

From Big Data to Smart Data

Computational Quantitative
Systems Pharmacology
Modeling of Brain Circuits

Hugo Geerts, PhD, Bach.Med., Pharma MBA

In Silico Biosciences, Inc. (ISB)
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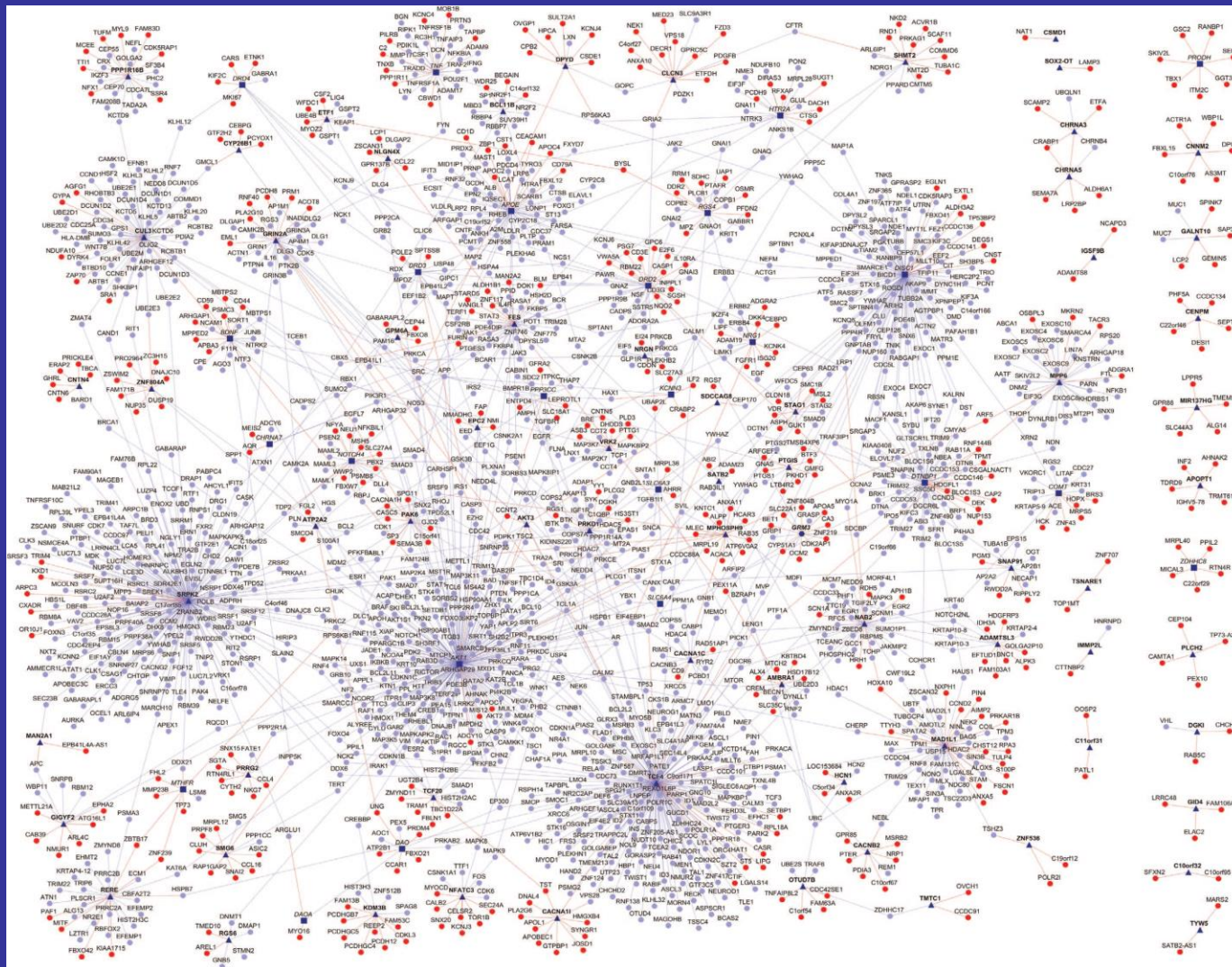
Computer Modeling in Health Care & Life Sciences



Meet Watson

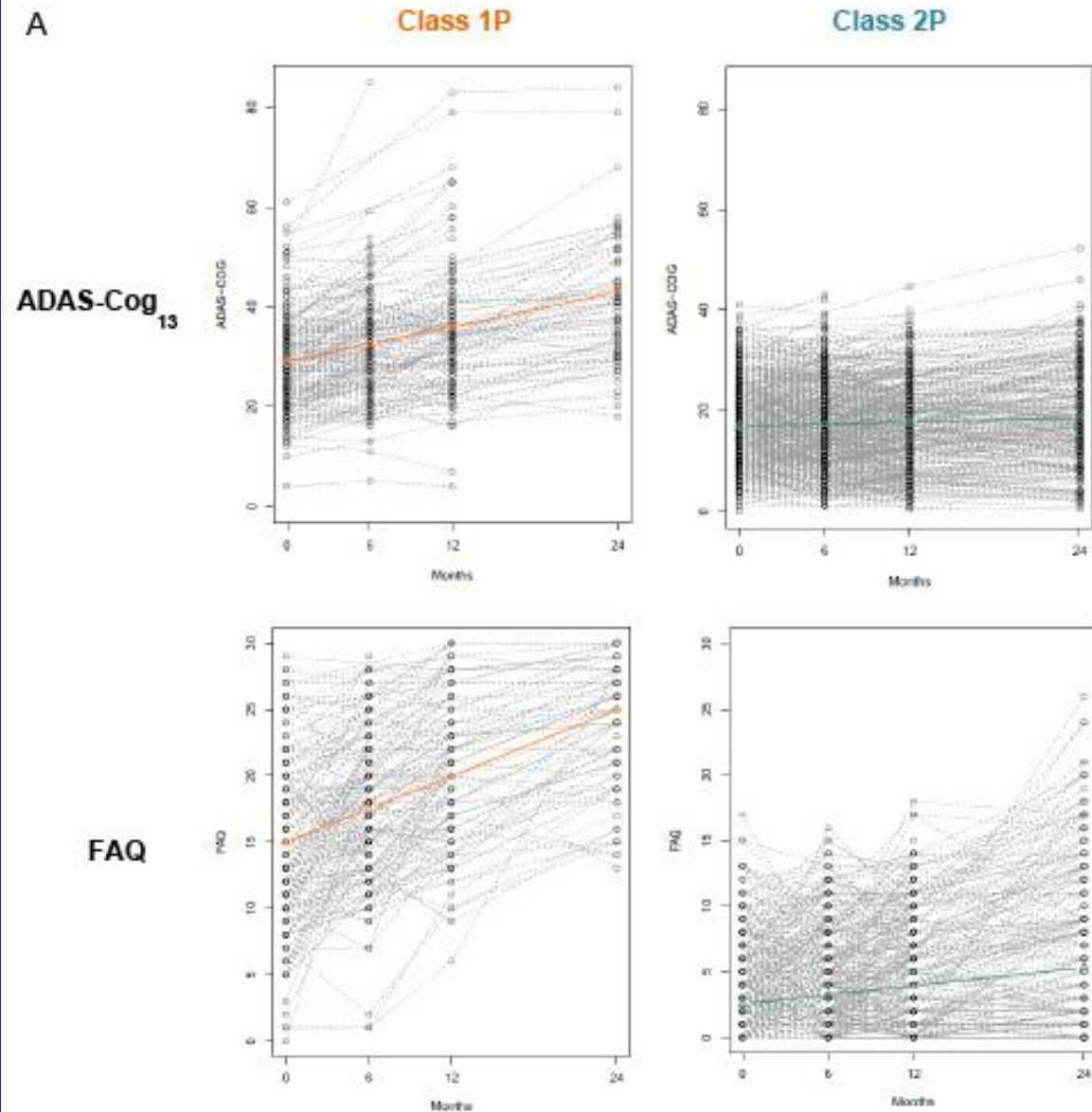
Watson is a technology that understands all forms of data and reasons and learns at scale.

From “Generic” Schizophrenia Interactome ...



Ganapathiraju 2016

To “Individual” patient trajectory



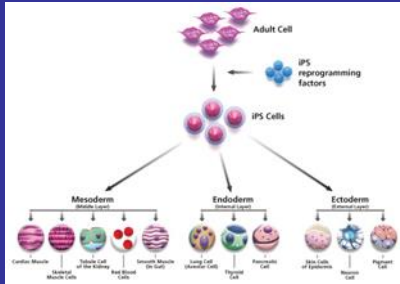
Comedications
Genotypes
Different drug metabolism
Different comorbidities
Different pathology trajectory

Trzepacz 2016

What can Pharma learn from Successful Industries (aeronautics, micro-electronics)?

- Formalize 'collective knowledge'
 - From information to knowledge (Big Data to Smart Data)
 - Use advanced modeling & simulations (CAD) approach to capture community-wide expertise & knowledge
 - Develop virtual in silico before actual physical prototype
- Embrace complexity
 - Circuit analysis : networks give rise to emergent properties that are not explained by single targets
 - Non-linear processes need mathematical modeling
- Failure analysis
 - More Extensive study of failed clinical trials needed
- Make output 'actionable' for Pharma R&D
 - Incomplete biology knowledge : sensitivity analysis, Pareto optimization, fuzzy statistics

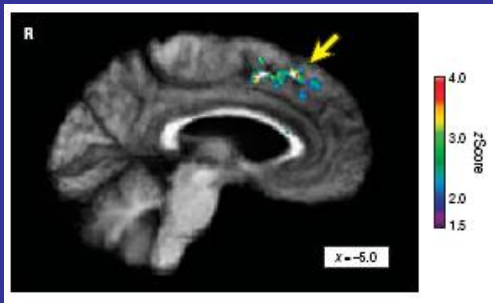
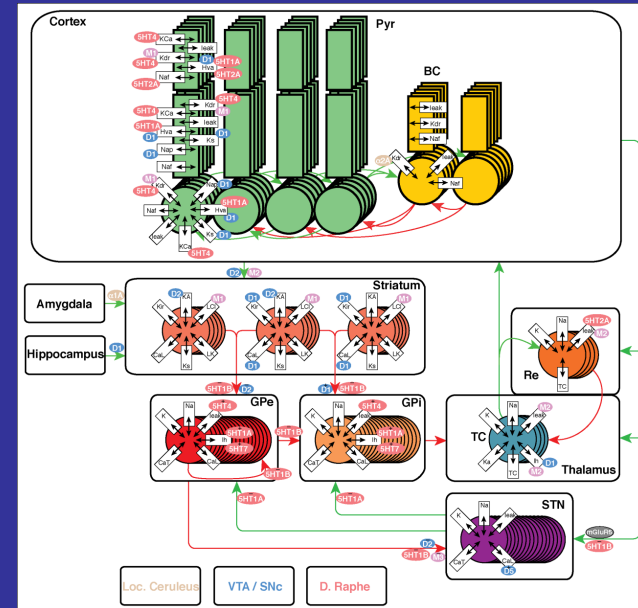
Quantitative Systems Pharmacology Integrates Various Modalities



Humanized
Cellular & Synaptic
Biology



Effect on Neuronal
Circuits in
non-human species

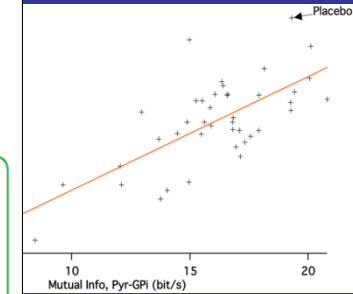
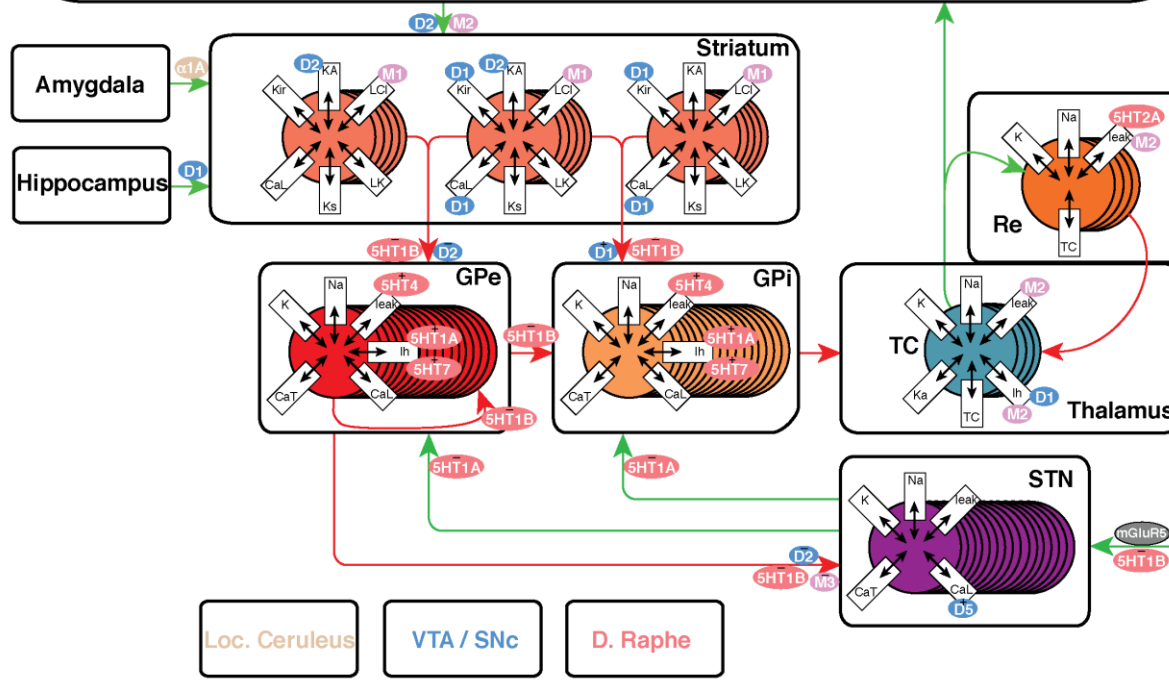


Human Clinical Data

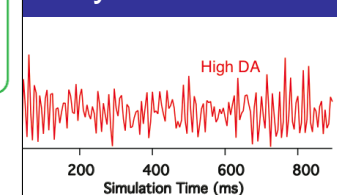
ion transfer PI

Figure 1 is a scatter plot showing the number of interneurons (Y-axis, 0 to 12) versus simulation time in seconds (X-axis, 0 to 10). The plot is divided into two regions: 'Pyr (stim)' on the left (0-4s) and 'Pyr (no stim)' on the right (4-10s). Data points are marked with 'x' and represent the number of interneurons at specific time points. The number of interneurons generally increases over time, starting from 0 at 0s and reaching a plateau of 10-12 after 4s.

Simulation Time (sec)	Number of Interneurons	Region
0.0	0	Pyr (stim)
0.5	0	Pyr (stim)
1.0	0	Pyr (stim)
1.5	0	Pyr (stim)
2.0	0	Pyr (stim)
2.5	0	Pyr (stim)
3.0	0	Pyr (stim)
3.5	0	Pyr (stim)
4.0	0	Pyr (no stim)
4.5	0	Pyr (no stim)
5.0	0	Pyr (no stim)
5.5	0	Pyr (no stim)
6.0	0	Pyr (no stim)
6.5	0	Pyr (no stim)
7.0	0	Pyr (no stim)
7.5	0	Pyr (no stim)
8.0	0	Pyr (no stim)
8.5	0	Pyr (no stim)
9.0	0	Pyr (no stim)
9.5	0	Pyr (no stim)
10.0	0	Pyr (no stim)
0.0	1	Pyr (stim)
0.5	1	Pyr (stim)
1.0	1	Pyr (stim)
1.5	1	Pyr (stim)
2.0	1	Pyr (stim)
2.5	1	Pyr (stim)
3.0	1	Pyr (stim)
3.5	1	Pyr (stim)
4.0	1	Pyr (no stim)
4.5	1	Pyr (no stim)
5.0	1	Pyr (no stim)
5.5	1	Pyr (no stim)
6.0	1	Pyr (no stim)
6.5	1	Pyr (no stim)
7.0	1	Pyr (no stim)
7.5	1	Pyr (no stim)
8.0	1	Pyr (no stim)
8.5	1	Pyr (no stim)
9.0	1	Pyr (no stim)
9.5	1	Pyr (no stim)
10.0	1	Pyr (no stim)
0.0	2	Pyr (stim)
0.5	2	Pyr (stim)
1.0	2	Pyr (stim)
1.5	2	Pyr (stim)
2.0	2	Pyr (stim)
2.5	2	Pyr (stim)
3.0	2	Pyr (stim)
3.5	2	Pyr (stim)
4.0	2	Pyr (no stim)
4.5	2	Pyr (no stim)
5.0	2	Pyr (no stim)
5.5	2	Pyr (no stim)
6.0	2	Pyr (no stim)
6.5	2	Pyr (no stim)
7.0	2	Pyr (no stim)
7.5	2	Pyr (no stim)
8.0	2	Pyr (no stim)
8.5	2	Pyr (no stim)
9.0	2	Pyr (no stim)
9.5	2	Pyr (no stim)
10.0	2	Pyr (no stim)
0.0	3	Pyr (stim)
0.5	3	Pyr (stim)
1.0	3	Pyr (stim)
1.5	3	Pyr (stim)
2.0	3	Pyr (stim)
2.5	3	Pyr (stim)
3.0	3	Pyr (stim)
3.5	3	Pyr (stim)
4.0	3	Pyr (no stim)
4.5	3	Pyr (no stim)
5.0	3	Pyr (no stim)
5.5	3	Pyr (no stim)
6.0	3	Pyr (no stim)
6.5	3	Pyr (no stim)
7.0	3	Pyr (no stim)
7.5	3	Pyr (no stim)
8.0	3	Pyr (no stim)
8.5	3	Pyr (no stim)
9.0	3	Pyr (no stim)
9.5	3	Pyr (no stim)
10.0	3	Pyr (no stim)
0.0	4	Pyr (stim)
0.5	4	Pyr (stim)
1.0	4	Pyr (stim)
1.5	4	Pyr (stim)
2.0	4	Pyr (stim)
2.5	4	Pyr (stim)
3.0	4	Pyr (stim)
3.5	4	Pyr (stim)
4.0	4	Pyr (no stim)
4.5	4	Pyr (no stim)
5.0	4	Pyr (no stim)
5.5	4	Pyr (no stim)
6.0	4	Pyr (no stim)
6.5	4	Pyr (no stim)
7.0	4	Pyr (no stim)
7.5	4	Pyr (no stim)
8.0	4	Pyr (no stim)
8.5	4	Pyr (no stim)
9.0	4	Pyr (no stim)
9.5	4	Pyr (no stim)
10.0	4	Pyr (no stim)
0.0	5	Pyr (stim)
0.5	5	Pyr (stim)
1.0	5	Pyr (stim)
1.5	5	Pyr (stim)
2.0	5	Pyr (stim)
2.5	5	Pyr (stim)
3.0	5	Pyr (stim)
3.5	5	Pyr (stim)
4.0	5	Pyr (no stim)
4.5	5	Pyr (no stim)
5.0	5	Pyr (no stim)
5.5	5	Pyr (no stim)
6.0	5	Pyr (no stim)
6.5	5	Pyr (no stim)
7.0	5	Pyr (no stim)
7.5	5	Pyr (no stim)
8.0	5	Pyr (no stim)
8.5	5	Pyr (no stim)
9.0	5	Pyr (no stim)
9.5	5	Pyr (no stim)
10.0	5	Pyr (no stim)
0.0	6	Pyr (stim)
0.5	6	Pyr (stim)
1.0	6	Pyr (stim)
1.5	6	Pyr (stim)
2.0	6	Pyr (stim)
2.5	6	Pyr (stim)
3.0	6	Pyr (stim)
3.5	6	Pyr (stim)
4.0	6	Pyr (no stim)
4.5	6	Pyr (



on's disease
ms are correlated
N rhythms.



How comprehensive is the QSP platform?

- For existing CNS-active drugs, representations of:
 - D1, D2, D3, D4
 - 5-HT1A, 5-HT1B, 5-HT2A, 5-HT2B, 5-HT2C, 5-HT3, 5-HT4, α 1A, α 2A, α 7 nAChR, α 4 β 2 nAChR, M1 mAChR, M2 mAChR
 - GABA-A α 1, GABA-A α 2, NMDA-NR2A, NMDA-NR2B, NMDA-NR2C AMPA
 - AChE, COMT, SERT, NET and DAT
 - mGluR2, mGluR5, 5-HT6, 5-HT7, NK3, GlyT1, H3
- Intracellular target implementation
 - cAMP-cGMP pathway (PDE10)
- Alzheimer Disease Modification
 - Beta-amyloid dynamics and their effect on cognition
- Common Genotypes based on imaging
 - COMTVal158Met, 5-HTTLPR s/l, APOE, D2DRTaq1A1, CACNA1C
- Calibrated Clinical Outcome
 - Schizophrenia : PANSS Total, PANSS Negative, Cognition
 - Alzheimer's Disease : ADAS-Cog, NPI
 - Parkinson's & Huntington's Disease : UPDRS
- Tau Pathology Modeling (in Preparation)

Quantitative Systems Pharmacology Provides Actual Value for Pharma R&D

Vol.2, No.3, 83-98 (2013)
<http://dx.doi.org/10.4236/aad.2013.23012>

Advances in Alzheimer's Disease

Systems pharmacology modeling in neuroscience: Prediction and outcome of PF-04995274, a 5-HT₄ partial agonist, in a clinical scopolamine impairment trial

Timothy Nicholas^{1*}, Sridhar Duvvuri¹, Claire Leurent¹, David Raunig^{1,3}, Tracey Rapp¹,
Phil Iredale¹, Carolyn Rowinski¹, Robert Carr², Patrick Roberts², Athan Spiros², Hugo Geerts²

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Journal of Parkinson's Disease 3 (2013) 569–580
DOI:10.3233/JPD-130211
IOS Press

569

Research Report

Phenotypic Screening of the Prestwick Library for Treatment of Parkinson's Tremor Symptoms using a Humanized Quantitative Systems Pharmacology Platform

Athan Spiros^a, Patrick Roberts^{a,b} and Hugo Geerts^{a,c,*}

 PLOS ONE

Blinded Prospective Evaluation of Computer-Based Mechanistic Schizophrenia Disease Model for Predicting Drug Response

Hugo Geerts^{1*}, Athan Spiros¹, Patrick Roberts¹, Roy Twyman², Larry Alphs³, Anthony A. Grace⁴

Citation: CPT Pharmacometrics Syst. Pharmacol. (2014) 3, e111; doi:10.1038/psp.2014.7
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www.nature.com/psp

Original Paper

Understanding responder neurobiology in schizophrenia using a quantitative systems pharmacology model: Application to iloperidone

Hugo Geerts^{1,2}, Patrick Roberts^{1,3}, Athan Spiros¹ and Steven Potkin⁴

Psychopharm

Journal of Psychopharmacology
1–11
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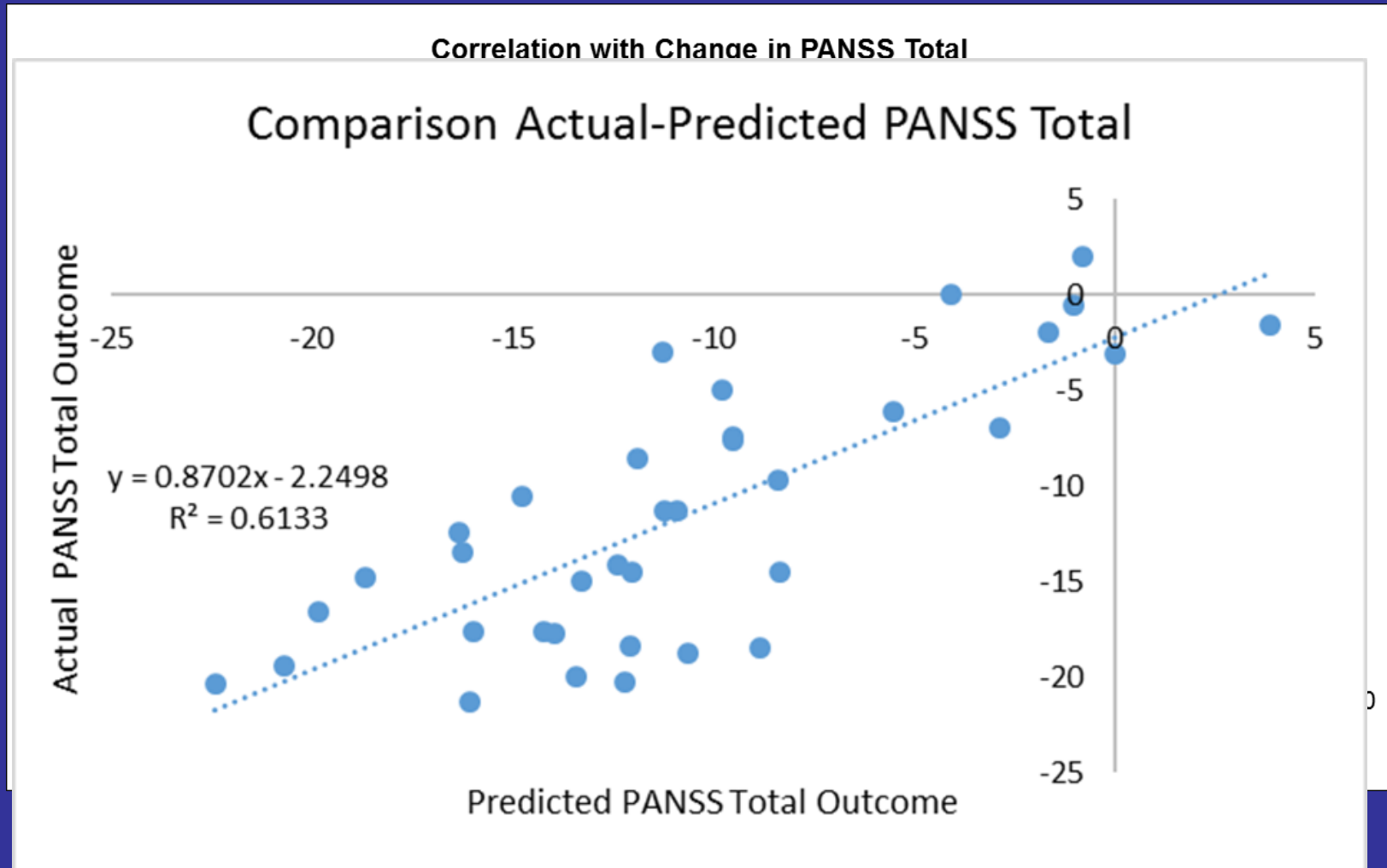
ORIGINAL ARTICLE

Prediction of Efficacy of Vabicaserin, a 5-HT_{2C} Agonist, for the Treatment of Schizophrenia Using a Quantitative Systems Pharmacology Model

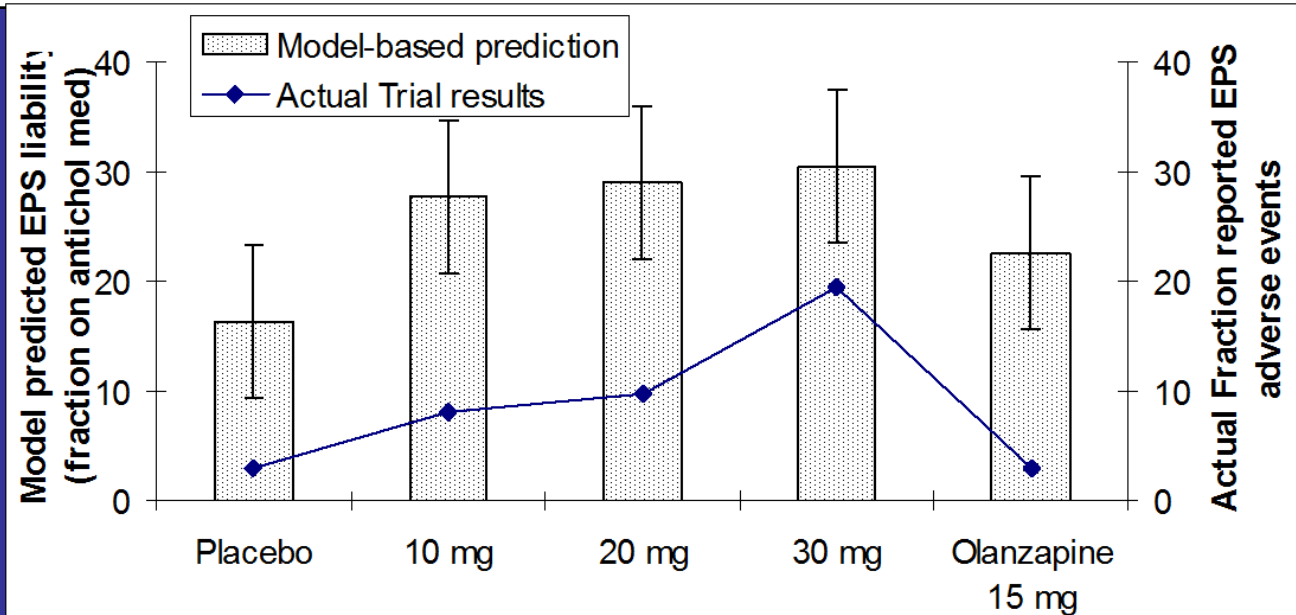
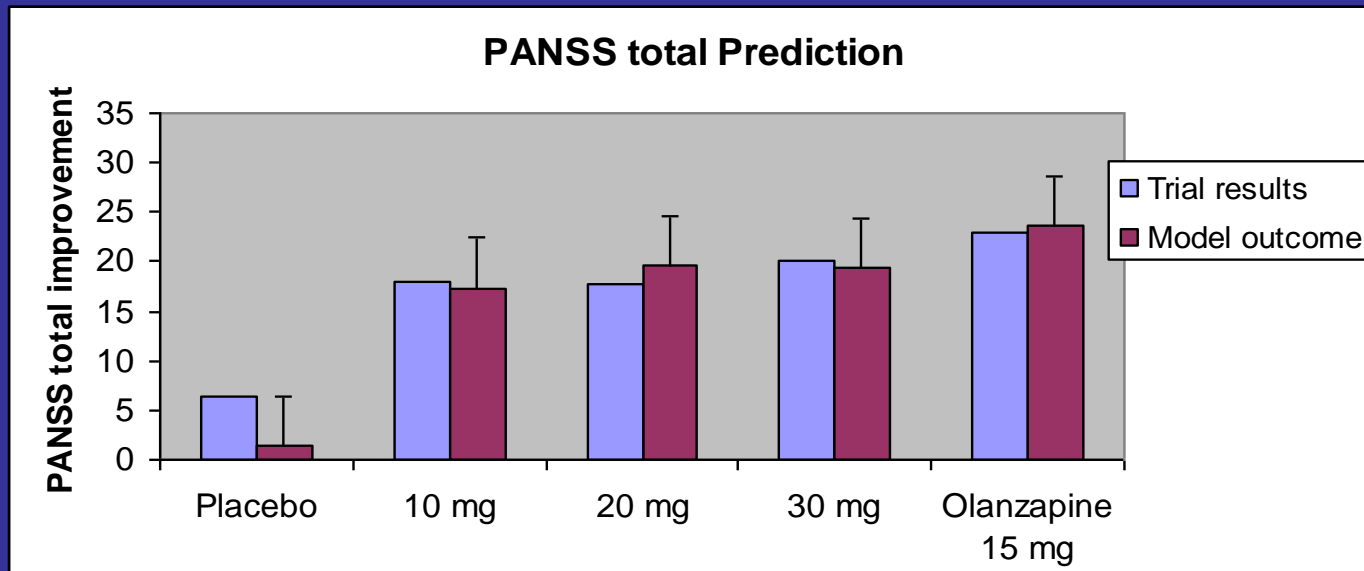
J Liu¹, A Ogden¹, TA Comery², A Spiros³, P Roberts^{3,4} and H Geerts^{3,5}

Calibration and Validation

PANSS Total



First Blinded Prediction of Clinical Outcome in Schizophrenia Could Have Saved Large Investment



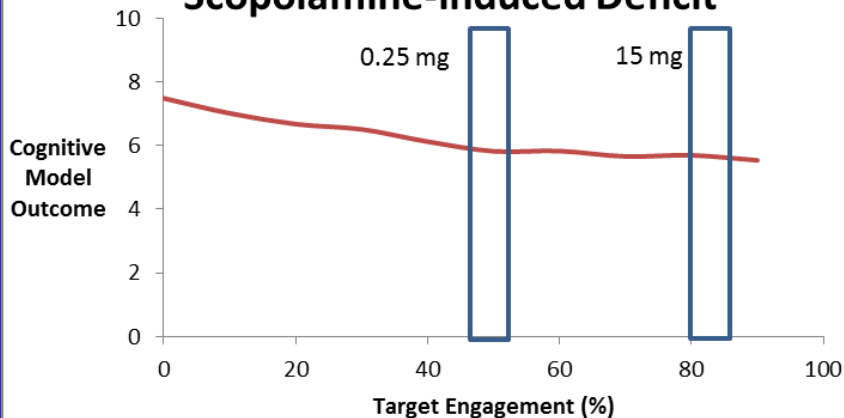
Geerts 2012
PlosOne

Effect of Comedications in Clinical Trial in CIAS

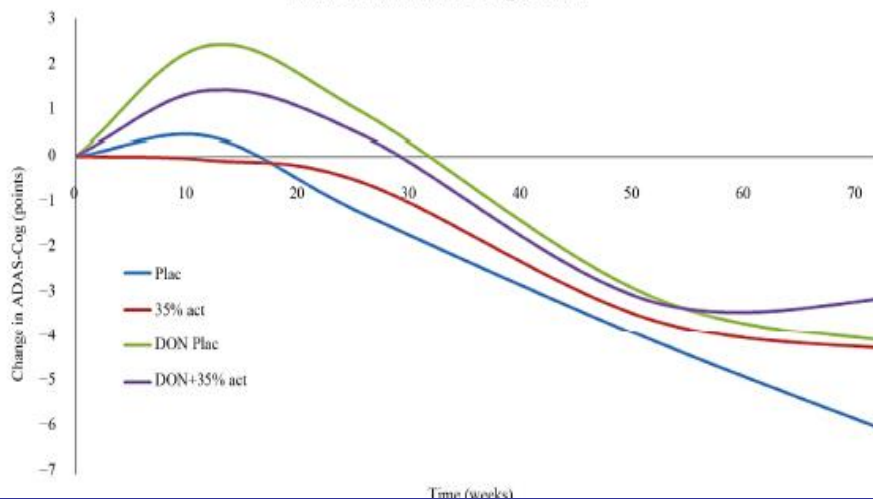
	Stand-alone	DON5	DON10	GAL8	GAL16	GAL24
MEM	0.13	0.16	0.08	0.18	0.07	0.02
RIS NoSmok	0.10	0.05	0.11	0.09	0.10	0.14
QUE NoSmok	0.06	-0.01	-0.05	0.00	0.00	-0.01
QUE400 NoSmok	0.09	0.03	-0.03	0.01	-0.07	0.06
QUE600 NoSmok	0.10	0.03	-0.01	0.01	-0.07	0.09
OLA NoSmok	0.08	0.23	0.29	0.09	0.21	0.07
ARI NoSmok	0.23	0.09	0.13	0.12	0.04	-0.01
HAL NoSmok	0.12	0.16	0.18	0.16	0.21	0.16
MEM-SMOK	0.13	0.12	-0.01	0.13	0.23	0.12
RIS SMOK	0.09	0.04	0.07	0.07	0.08	0.18
QUE SMOK	0.02	0.00	-0.02	-0.01	-0.03	-0.03
QUE400 SMOK	0.05	0.00	-0.03	0.00	-0.04	-0.04
QUE600 SMOK	0.01	-0.02	-0.02	-0.02	-0.03	-0.02
OLA SMOK	0.02	0.00	-0.02	-0.01	-0.03	-0.03
ARI SMOK	0.11	0.05	0.03	0.05	0.04	-0.03
HAL SMOK	0.21	0.20	0.16	0.12	0.16	0.13

QSP Model Correctly Predicted Unexpected Ph 1 Clinical Outcome

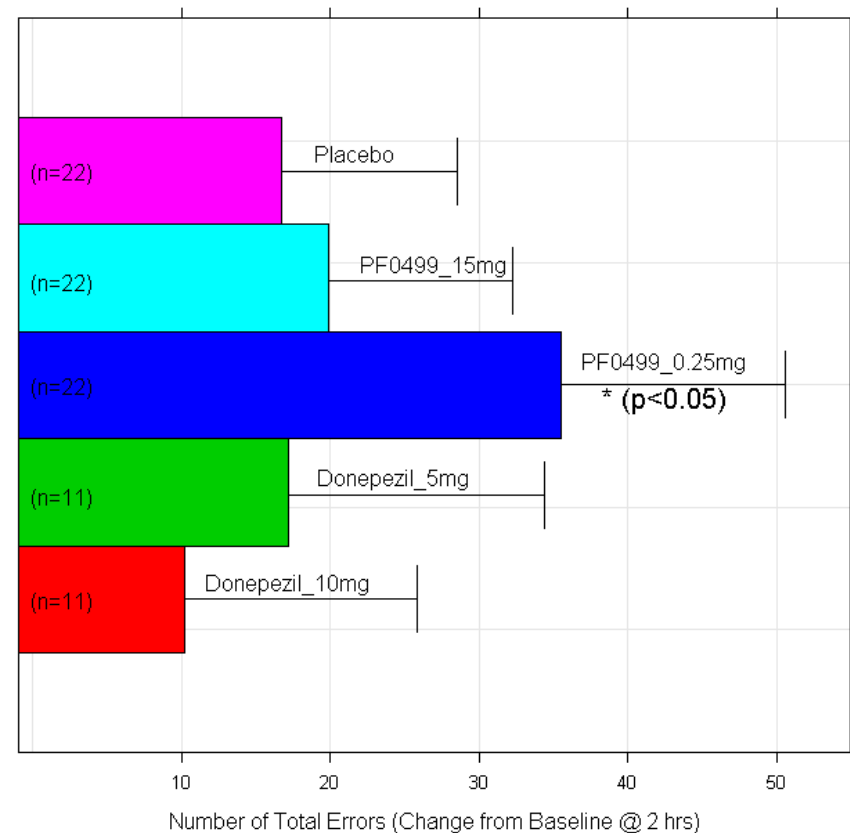
5-HT₄ Partial Agonist PF-04995274 in Scopolamine-induced Deficit



Simulated Outcome for 35% 5-HT_{4R} Activation

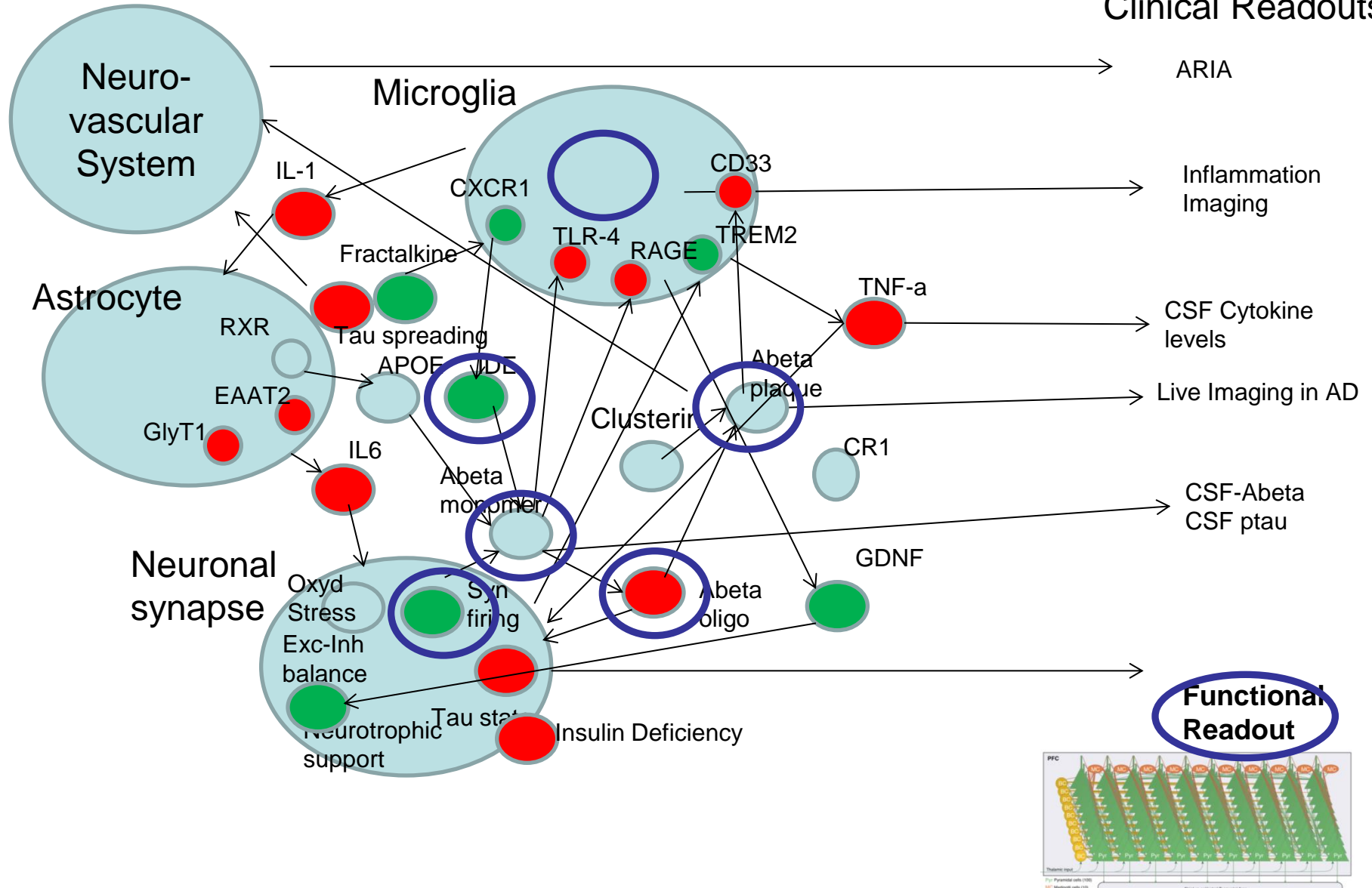


Change from Baseline in GMLT at 2 hours

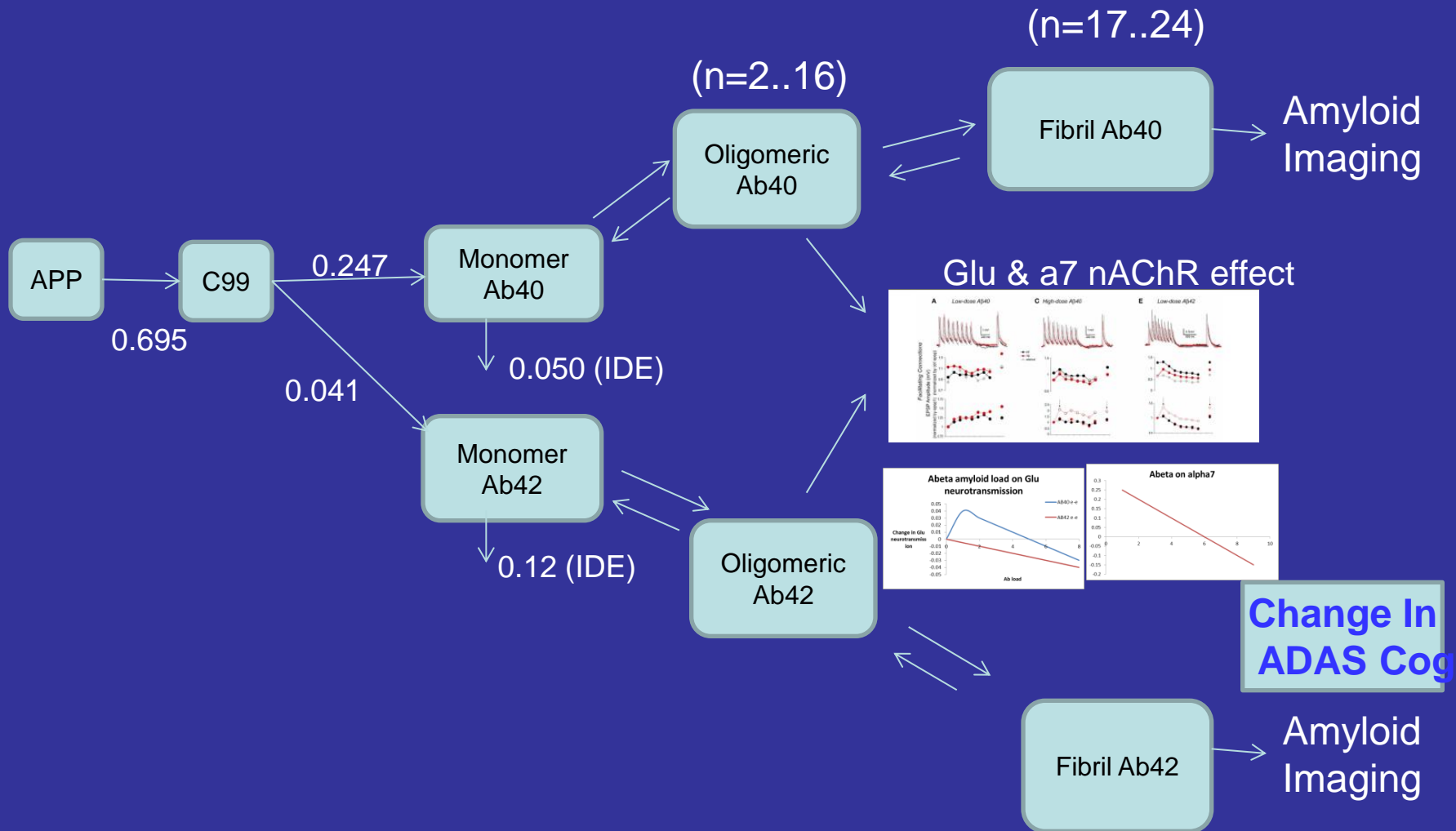


Cognition in Alzheimer's Disease

Clinical Readouts



Amyloid Modulation



Cell Biology

Cell Biology



QSP Support for Key Pharma R&D Questions

- Preclinical
 - Target Identification' to 'validation'
 - Rationally designed multitarget pharmacology
 - In what direction and how much do we need to change pathway of Interest for a clinically meaningful outcome?
 - Support selection of clinical candidate
- Clinical
 - Dose-response monotonic or inverse U-shape?
 - Target Engagement
 - Optimal dose vs MTD
 - Impact of genotypes on clinical dose-response
 - Impact of comedications on clinical dose-response
 - Selection of patient population : targeted therapies

The Human Avatar

A Humanized Quantitative Systems Pharmacology Approach

Athan Spiros
Patrick Roberts
Ruggero Scorcione
Leif Finkel
John Dani
Robert Carr