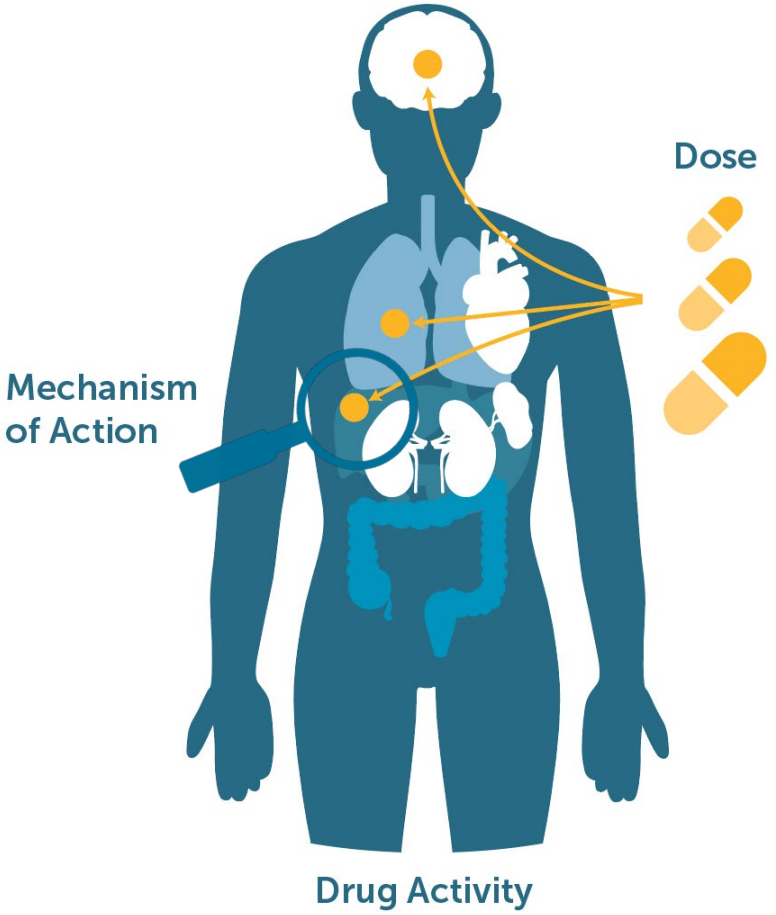
Physiologically-based pharmacokinetics (PBPK)
Simcyp Simulator



Predictive Modeling - PD

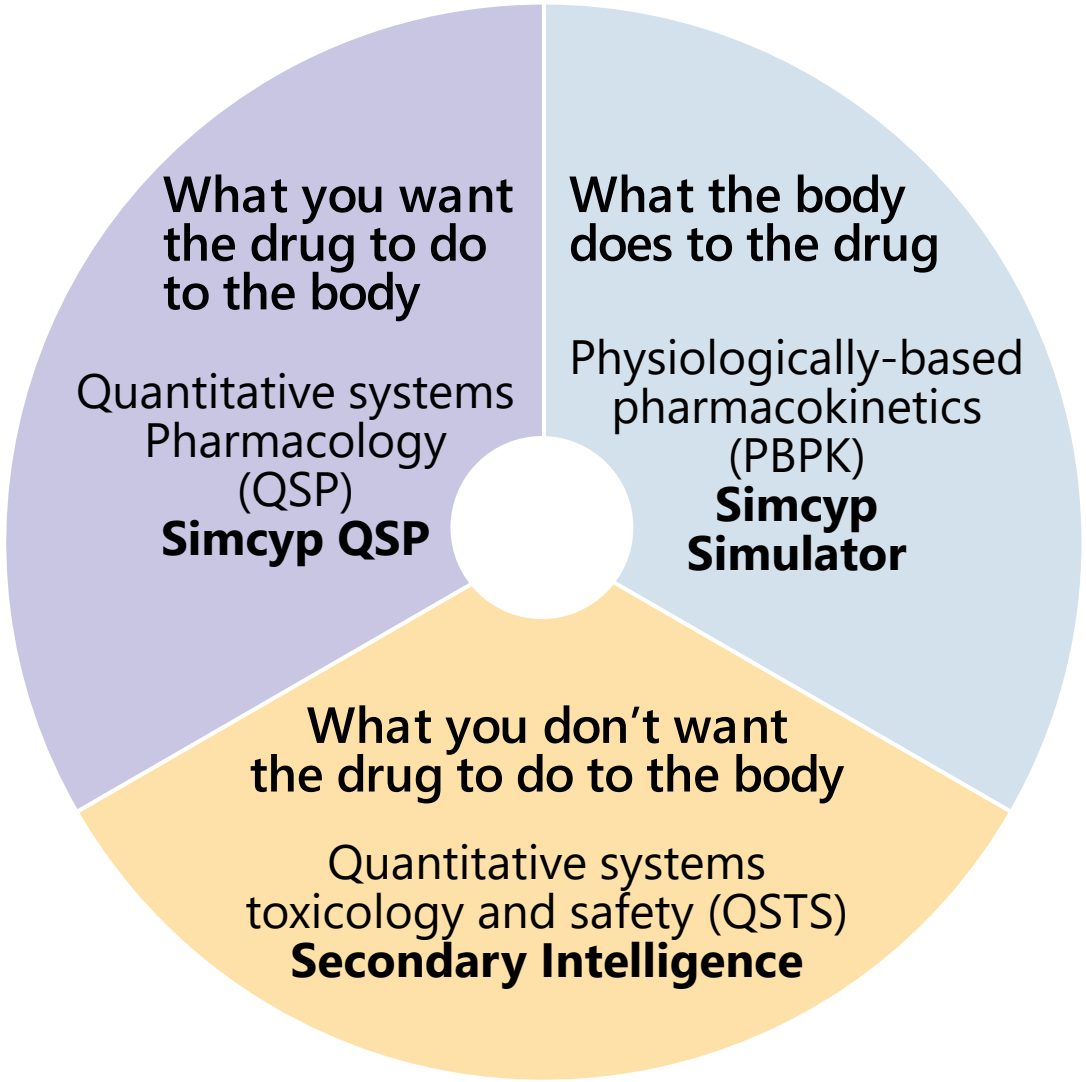
Mechanistic biosimulation is used to quantitatively predict, without human or animal studies…

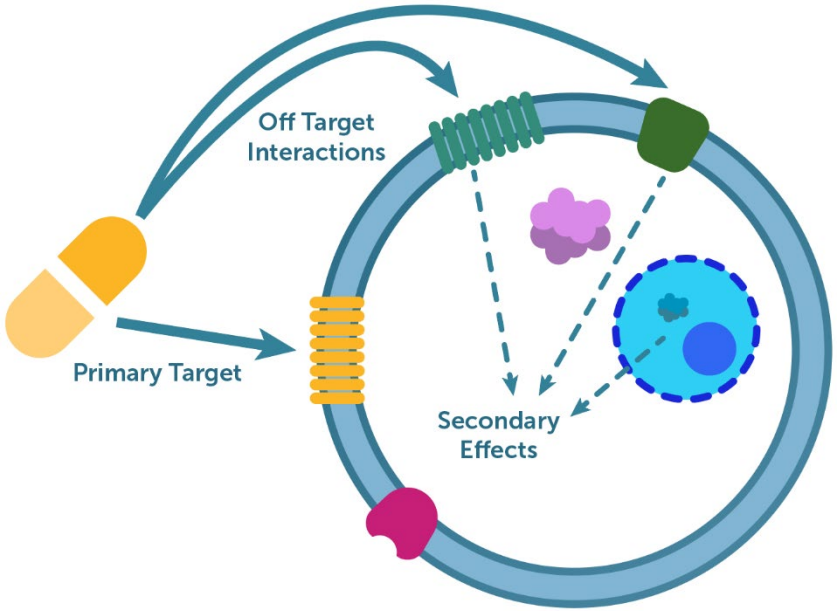




Predictive Modeling - Toxicity

Mechanistic biosimulation is used to quantitatively predict, without human or animal studies…

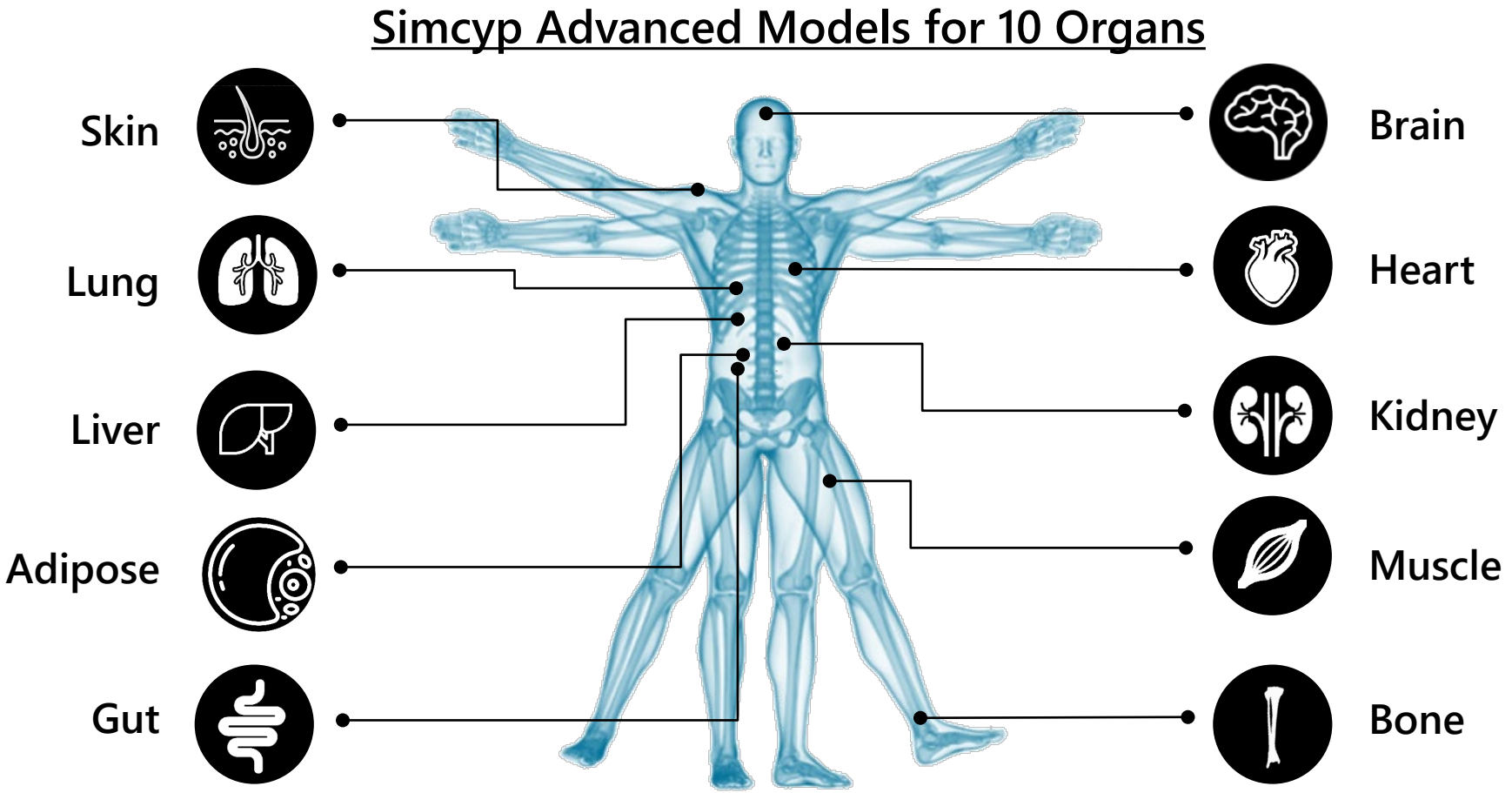




Adapted from Jenkinson et al., 2020

Predictive Power of Biosimulation with Virtual Patients

Biosimulation uses computer-based models of biological systems to predict how the body affects the drug and how the drug affects the body.



3 Areas of Significant Impact of Simcyp Simulator

Clinical Trial Waivers

Extrapolation to Special Populations

Reduction in Study Patients

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Simulating Virtual Patients and Waiving Clinical Studies

More than 275 label claims for 90 novel drugs using the Simcyp Simulator

	**ONCOLOGY**	Agios	Tibsovo *(ivosidenib)*	Genentech	Alecensa *(alectinib)*	Novartis	Odomzo *(sonidegib)*
		Amgen	Blincyto *(blinatumomab)*	Genentech	Cotellic *(cobimetinib)*	Novartis	Piqray *(alpelisib)*
		Ariad	Alunbrig *(brigatinib)*	Genentech	Polivy *(polatuzumab vedotin-piiq)*	Novartis	Rydapt *(midostaurin)*
		Ariad (Takeda)	Iclusig *(ponatinib)*	Genentech	Rozlytrek *(entrectinib)*	Novartis	Tabrecta *(capmatinib)*
		AstraZeneca	Calquence *(acalabrutinib)*	Incyte	Pemazyre *(pemigatinib)*	Novartis	Zykadia *(ceritinib)*
		AstraZeneca	Lynparza *(olaparib)*	Janssen	Balversa *(erdafitinib)*	Pfizer	Bosulif *(bosutinib)*
		AstraZeneca	Tagrisso *(osimertinib)*	Janssen	Erleada *(apalutamide)*	Pfizer	Lorbrena *(lorlatinib)*
		Beigene	Brukinsa *(zanubrutinib)*	Lilly	Retevmo *(selpercatinib)*	Pharmacyclics	Imbruvica *(ibrutinib)*
		BluePrint Medicines	Ayvakit *(avapritinib)*	Lilly	Verzenio *(abemaciclib)*	Sanofi	Jevtana *(cabazitaxel)*
		Celgene	Inrebic *(fedratinib hydrochloride)*	Loxo Oncology	Vitrakvi *(larotrectinib)*	Seattle Genetics	Tukysa *(tucatinib)*
		Daiichi Sankyo	Turalio *(pexidartinib)*	Novartis	Farydak *(panobinostat)*	Spectrum	Beleodaq *(tucatinib)*
		Eisai	Lenvima *(lenvatinib)*	Novartis	Kisqali *(ribociclib succinate)*	Takeda	Exkivity *(mobocertinib)*
		EMD Serono	Tepmetko *(tepotinib hydrochloride)*	Novartis	Scemblix *(asciminib)*	Verastem	Copiktra *(duvelisib)*
	**RARE DISEASE**	AkaRx (Eisai)	Doptelet *(avatrombopag maleate)*	Global Blood Therapeutics	Oxbryta *(voxelotor)*	Novartis	Isturisa *(osilodrostat)*
		AstraZeneca	Koselugo *(selumetinib)*	Intercept	Ocaliva *(obeticholic acid)*	PTC Therapeutics	Emflaza *(deflazacort)*
		Auriana	Lupkynis *(voclosporin)*	Kadman	Rezurock *(belumosudil)*	Sanofi Genzyme	Cerdelga *(eliglustat tartrate)*
		Genentech	Enspryng *(satralizumab)*	Merck	Welireg *(belzutifan)*	Vertex	Symdeko *(tezacaftor/ivacaftor)*
		Genentech	Evrysdi *(risdiplam)*	Mirum	Livmarli *(maralixiba)*	Vertex	Trikafta *(elexacaftor/ivacaftor/tezacaftor)*
	**CENTRAL NERVOUS SYSTEM**	AbbVie	Rinvoq *(upadacitinib)*	Eisai	Dayvigo *(lemborexant)*	Lilly	Reyvow *(lasmiditan succinate)*
		AbbVie	Qulipta *(atogepant)*	GW Research	Epidiolex *(cannabidiol)*	Novartis	Mayzent *(siponimod fumaric acid)*
		Alkermes	Aristada *(aripiprazole lauroxil)*	Janssen	Ponvory *(ponesimod)*	UCB	Briviact *(brivaracetam)*
		Alkermes	Lybalvi *(olanzapine; samidorphan)*	Kyowa Kirin	Nourianz *(istradefylline)*		
	**INFECTIOUS DISEASE**	Gilead	Veklury *(remdesivir)*	Merck	Prevymis *(letermovir)*	Tibotec	Edurant *(rilpivirine)*
		GSK	Dectova *(zanamivir)*	Nabriva	Xenleta *(lefamulin acetate)*	VIIV	Cabenuva Kit *(cabotegravir, rilpivirine)*
		Janssen	Olysio *(simeprevir)*	Novartis	Egaten *(triclabendazole)*		
		Merck	Pifeltro *(doravirine)*				
	GASTROENTEROLOGY	AstraZeneca	Movantik *(naloxegol)*	Shionogi	Symproic *(naldemedine)*	Shire	Motegrity *(prucalopride)*
		Helsinn	Akynzeo *(fosnetupitant/palonosetron)*				
	**CARDIOVASCULAR**	Actelion (J & J)	Opsumit *(macitentan)*	Johnson & Johnson	Xarelto *(rivaroxaban)*	Pfizer	Revatio *(sildenafil)*
	**OTHER**	AbbVie	Orilissa *(elagolix)*	Janssen	Invokana *(canagliflozin)*	Merck	Steglatro *(ertugliflozin)*
		Galderma	Aklief *(trifarotene)*	Lilly	Olumiant *(baricitinib)*	Takeda	Livenicity *(Marubivar)*

Benefits Across the R&D Cycle

Discovery/Nonclinical

- Animal to human extrapolation
- Early formulation assessment
- Early drug interaction risk assessment
- First-in-human dose prediction

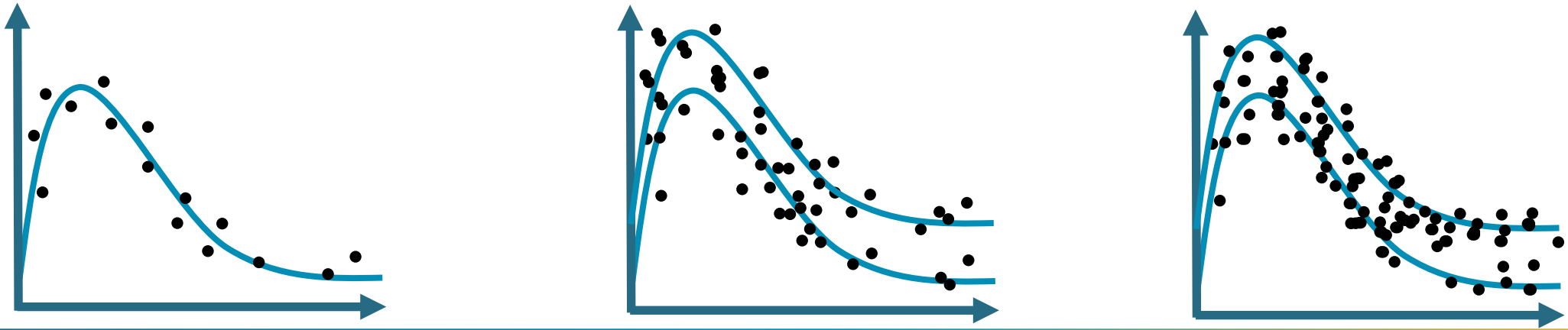
Early Development

- First-in-human single/multiple dose exposure
- Drug-drug interactions
- Absorption, food effect and formulation modelling

Late Development

- Drug-drug interactions
- Pediatric and special populations
- Organ impairment modelling
- Label claims in lieu of clinical study

What is best target and modality in a given pathway, what is optimal indication for our asset, how can we improve effectiveness via combination therapy



"Learn and confirm" with continuous Model Refinement, Verification and Validation

Predicting CNS exposure using mechanistic PBPK models

Journal of Pharmacokinetics and Pharmacodynamics
https://doi.org/10.1007/s10928-021-09776-7

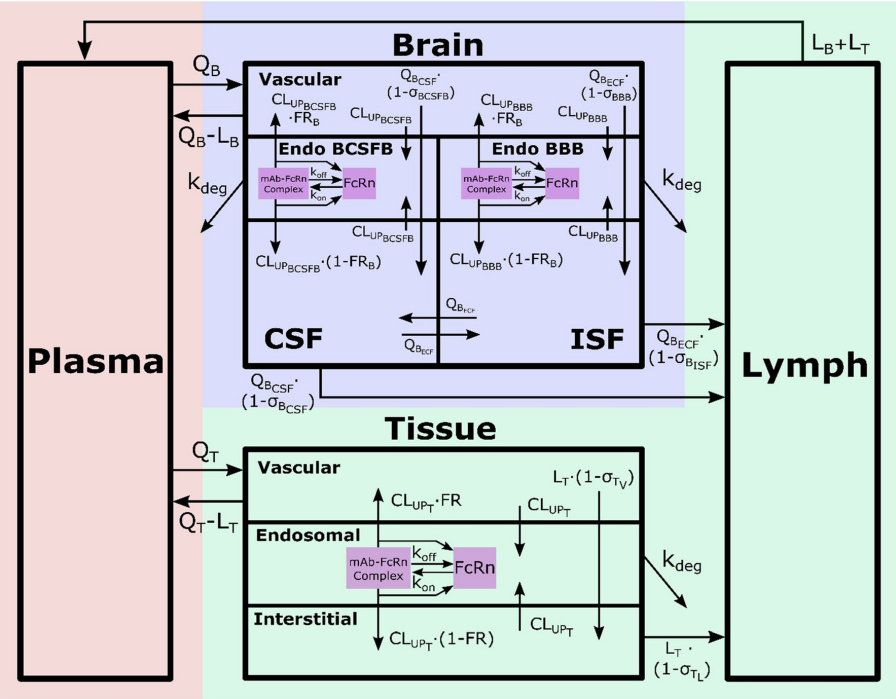
MERCK CERTARA

ORIGINAL PAPER

Minimal brain PBPK model to support the preclinical and clinical development of antibody therapeutics for CNS diseases

Peter Bloomingdale[1] · Suruchi Bakshi[2] · Christian Maass[3] · Eline van Maanen[4] · Cesar Pichardo-Almarza[5] · Daniela Bumbaca Yadav[1] · Piet van der Graaf[6] · Nitin Mehrotra[1]

Received: 8 April 2021 / Accepted: 29 July 2021



Abstract Details

Title: A combined minimal PBPK-target occupancy model predicts clinically observed PK and target occupancy kinetics of anti- α-Syn antibodies in plasma and CSF.

Authors: Jonna Petzold - *Certara and Kings College London, United Kingdom*; Suruchi Bakshi - *Certara*; Cesar Pichardo-Almarza - *Certara*

Session: Poster Live - Neuropharmacology - Online, Worldwide, 07/09/2021, 12:30 - 13:15

Applications:

- Translational research
- FIH dose predictions
- Complex biologicals
- Shuttle antibodies
- Clinical development: link to CNS biomarkers
- Bridge to special populations (i.e. pediatrics)

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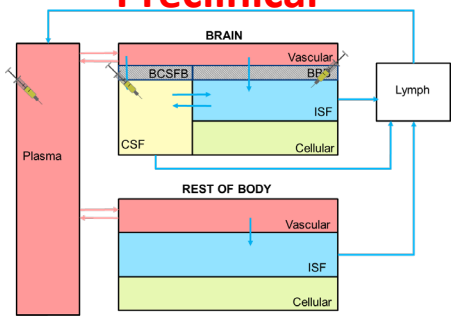
PBPK to Guide Translation in CNS Drug Development

Physiological Data

(Specific to species, population or individual)

- CSF/ISF production rate
- CSF/ISF volume
- Brain vascular volume
- Total brain volume
- Surface area of the BBB
- Surface area of the BCSF barrier
- Body weight, height, age

Preclinical



Mouse

Rat

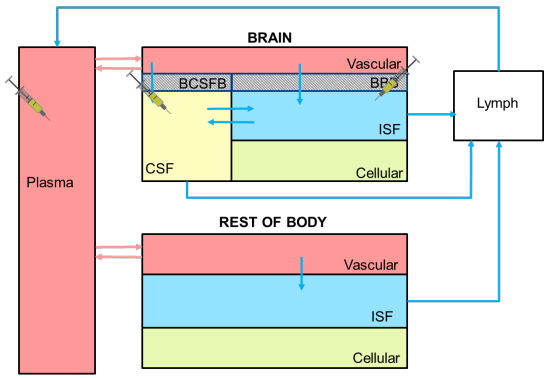
NHP

Translation

Drug Data

- Hydrodynamic radius: size dependent distribution via convection and diffusion
- Receptor mediated transport processes
- Routes of Administration

Clinical



Virtual patient e.g. neonates, children.

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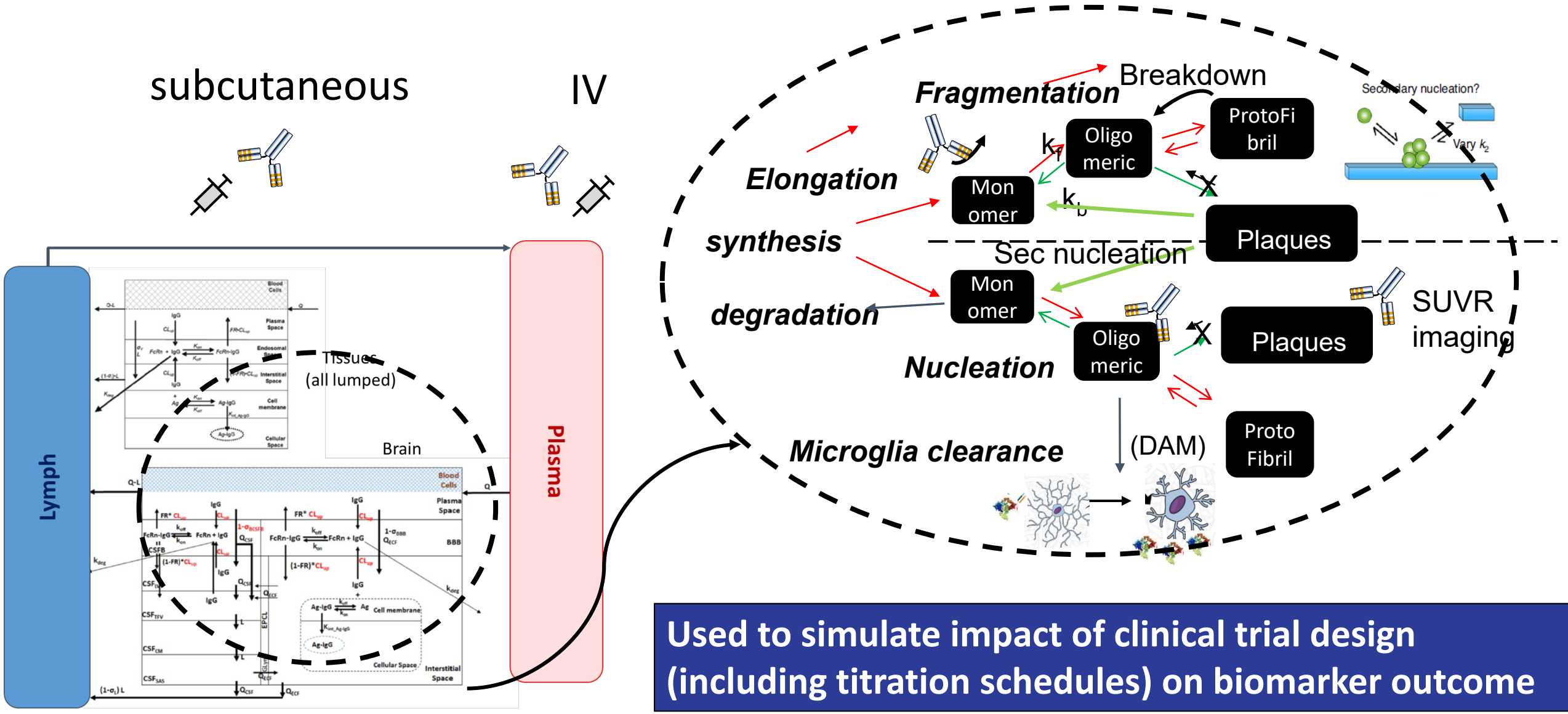
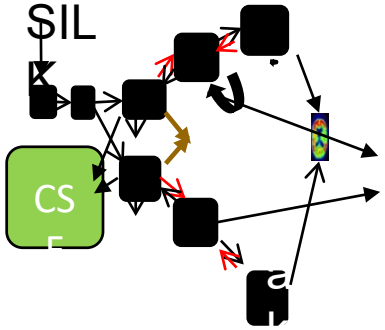
Coupling PBPK model to Amyloid Aggregation QSP Platform



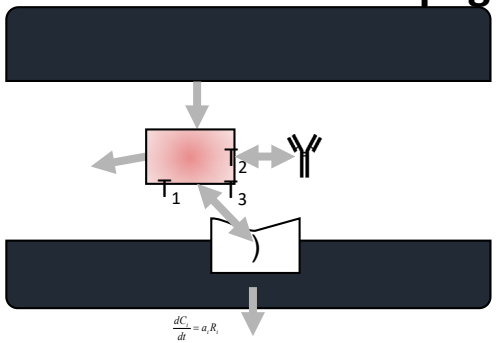
Used to simulate impact of clinical trial design (including titration schedules) on biomarker outcome

Certara's Neuro QSP Platform

Protein Aggregation



Proteostasis and Propagation



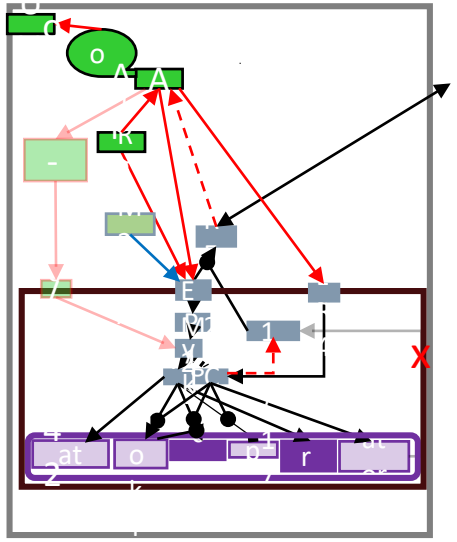
Internalization

Axon Terminal

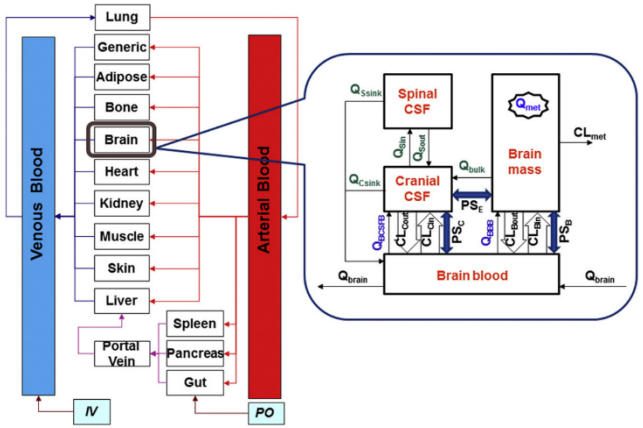
Pathology Progression

Impact on pathology

neuroinflammation



Biomarker



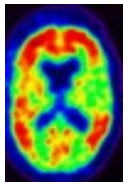
Therapies

Biomarkers

CSF marker

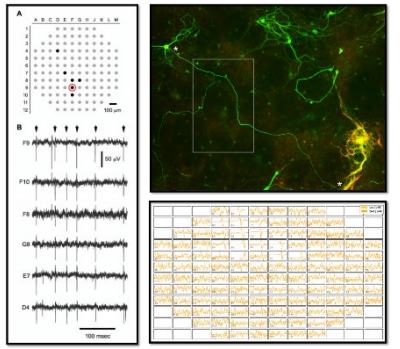
Plasma marker

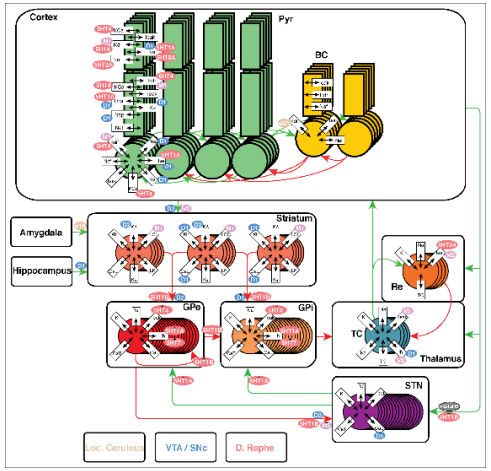
Imaging



Neuronal Functioning

Regulatory accepted clinical scales





Disease Indication

- Alzheimer's *
- Tauopathies
- Parkinson's *
- Huntington's *
- ALS

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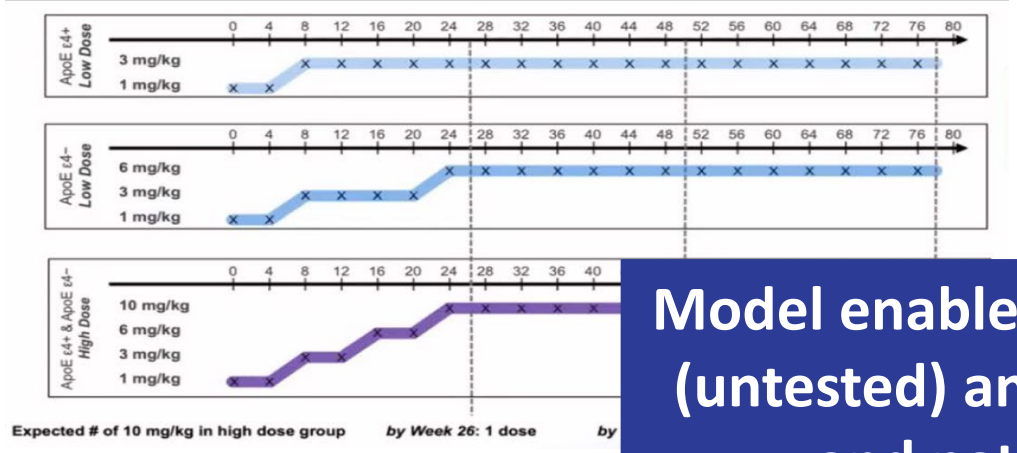
Amyloid Aggregation Model – SUVr Biomarker

Aducanumab Phase 3 trial titration schedule

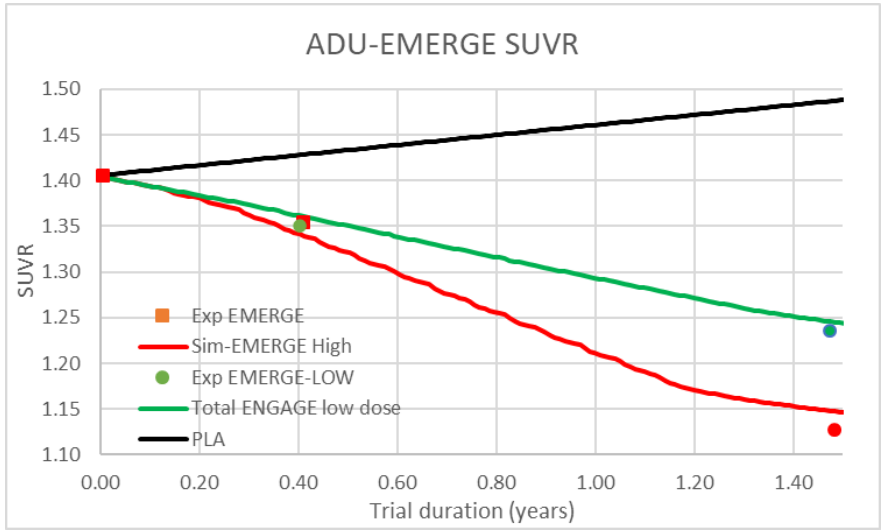


Amyloid antibody affinities for different peptides

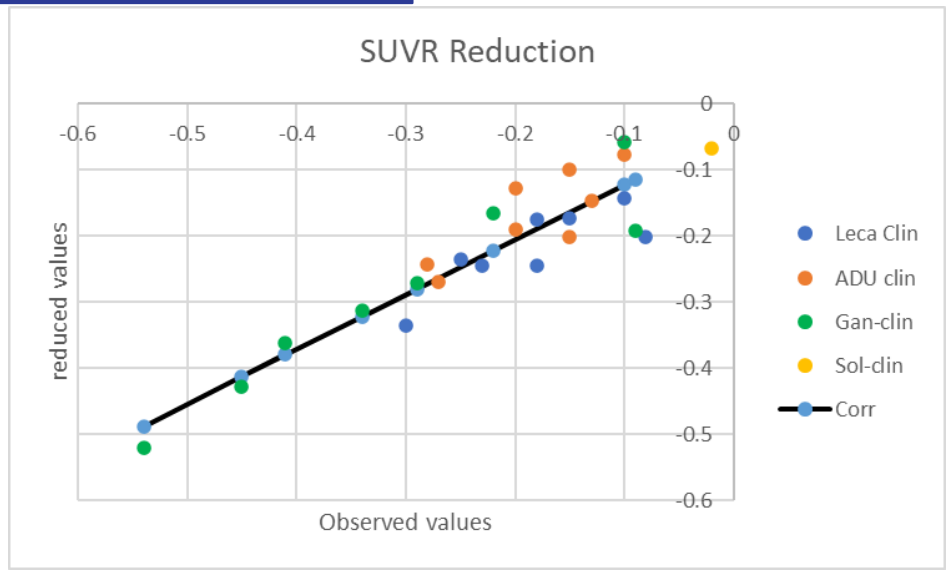
	Aβ Species			
Antibody	**Monomer**	**Aggregate (Oligomer, Protofibril)**	**Fibril**	**Ratio (Preference for Aggregate over Monomer)**
Solanezumab	~2 nM	Low	0	Intermediate
Bapineuzumab	2.3 nM	Similar	Similar	~1
		Similar to fibril	35 nM	7.1
		1.2 nM	0.6 nM	14.2
		~0.93 nM[b]	6.82 nM	>4000
		92 nM[b]	31.2 nM	>50

Model enables extrapolation to new (untested) antibodies, trial designs and patient populations

Aducanumab Phase 3 t…



… different antibodies



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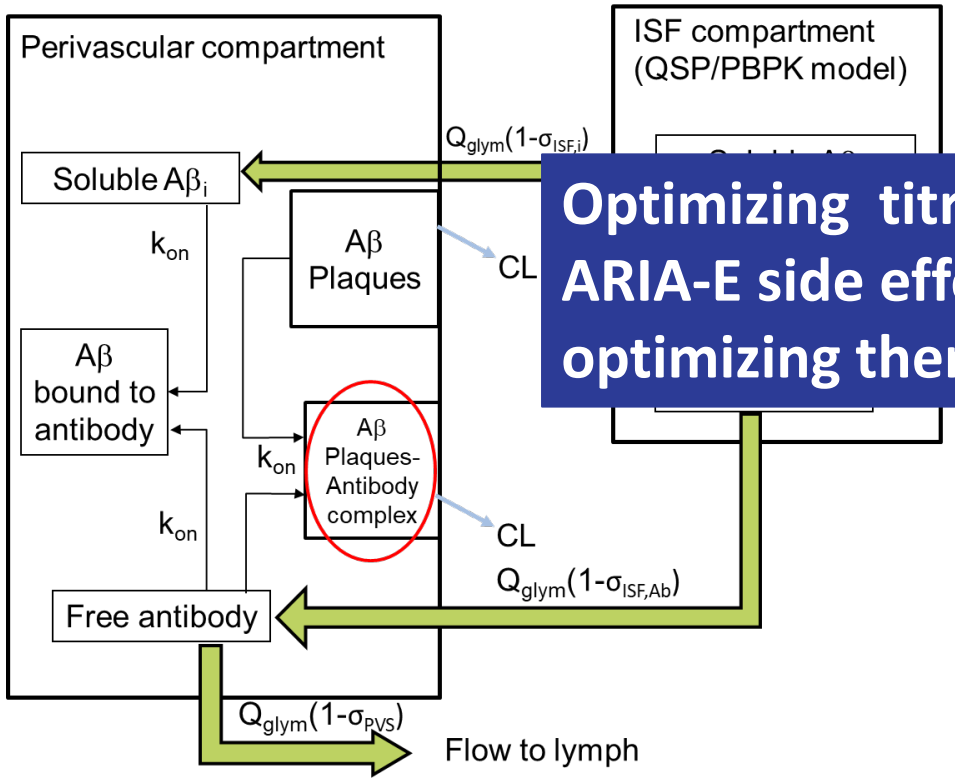
ARIA-E Implementation and Qualification

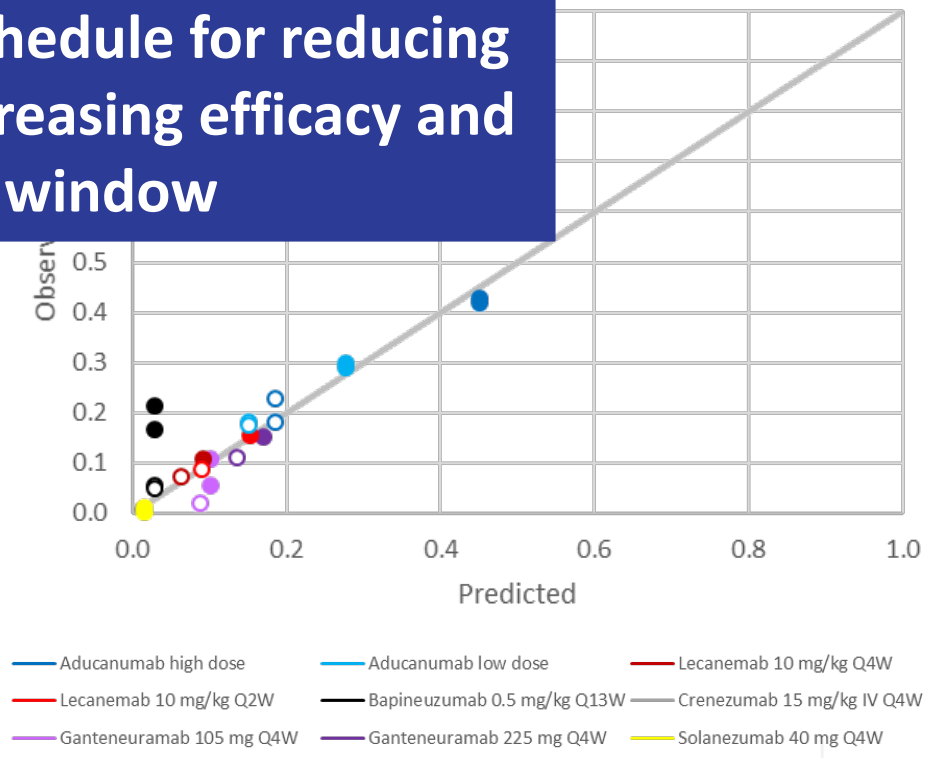
- Major side-effect of amyloid therapeutics limiting market uptak
- Most are asymptomatic, but in a few cases can cause seizures and even death
- Can be mitigated by titration

Perivascular QSP Model



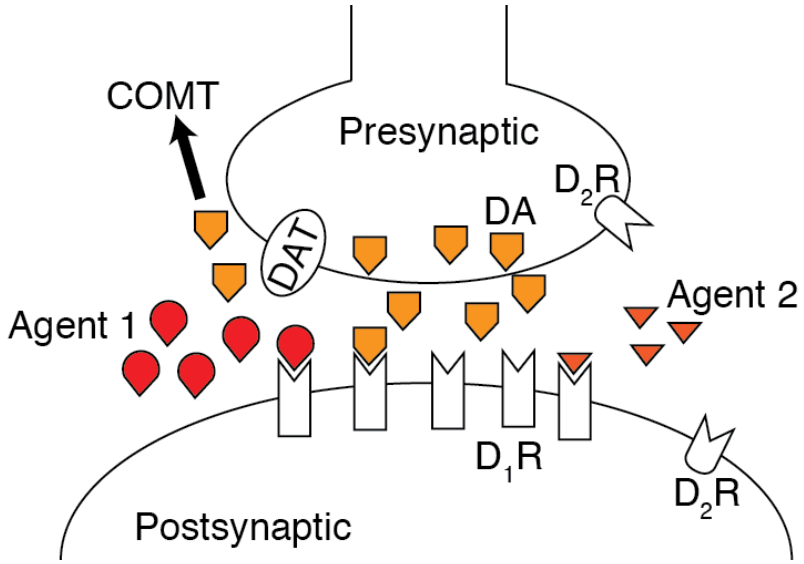
Optimizing titration schedule for reducing ARIA-E side effects, increasing efficacy and optimizing therapeutic window

Calibration with different antibodies

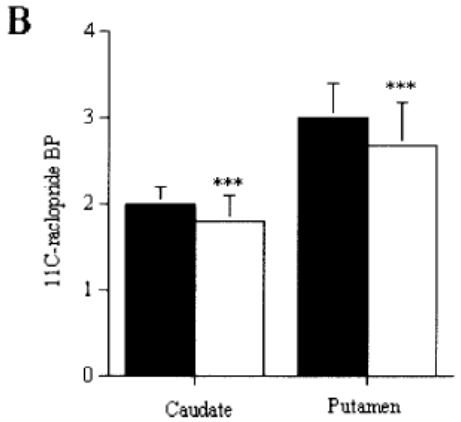


Target Engagement in Parkinson's Disease with PET imaging

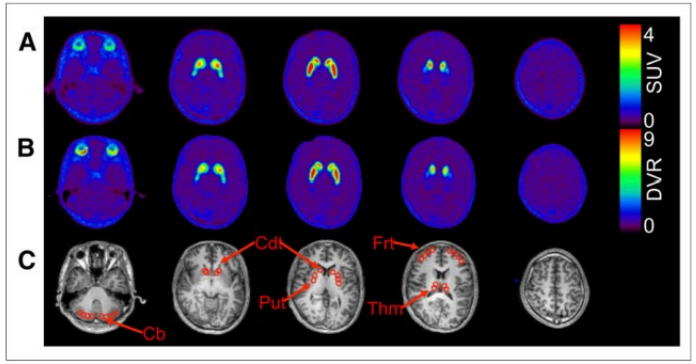
QSP Model of Dopaminergic synapse



Detailed QSP modeling of synaptic physiology and binding of neurotransmitter, drugs and tracer with appropriate affinities



^{11}C-raclopride displacement after L-DOPA treatment estimates brain L-DOPA concentration (Paveese 2006)

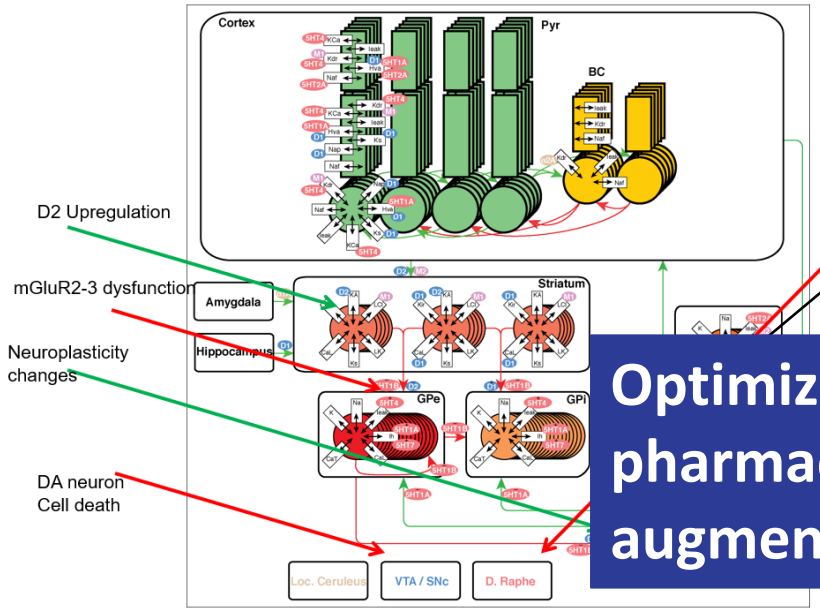


^{11}C-preladenant reports on binding to adenosine A2A receptors (Sakata 2017)

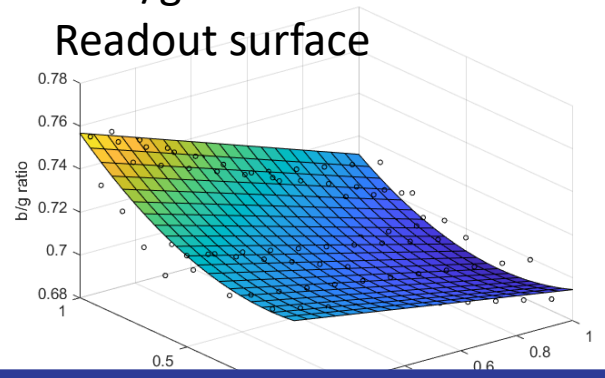
Model used to estimate target exposure and engagement, and to predict patient-patient variablitiy

Clinical Time-OFF in Parkinson's Disease

Parkinson's Disease QSP Model



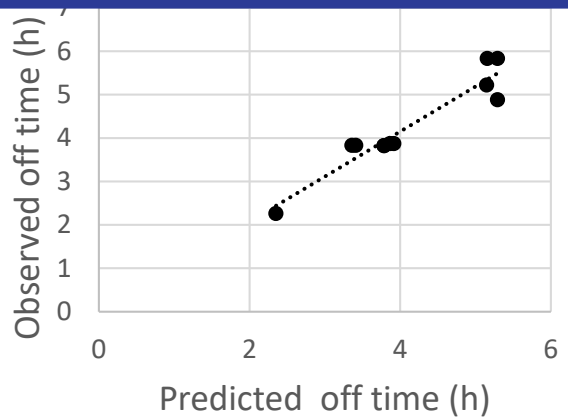
Beta/gamma Power Readout surface

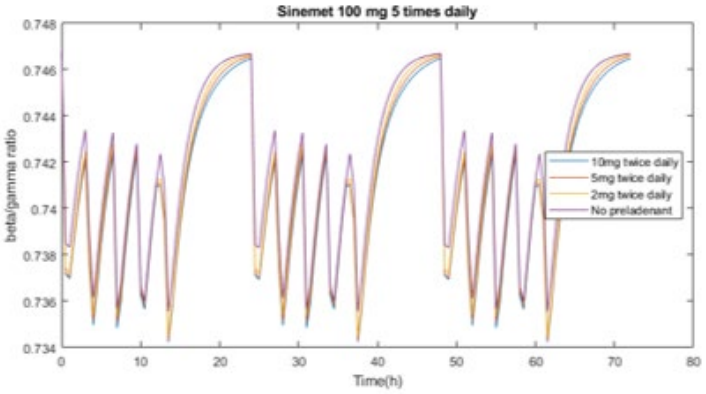


State diagram relating DA deficit (pathology& L-DOPA treatment) and A2A mediated D2R coupling to beta/gamma power readout

Optimizing A2A antagonist PK profile and pharmacology for decreasing Time-OFF in augmentation to standard-of-care treatment

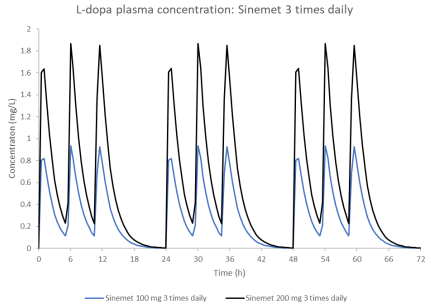
Preladenant augmentation therapy



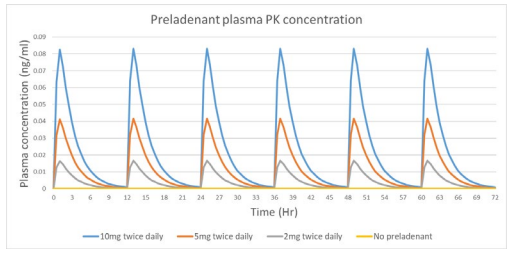


Mechanism-based PK-PD coupling

L-DOPA PK



Preladenant PK



Case study: α-Synuclein modulators for PD

Are all α-Synuclein modulators are equal?

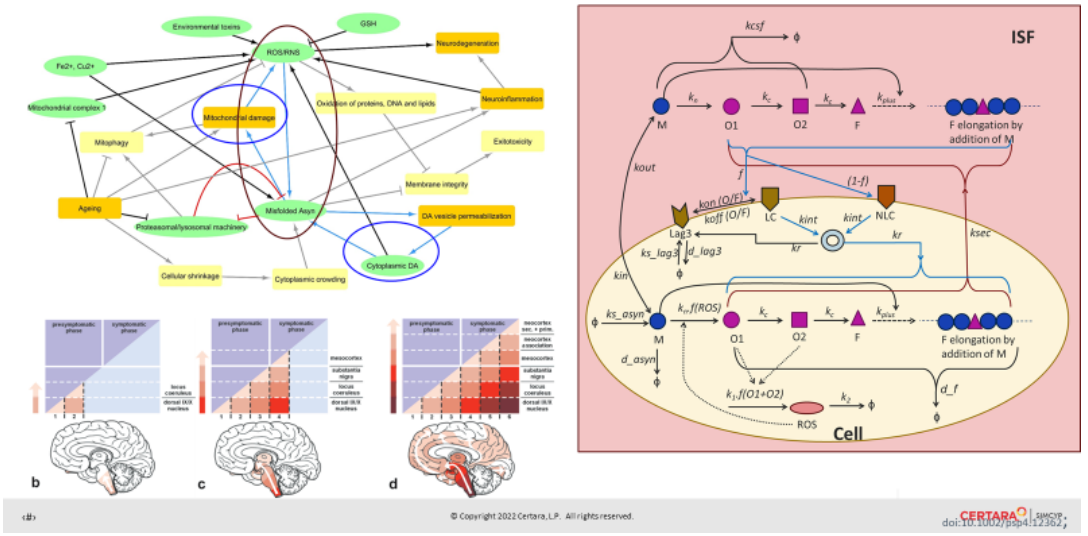
Table 1. Drug-based clinical trials targeting α-synuclein accumulation directly or indirectly.

	Molecule	Mechanism	Clinical Trial Phase	Year	Location of Trial	Reference
Immunotherapy	PRX002	Monoclonal antibody targeting C-terminal sequence of α-syn (amino acids 118–126)	1 (healthy volunteers)	2016	United States	NCT02095171 [190]
			1 (healthy volunteers and PD patients)	2017	United States	NCT02157714 [191]
			2 (PD patients)	Active	United States	NCT03100149
	MEDI1341	Monoclonal antibody targeting C-terminal sequence of α-syn	1 (healthy volunteers)	Recruiting	United States, United Kingdom	NCT03272165
	BIIB054	Monoclonal antibody targeting N-terminal aggregated forms of α-syn	1 (healthy volunteers and PD patients)	2018	United States	NCT02459886 [198]
			2 (PD patients)	Recruiting	United States, Japan	NCT03318523 NCT03716570
	BAN0805	Antibody targeting protofibrils of α-syn	1 (healthy volunteers)	Recruiting	United States	NCT04127695
	PD01/PD03 Affitopes	Vaccines targeting the C-terminal sequence of α-syn via small peptides	1 and 2 (healthy volunteers and PD patients)	2018	Austria	NCT01568099 NCT02216188
Clearance	Nilotinib	Tyrosine kinase Abelson (cAbl) inhibitor	1 (PD, PDD and DLB patients)	2016	United States	NCT02281474 [329]
			2 (PD patients)	2019	United States	NCT02954978 [330]
	Ambroxol	Pharmacological chaperone of β-glucocerebrosidase	2 (PDD patients)	Recruiting	Canada	NCT02914366 [348]
			2 (PD patients)	2020	United Kingdom	NCT02941822 [349]
Small molecules	ANLE138B	Small molecule targeting oligomeric forms of α-syn	1 (healthy volunteers)	Recruiting	United Kingdom	NCT04208152
	NPT200-11	Small molecule targeting the C-terminal region of α-syn	1 (healthy volunteers)	2016	United States	NCT02606682
Anti-oxidants	CoQ10 + Vitamin E	Antioxidant activity	3 (early PD patients)	2013	United States	NCT00740714
Metals	Deferiprone	Chelation of iron	1 (PD patients)	2012	France	NCT00943748 [434]
			2 (PD patients)	2019, Recruiting	France, Canada, Austria	NCT02728843 NCT02655315

Abbreviations: α-syn, α-synuclein; PD, Parkinson's Disease; DLB, Dementia with Lewy Bodies; PDD, Parkinson's Disease Dementia.

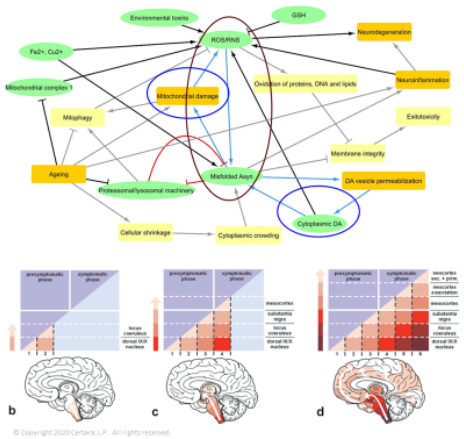
Biomolecules **2020**, *10*, 391; doi:10.3390/biom10030391

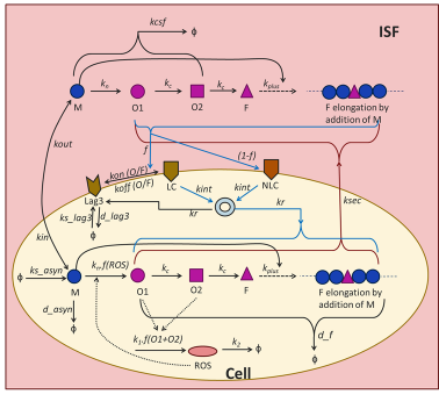
QSP model of PD pathogenesis and propagation



From Model to Virtual Patient

QSP model of PD pathogenesis and propagation

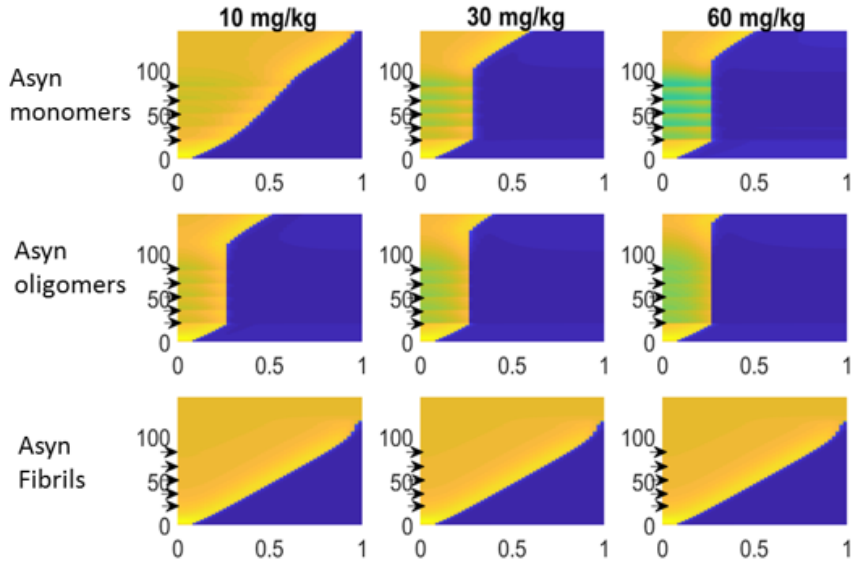


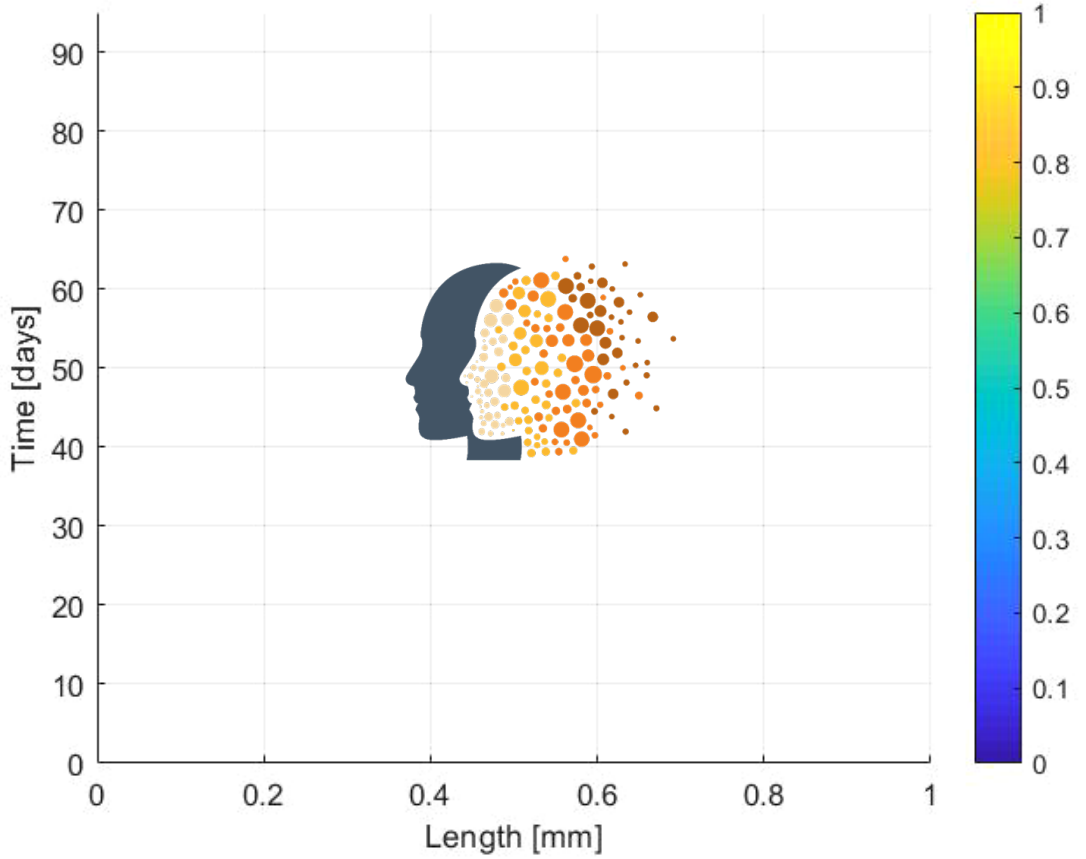


REVIEW

Mathematical Biology Models of Parkinson's Disease

doi:10.1002/psp4.12362





Virtual *versus* Actual Patients

Molecule	**prasinezumab** (anti-αSynuclein, RG7935, PRX002)
Indication	**Parkinson's disease**
Phase/study	**Phase II PASADENA**
# of patients	N=316
Design	• Randomized, double-blind, placebo-controlled study to evaluate the efficacy of prasinezumab in participants with early PD (52 weeks (Part 1) plus a 52-week blinded extension (Part 2))
Primary endpoint	• Change from baseline in Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) total score (sum of Parts I, II, and III) at week 52
Status	• Study did not meet its primary objective, but showed signals of efficacy • Roche is evaluating data to determine next steps • The 52-week blinded extension (Part 2) is ongoing
CT Identifier	NCT03100149
Collaborator	Prothena

Phase 2 study of BIIB054 in Parkinson's disease did not achieve proof-of-concept

- Study did not meet primary or secondary endpoints
- Biogen has discontinued development of BIIB054 and will apply learnings to future efforts in Parkinson's disease

Target	Prasinezumab[1]	BIIB054[2]	MEDI1341
αSyn monomers	20 nM	400 nM	**74 pM**
αSyn oligomers	?	?	
	48pM for aggregates		78 pM for aggregates
αSyn fibrils	?	**0.5 nM**	

Model-predicted efficacy:

MEDI 1341 > Prasinezumab > BIIB054

[1]Jankovich *et al.* 2018

[2] Weihofen *et al.* 2015

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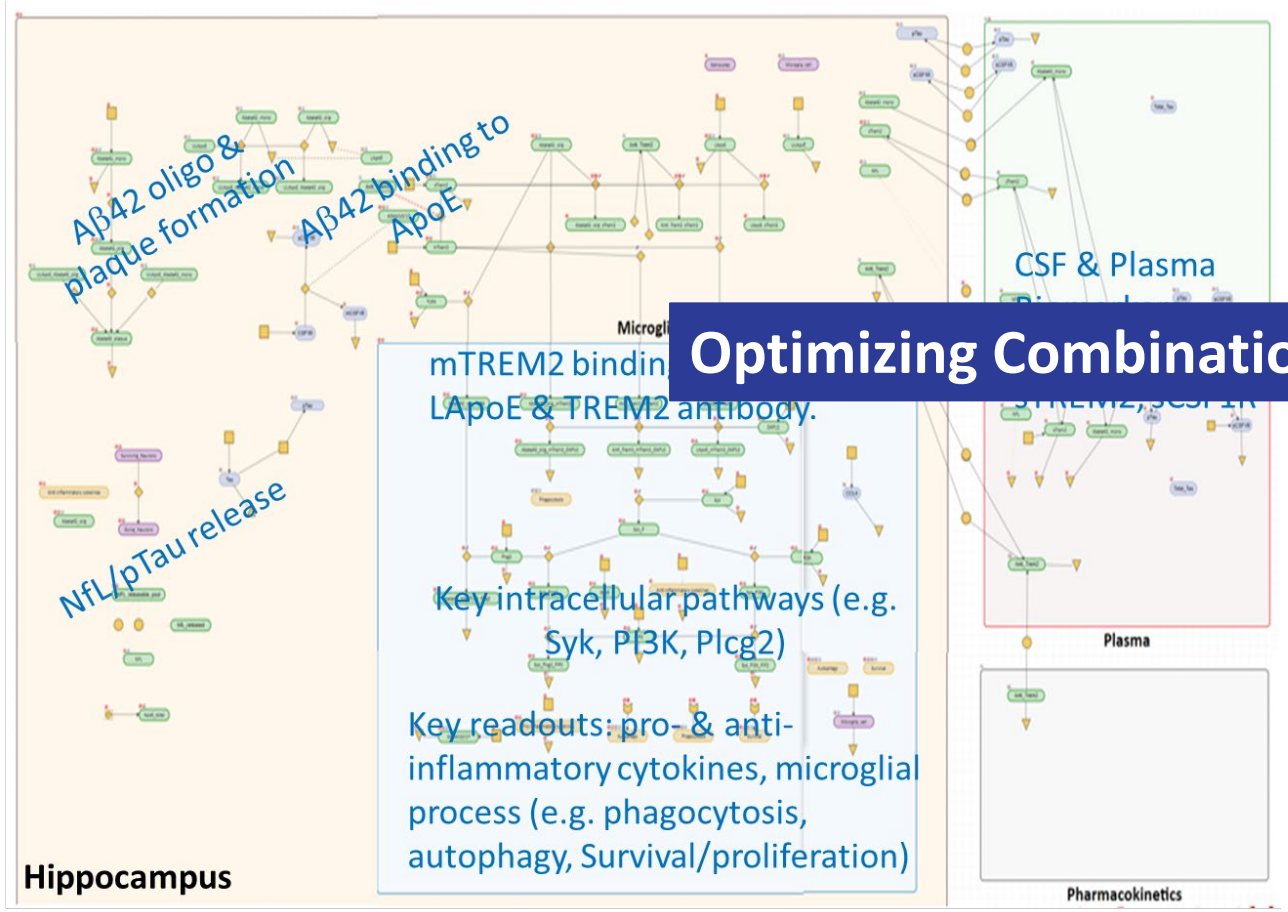
Amyloid biomarker with Microglia Interventions

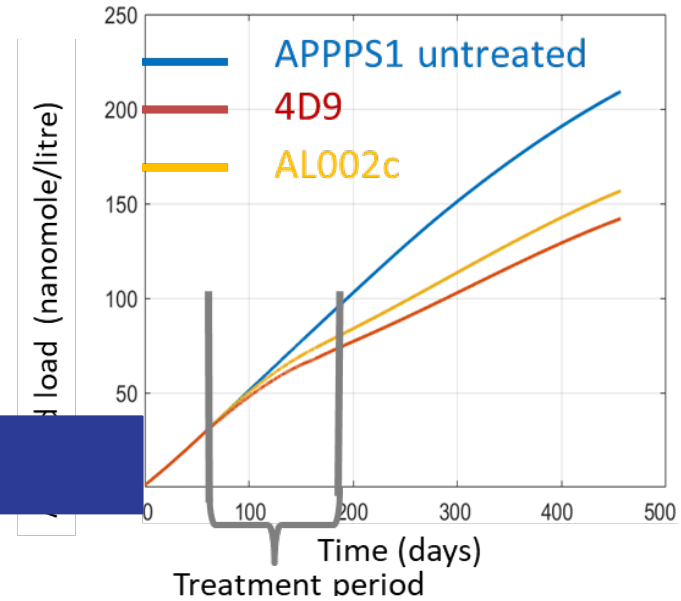
Microglia TREM2 pathway QSP Model



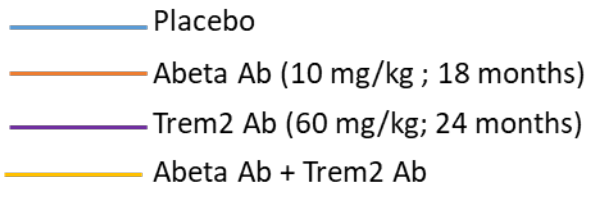
Optimizing Combination Therapy

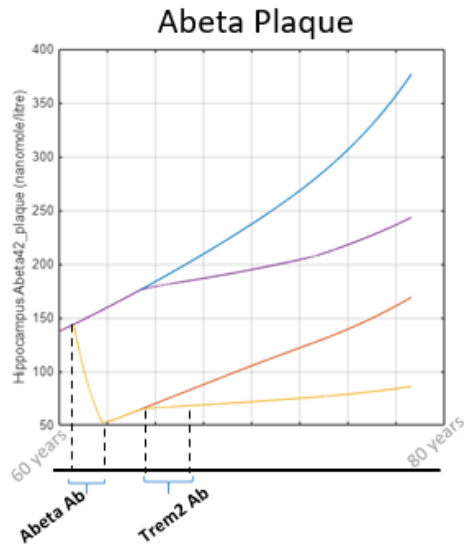
Preclinical Tg mouse model

4D9 : shedding antibody activator



Human AD patient





More information at Certara Booth

QSP model of neuroinflammation: Effect of TREM2 stimulation on microglial activation and function in the context of Alzheimer's disease

Viji Chelliah[2], Uddipan Sarma[2], Douglas Chung[2], Hugo Geerts[2], Piet H van der Graaf[2,3], Cheryl Leyns[1], Matthew Kennedy[1], Julie Stone[1], Peter Bloomingdale[1]
[1]Merck & Co., Inc., Kenilworth, NJ, USA, [2]Certara UK Limited, United Kingdom; [3]University of Leiden, The Netherlands

QSP model describing the dynamics of microglial phenotypes: Effect on treatments targeting microglia

Uddipan Sarma[2], Douglas Chung[2], Julie Stone[1], Peter Bloomingdale[1], Hugo Geerts[2], Piet H van der Graaf[2,3], Viji Chelliah[2]
[1]Merck & Co., Inc., Kenilworth, NJ, USA, [2]Certara UK Limited, United Kingdom; [3]University of Leiden, The Netherlands

Quantitative Systems Pharmacology (QSP) of Amyloid Pathology in Alzheimer's Disease : Multiscale Computational Modeling and Applications to Antibody Therapy

A. Cabal[1], H. Geerts[2], M. Walker[2], R. Rose[2], Silke Bergeler[2], E. Schuck[1], A. Akihiko Koyama[1], S. Yasuda[1], L. Reyderman[1], C. Swanson[1]
[1]Eisai, NJ, USA, [2]Certara UK Limited, United Kingdom

Impact of Standard of Care medications on Off-time readouts in clinical trials. A Quantitative Systems Pharmacology (QSP) approach

Emma Mitchell, Rachel Rose, Hugo Geerts
Certara Simcyp UK

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