From Big Data to Smart Data

Computational Quantitative Systems Pharmacology Modeling of Brain Circuits

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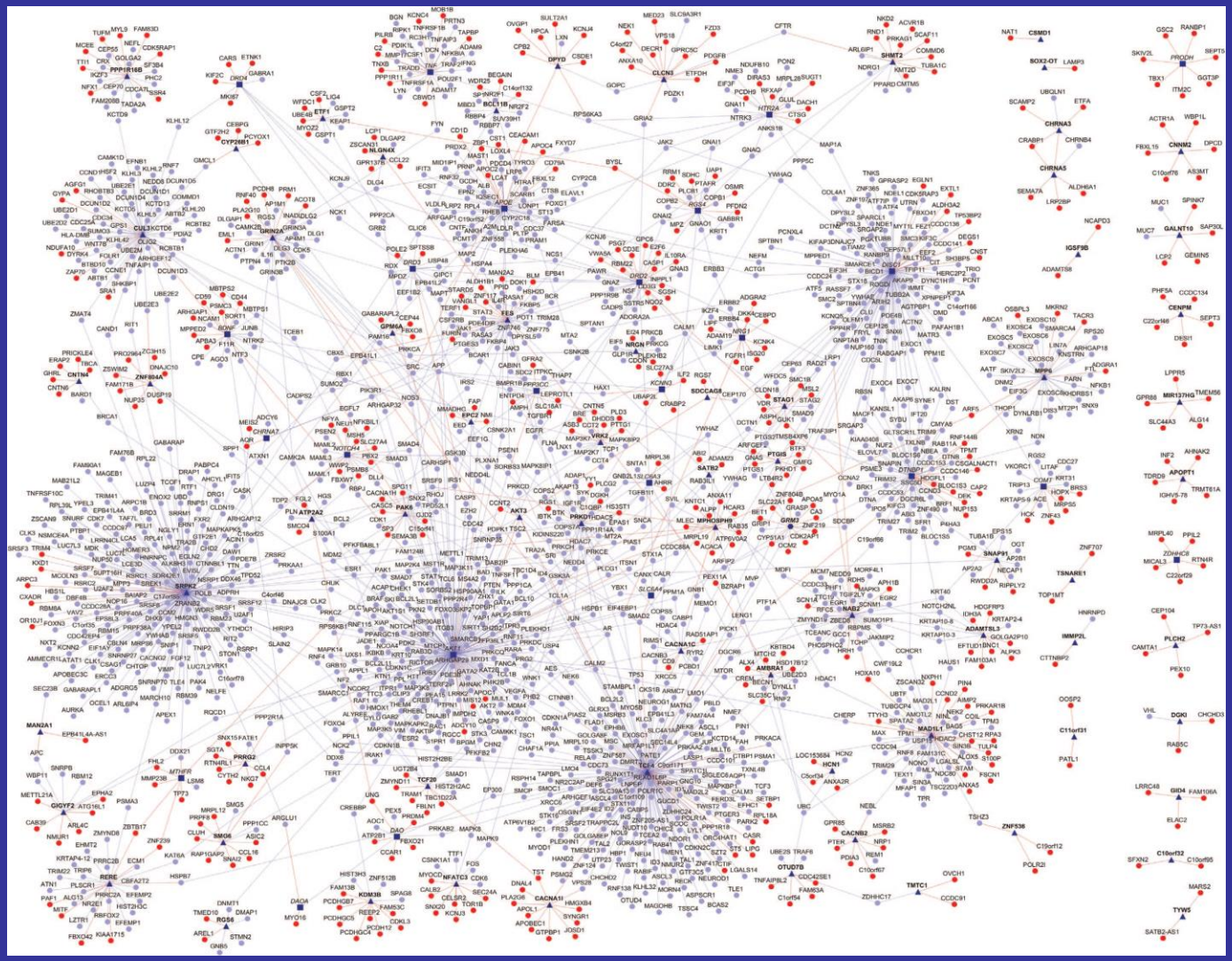
In Silico Biosciences, Inc. (ISB)
University of Pennsylvania

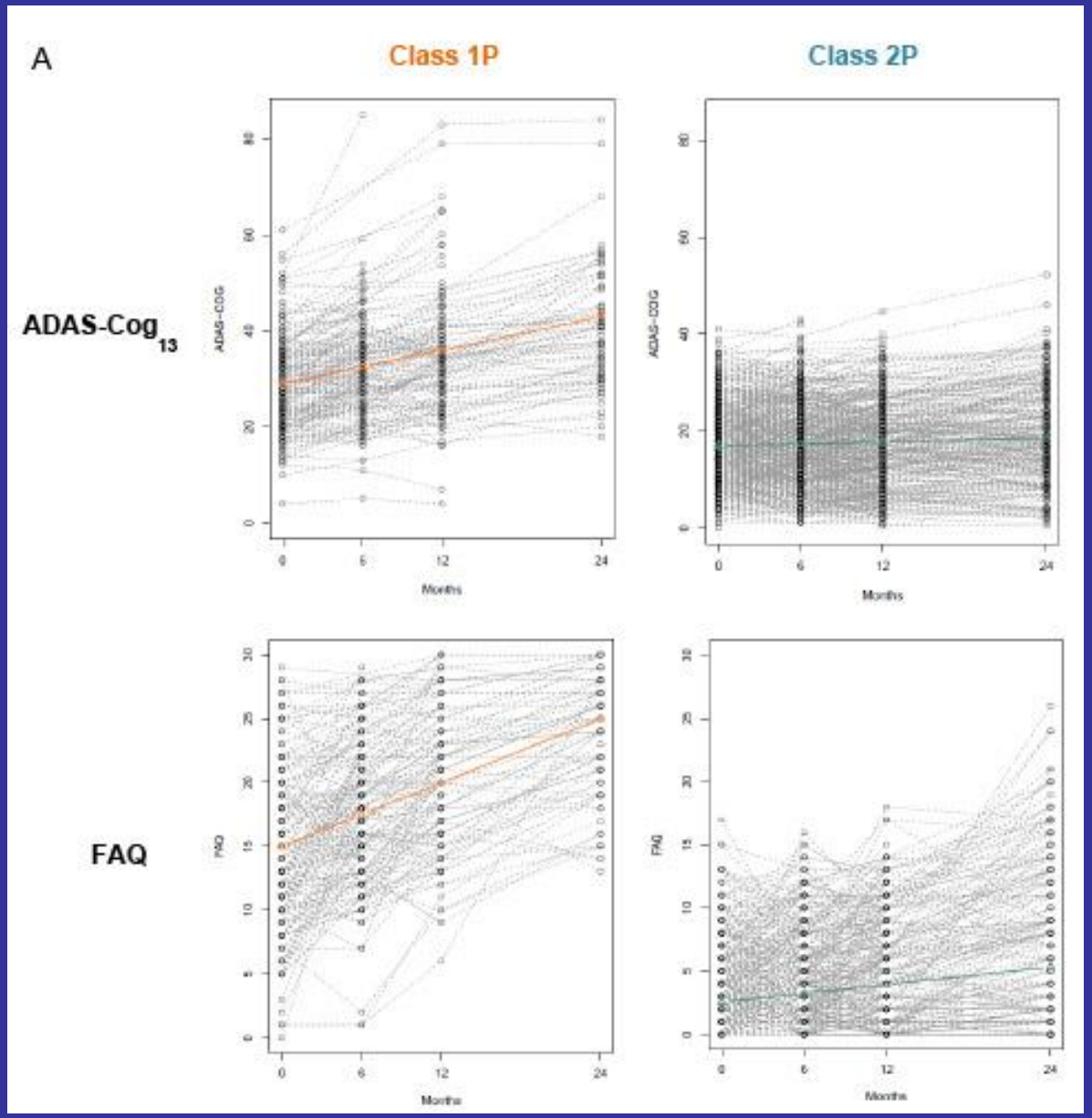
Computer Modeling in Health Care & Life Sciences

From “Generic” Schizophrenia Interactome …



Ganapathiraju 2016

To “Individual” patient trajectory



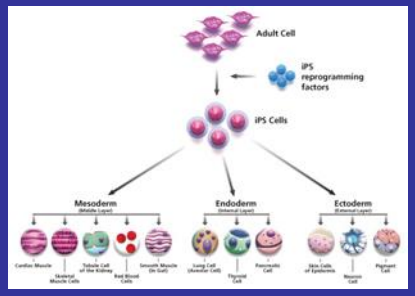
Comedications
Genotypes
Different drug metabolism
Different comorbidities
Different pathology trajectory

Trzepacz 2016

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

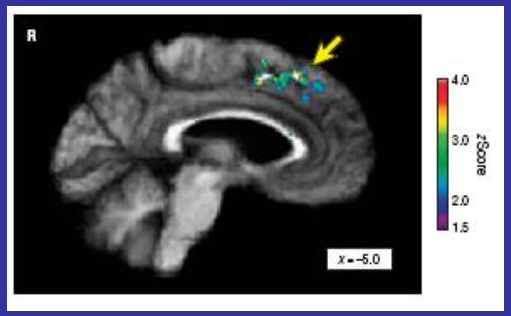
- Formalize ‘collective knowledge’
  - From information to knowledge (Big Data to Smart Data)
  - Use advanced modeling & simulations (CAD) approach to capture community-wide expertise & knowledge
  - Develop virtual in silico before actual physical prototype
- Embrace complexity
  - Circuit analysis : 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

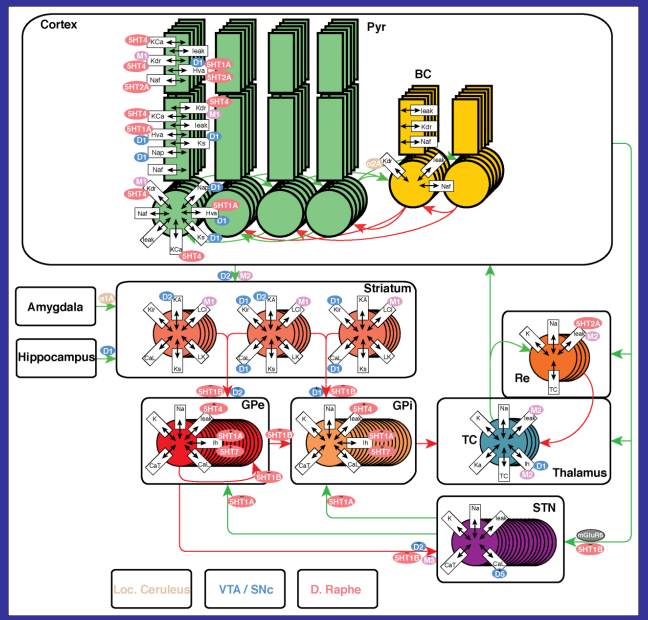


Humanized Cellular & Synaptic Biology

Effect on Neuronal Circuits in non-human species

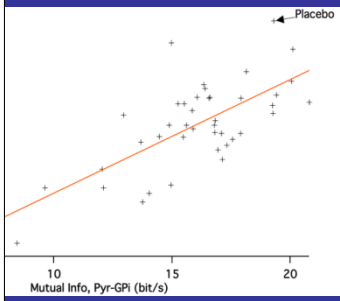


Human Clinical Data

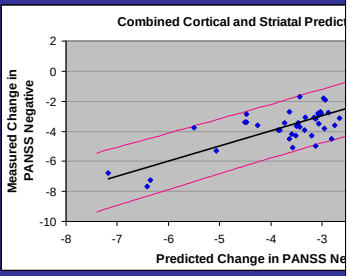


In Silico Disease Model for Different Indications and Clinical Scales

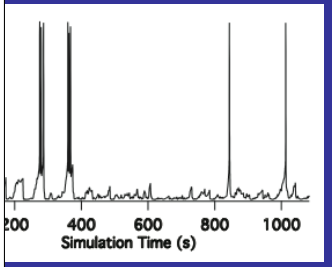
PANSS Total as mutual
ion transfer
PI



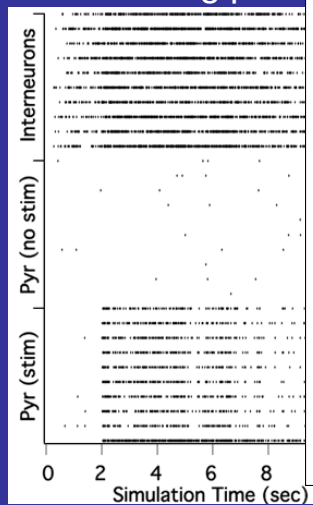
Negative PANSS
correlated with s
and cortical excit



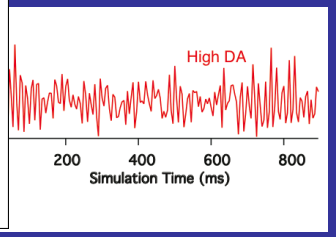
gton's disease
oms are correlated
C excitability.

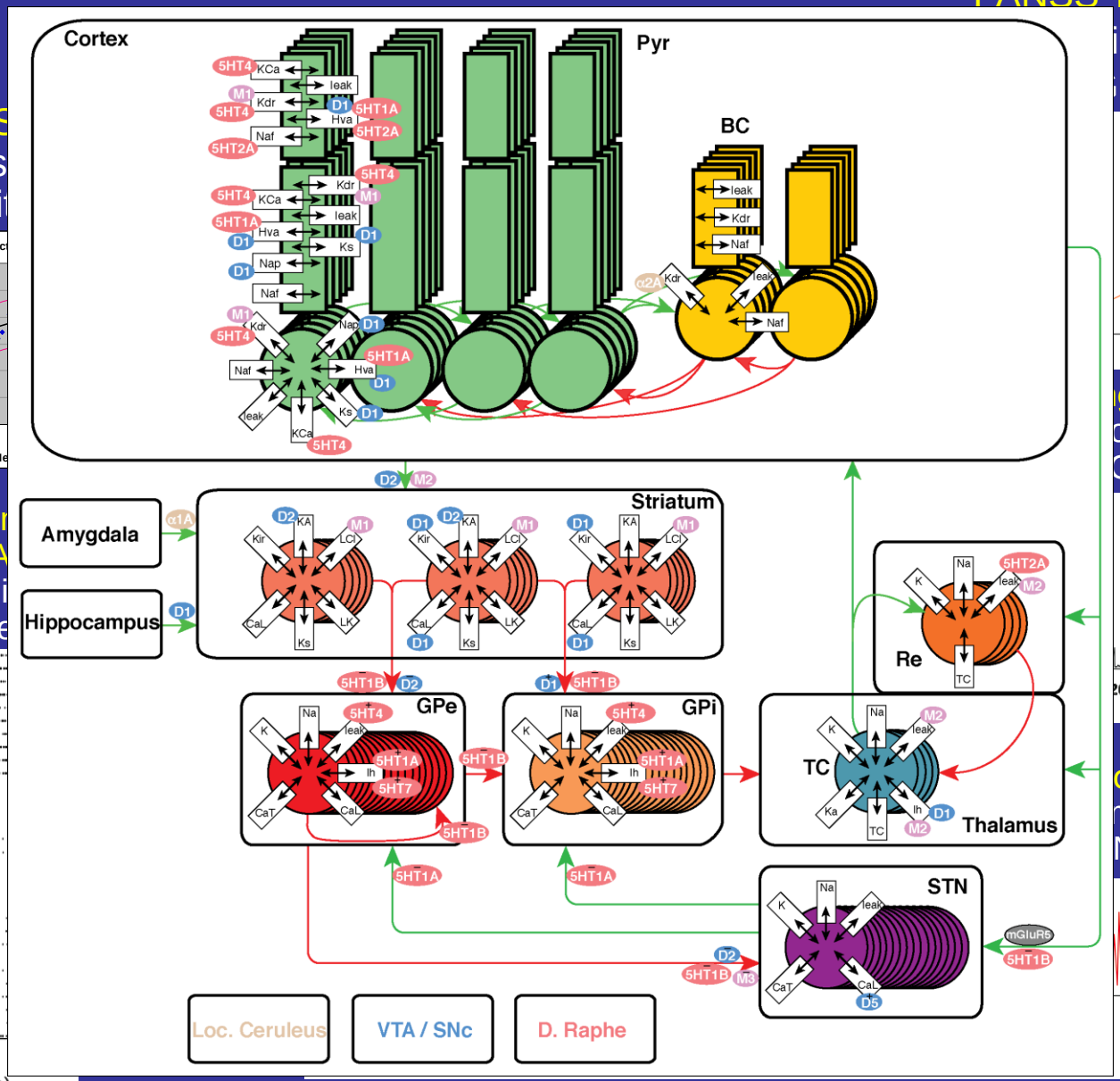


Cognitive symptor
schizophrenia & A
correlated dynami
cortical firing patte



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, α1A, α2A, α7 nAChR, $\alpha 4\beta 2$ nAChR, M1 mAChR, M2 mAChR
  - GABA-A $\alpha 1$, GABA-A $\alpha 2$, 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)
- Azheimer 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-HT$_4$ partial agonist, in a clinical scopolamine impairment trial

Timothy Nicholas[1*], Sridhar Duvvuri[1], Claire Leurent[1], David Raunig[1,3], Tracey Rapp[1], Phil Iredale[1], Carolyn Rowinski[1], Robert Carr[2], Patrick Roberts[2], Athan Spiros[2], Hugo Geerts[2]

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

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,*]

OPEN ACCESS Freely available online

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

Hugo Geerts[1]*, Athan Spiros[1], Patrick Roberts[1], Roy Twyman[2], Larry Alphs[3], Anthony A. Grace[4]

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

www.nature.com/psp

ORIGINAL ARTICLE

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

J Liu[1], A Ogden[1], TA Comery[2], A Spiros[3], P Roberts[3,4] and H Geerts[3,5]

Original Paper

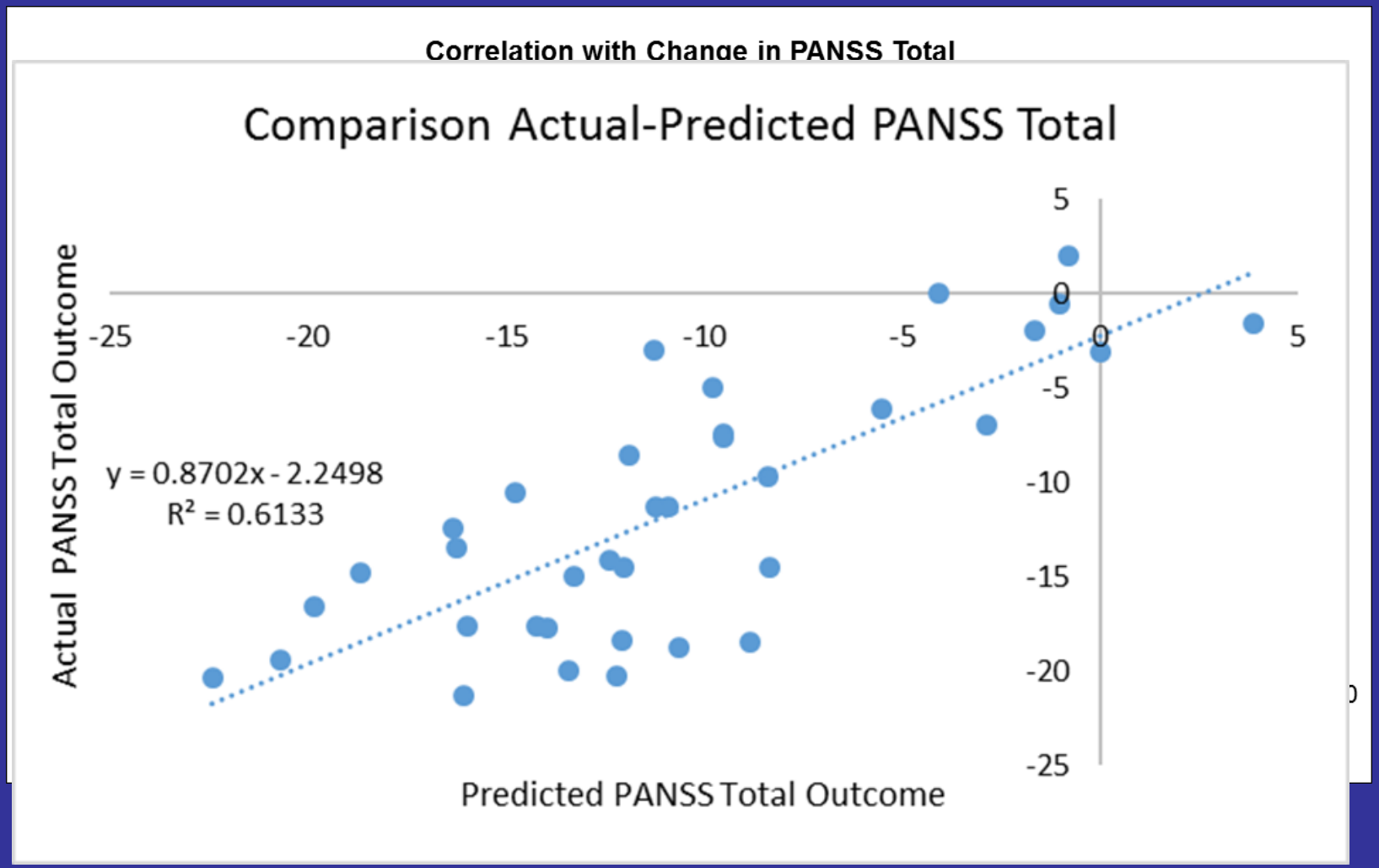
Understanding responder neurobiology in schizophrenia using a quantitative systems pharmacology model: Application to iloperidone

Hugo Geerts[1,2], Patrick Roberts[1,3], Athan Spiros[1] and Steven Potkin[4]

Psychopharm
Journal of Psychopharmacology
1–11

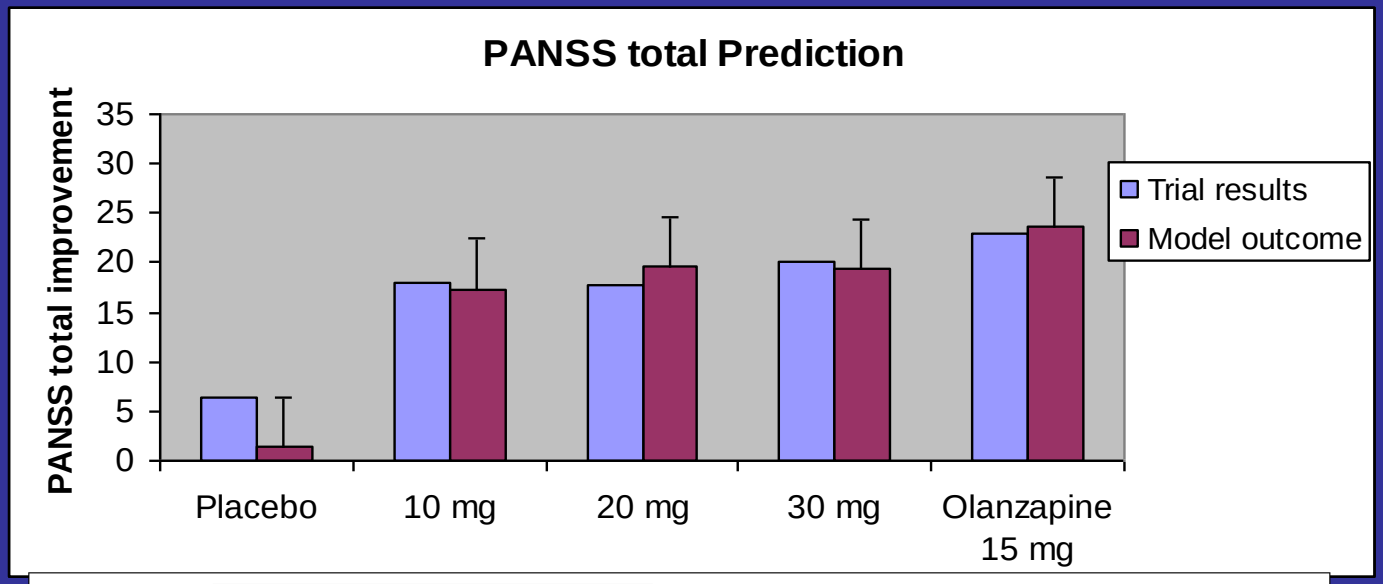
DOI: 10.1177/0269881114568042
jop.sagepub.com
SAGE

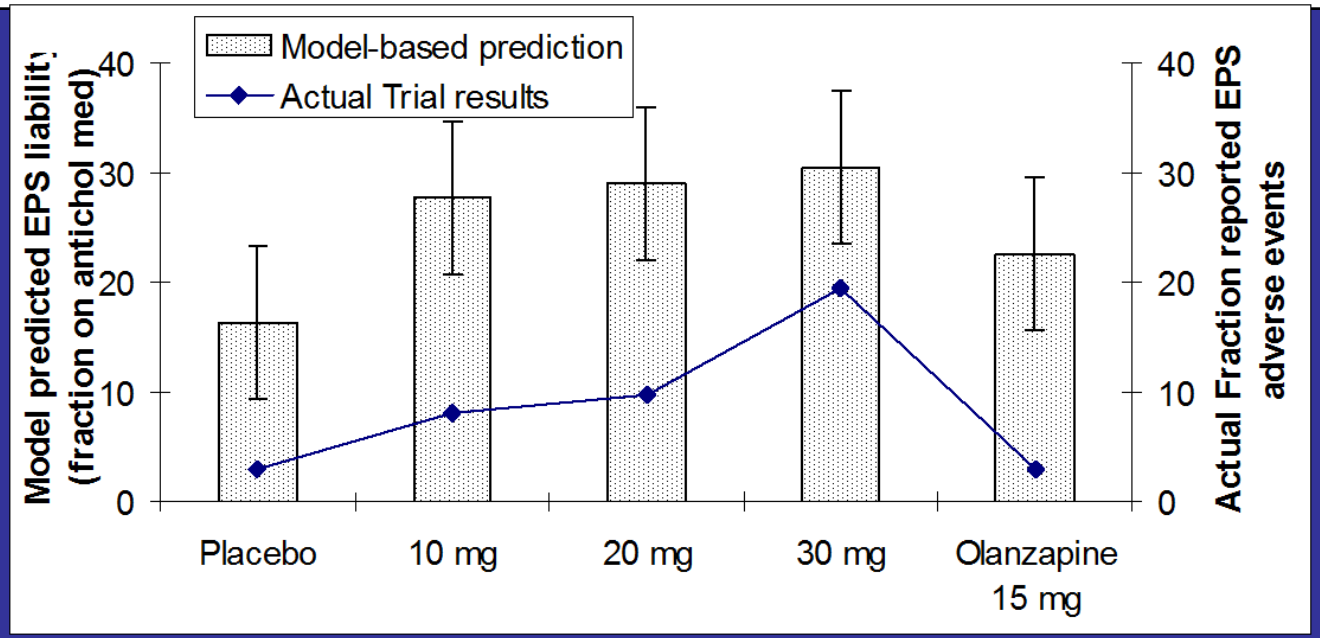
Calibration and Validation PANSS Total



Spiros 2016 under review

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





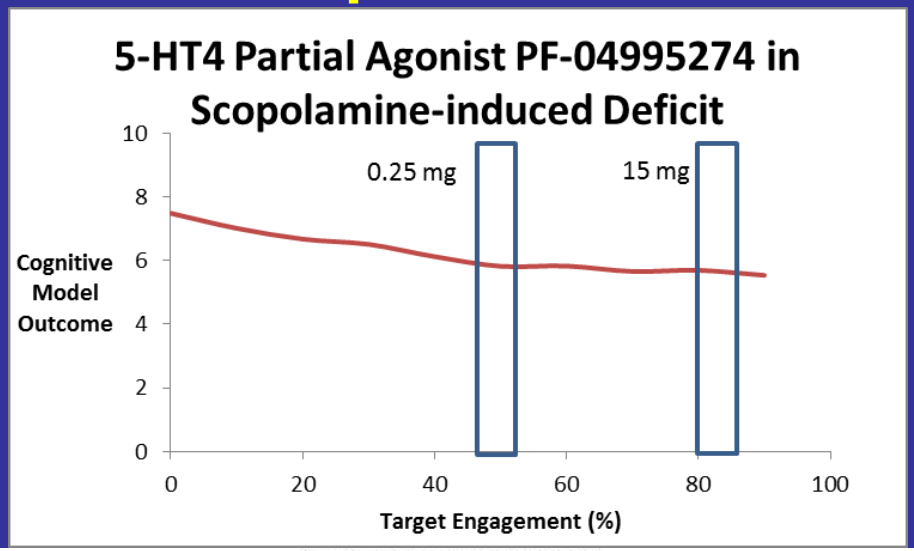
Geerts 2012
PlosOne

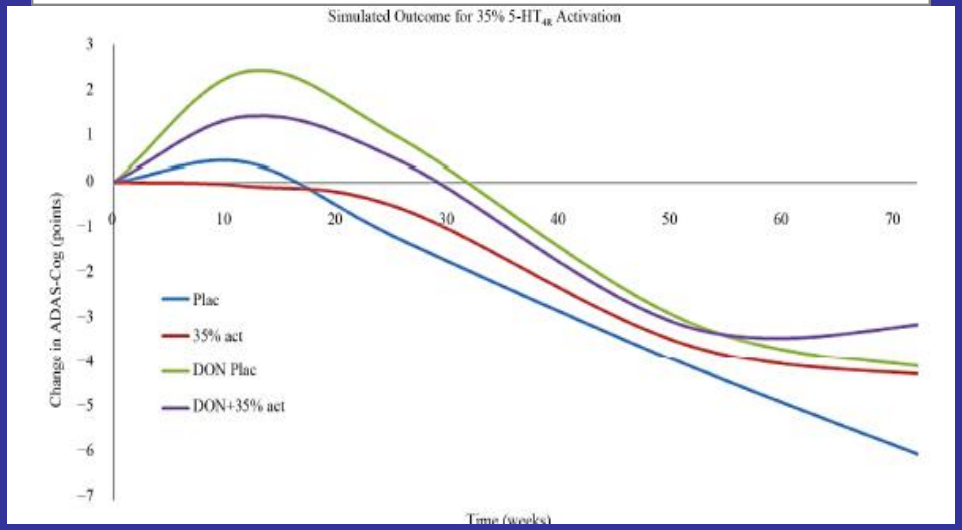
Effect of Comedications in Clinical Trial in CIAS

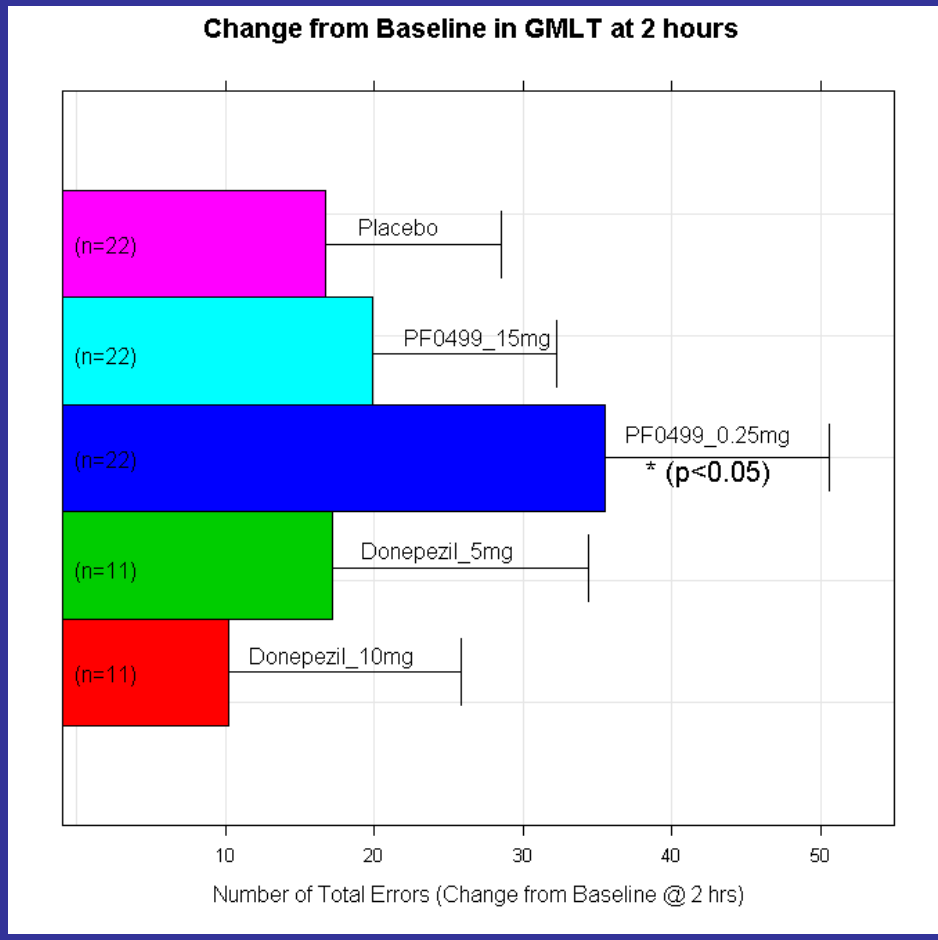
	Stand-alone	DON5	DON10	GAL8	GAL16	GAL24
MEM	0.13	0.16	0.08	0.18	0.07	0.02
RIS NoSmok	0.10	0.05	0.11	0.09	0.10	0.14
QUE NoSmok	0.06	-0.01	-0.05	0.00	0.00	-0.01
QUE400 NoSmok	0.09	0.03	-0.03	0.01	-0.07	0.06
QUE600 NoSmok	0.10	0.03	-0.01	0.01	-0.07	0.09
OLA NoSmok	0.08	0.23	0.29	0.09	0.21	0.07
ARI NoSmok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

Geerts 2016

QSP Model Correctly **Predicted** Unexpected Ph 1 Clinical Outcome

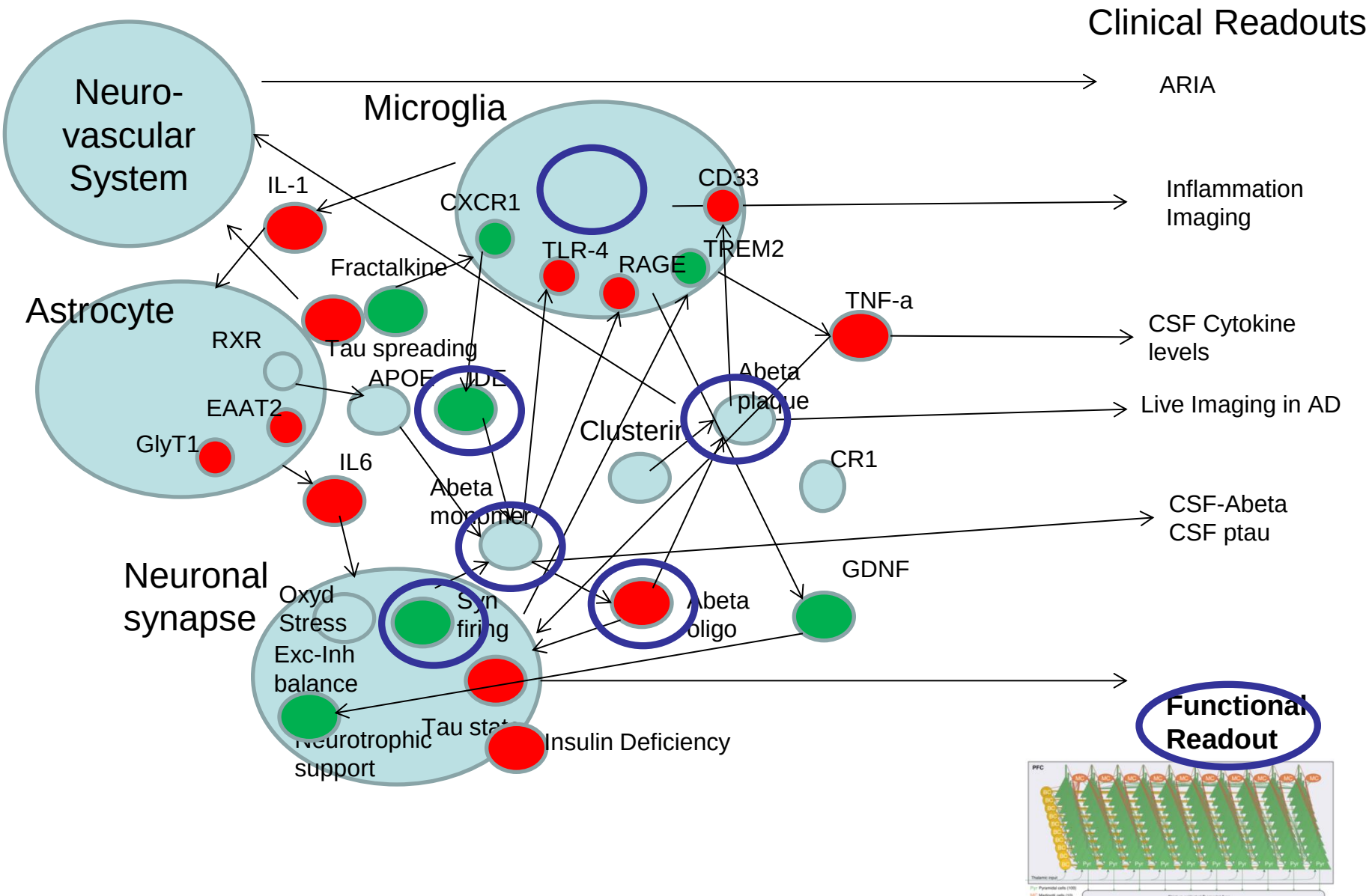




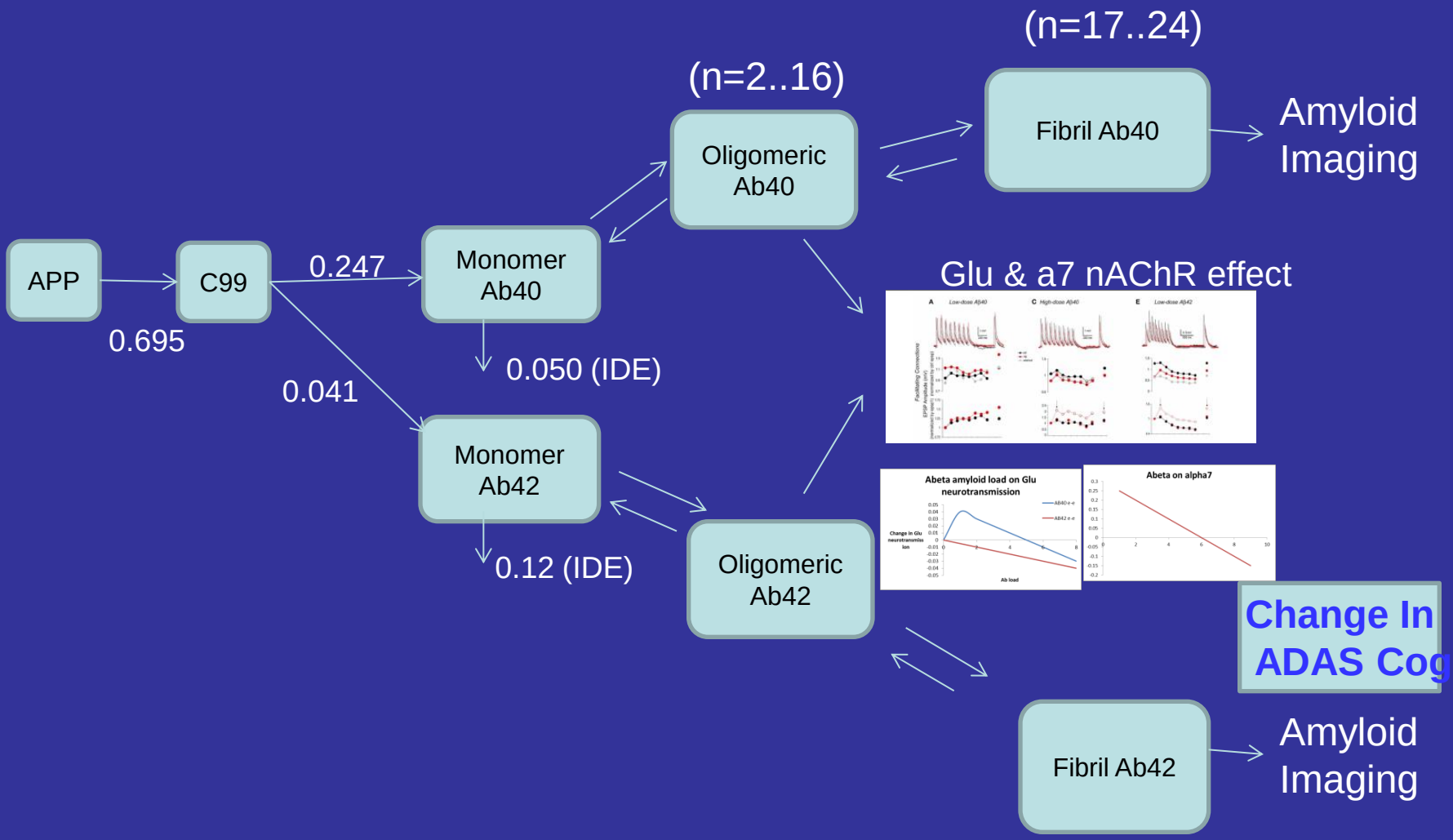


Nicholas 2013

Linking Amyloid Modulation To Cognition in Alzheimer's Disease

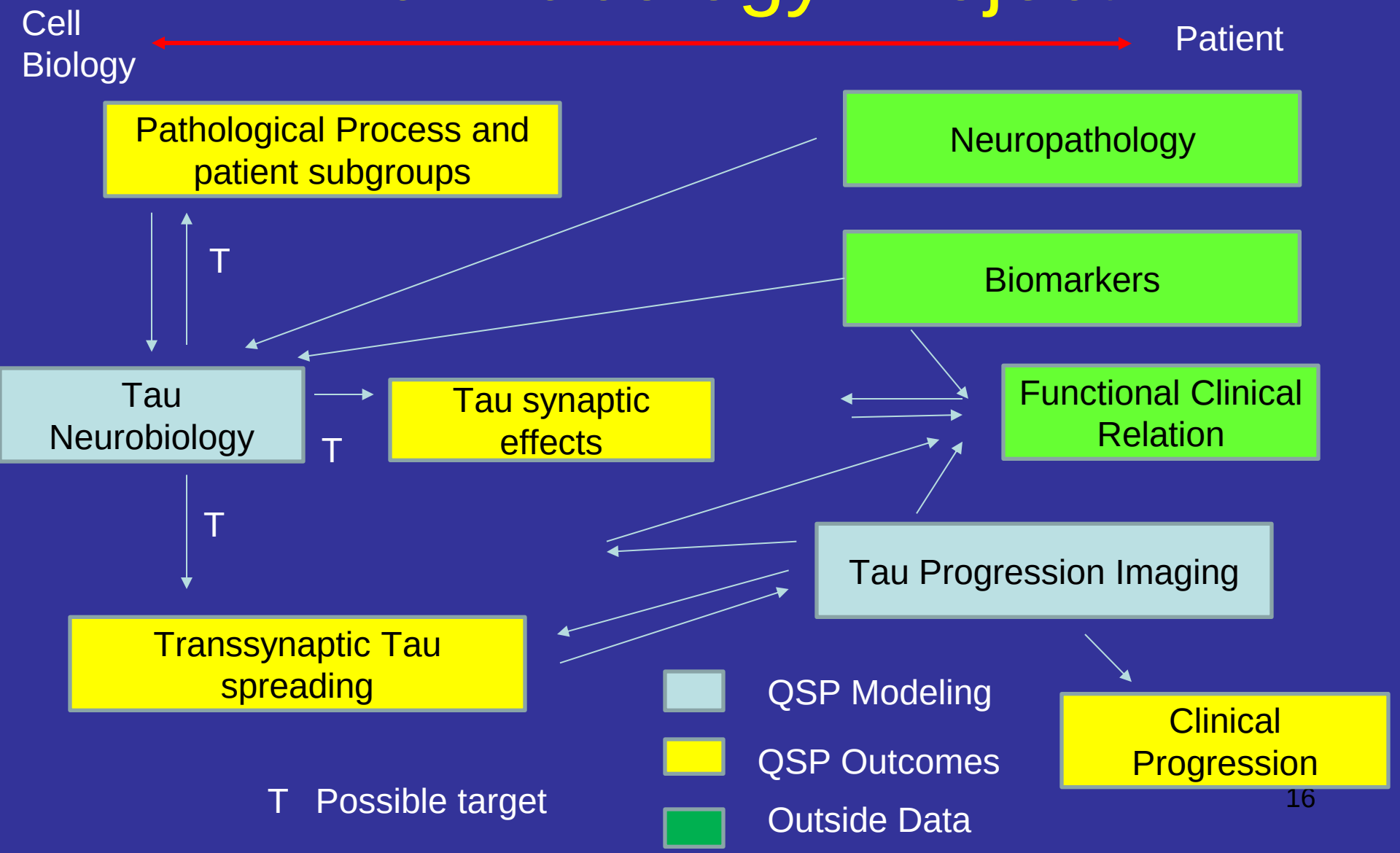


Amyloid Modulation



Potter 2013, Garai 2012, Wang 2014, Doraiswamy 2015

Tau Quantitative Systems Pharmacology Project



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