Webinar

Of Mice and Men.

Bridging the Translational Disconnect in CNS R&D

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Panel

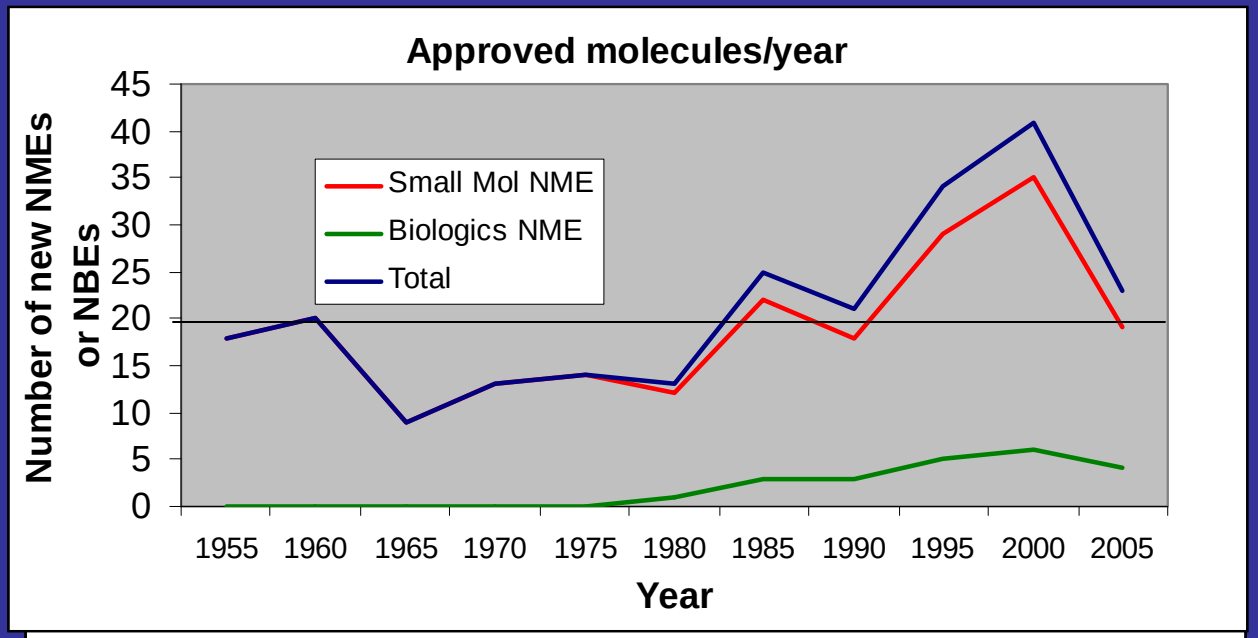
- Prof. Kurt Brunden, Director Drug Discovery, CNDR, University of Pennsylvania
- Dr. Kevin Felsenstein, Research Fellow Envivo Therapeutics
- Prof William Honer, Professor of Psychiatry at University of British Columbia
- Prof. Steven Arnold, Professor of Psychiatry at University of Pennsylvania
- Dr. Weidong Li, UCLA
- Dr. Mike Sasner, Jackson Laboratory
- Dr. Akira Sawa, Johns Hopkins School of Medicine

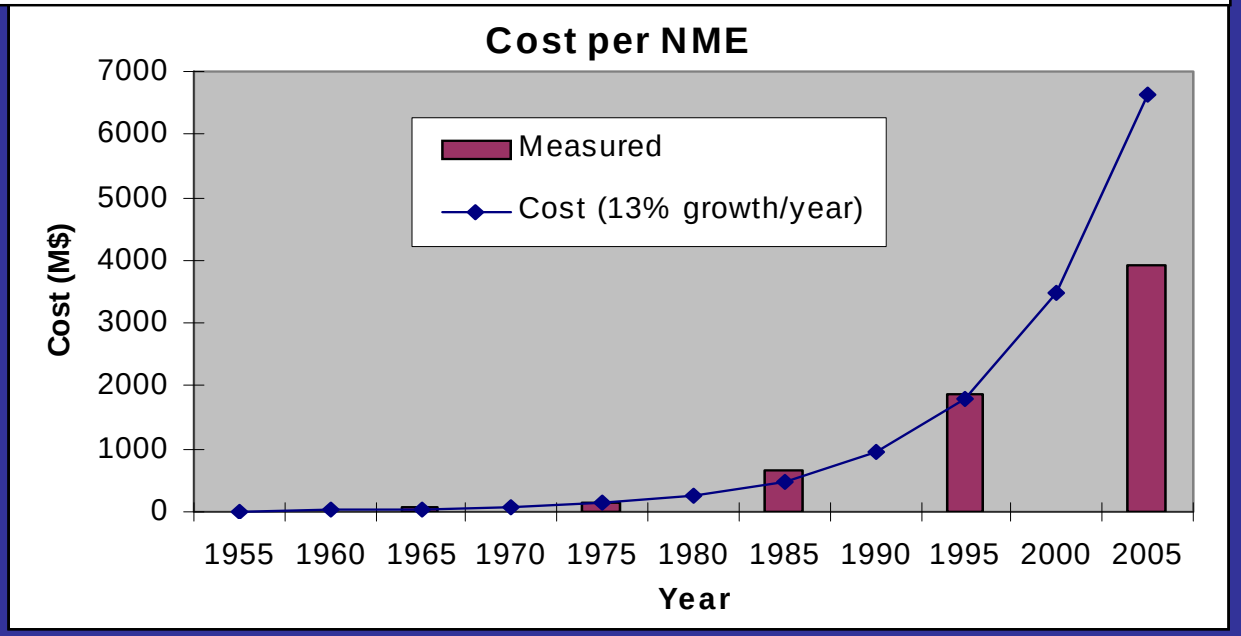
- Disclaimer : Hugo Geerts is an employee of In Silico Biosciences

Dr. Paul Janssen
1926-2003

“In order to solve complex problems, you need a drug with complex pharmacology ...”

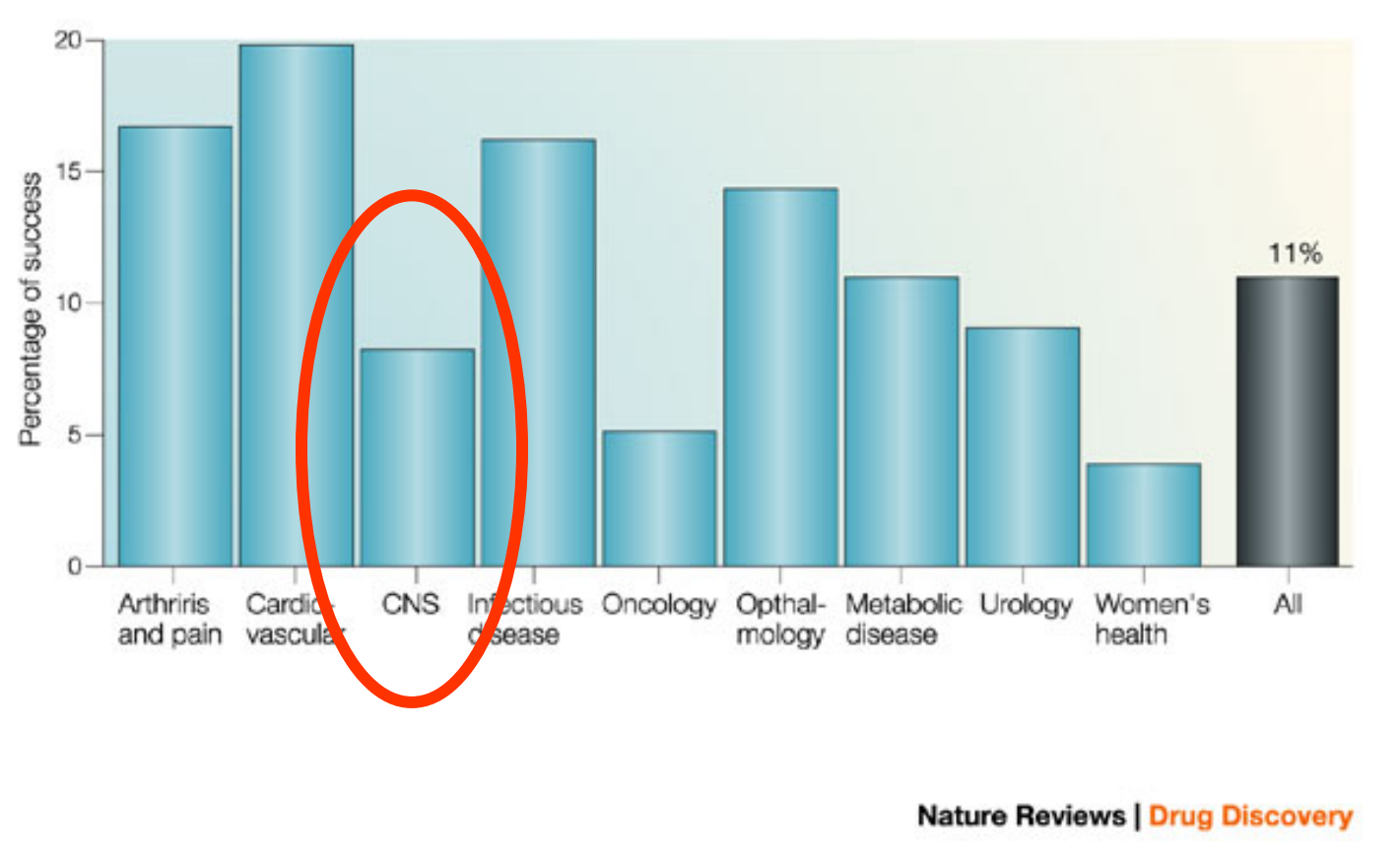
The innovation gap





Munoz 2009

Success rates for CNS drugs



- >90% of CNS compounds fail to reach registration
- >40% are failures of efficacy
- Avoiding high failure rates for CNS medicines requires a coherent research strategy

5

Kola and Landis, Nature Reviews, 2004

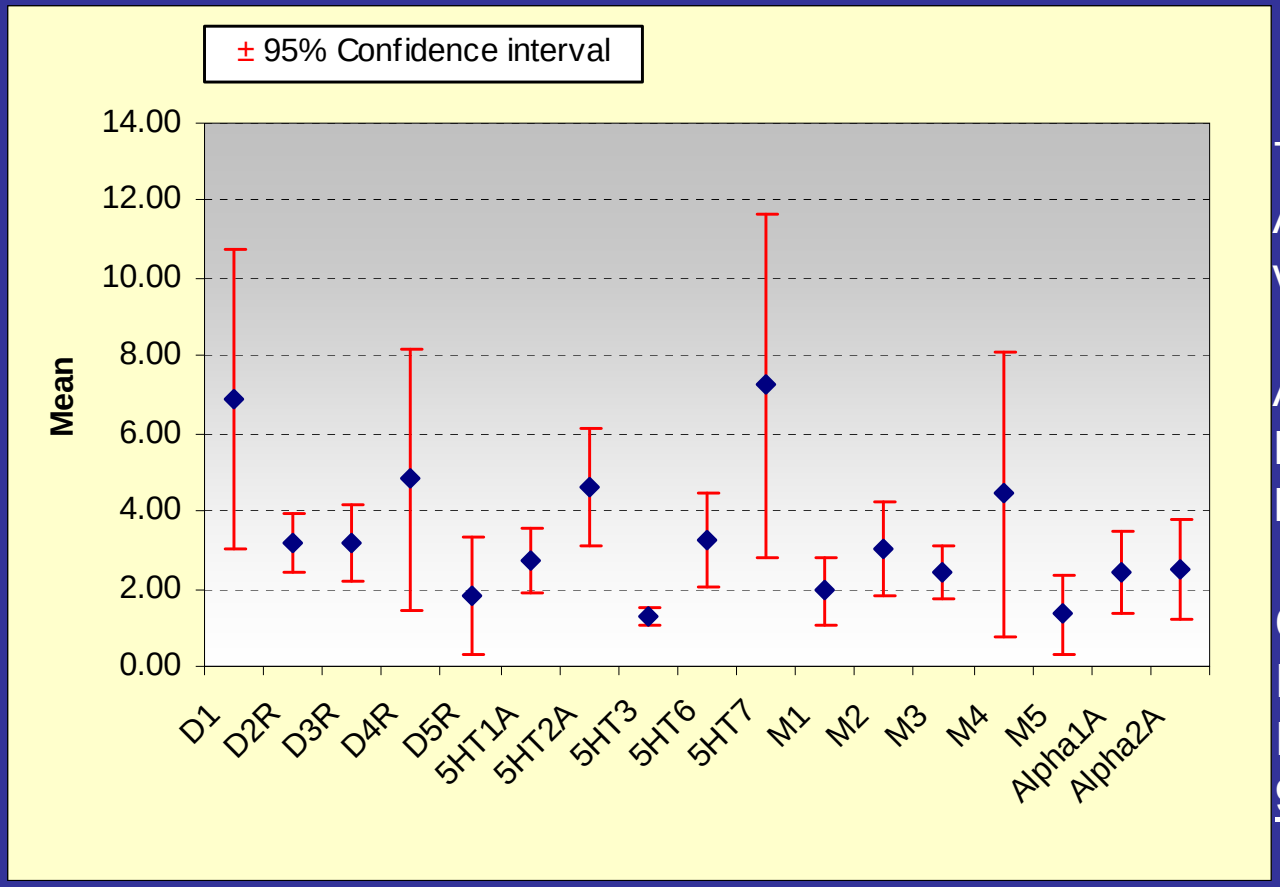
Animal models in Drug R&D

- All drugs in clinical development have passed (some) animal studies for efficacy and toxicity
- Of all drugs that work in animals and are safe, only 7-10 % work in humans without major safety problems
- Animal models are great to identify and dissect the molecular basis of key biological processes; so why do so many drugs fail in the clinic?

- Disclaimer : The author has no intention of being complete in ‘limitations’ or ‘solutions’

Limitations of animal models

1. Many drugs have different affinity on key human vs rat receptors



764 Agents-hot ligands pairs
Affinity data in rat
vs human receptors

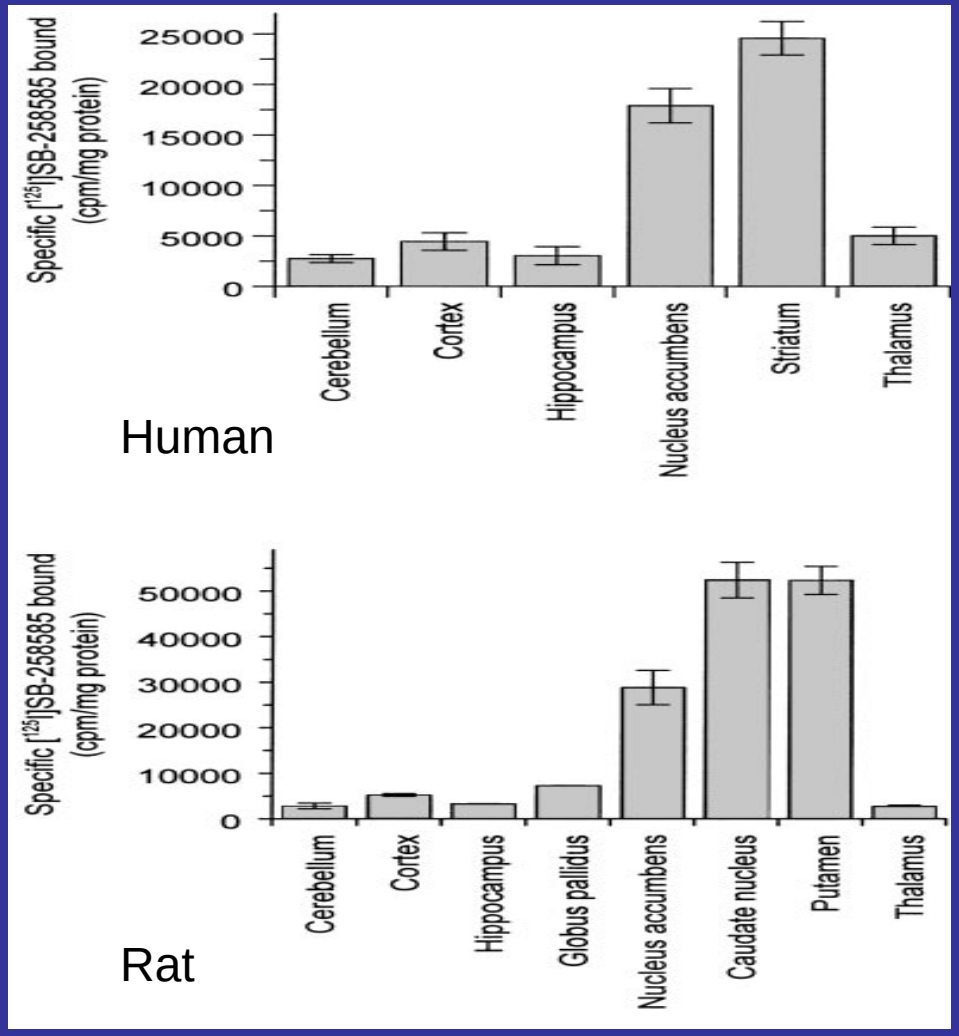
Affinity Ratio =
If Rat>Human, Rat/Human
If Human>Rat, Human/Rat

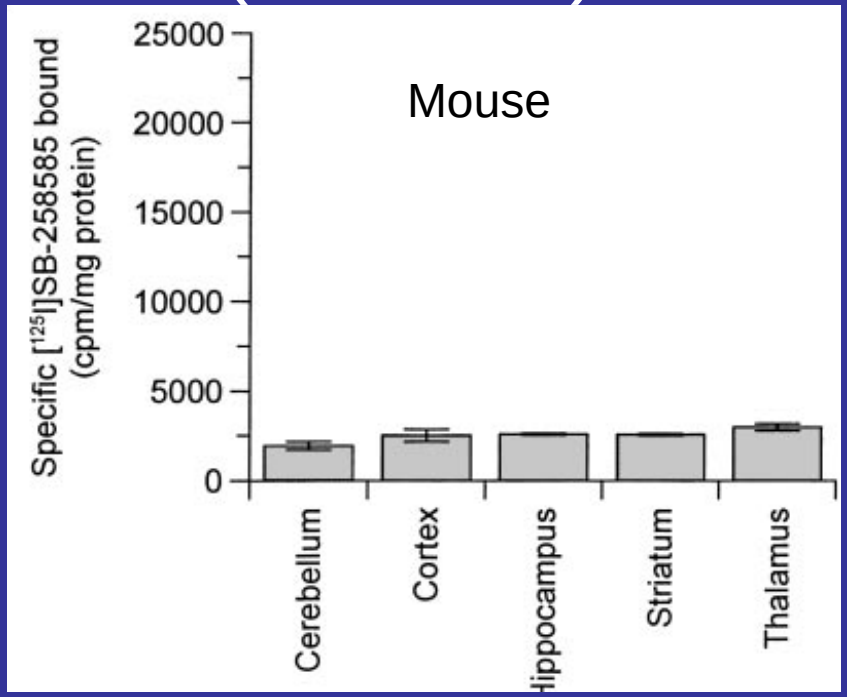
Clinical Example :
Risperidone metabolite
D1/D2 affinity ratio is
90 in rat, but **3** in human

Geerts 2010, in preparation

Limitations of animal models

2. Differential wiring of certain neurotransmitter circuits (5-HT6 R)

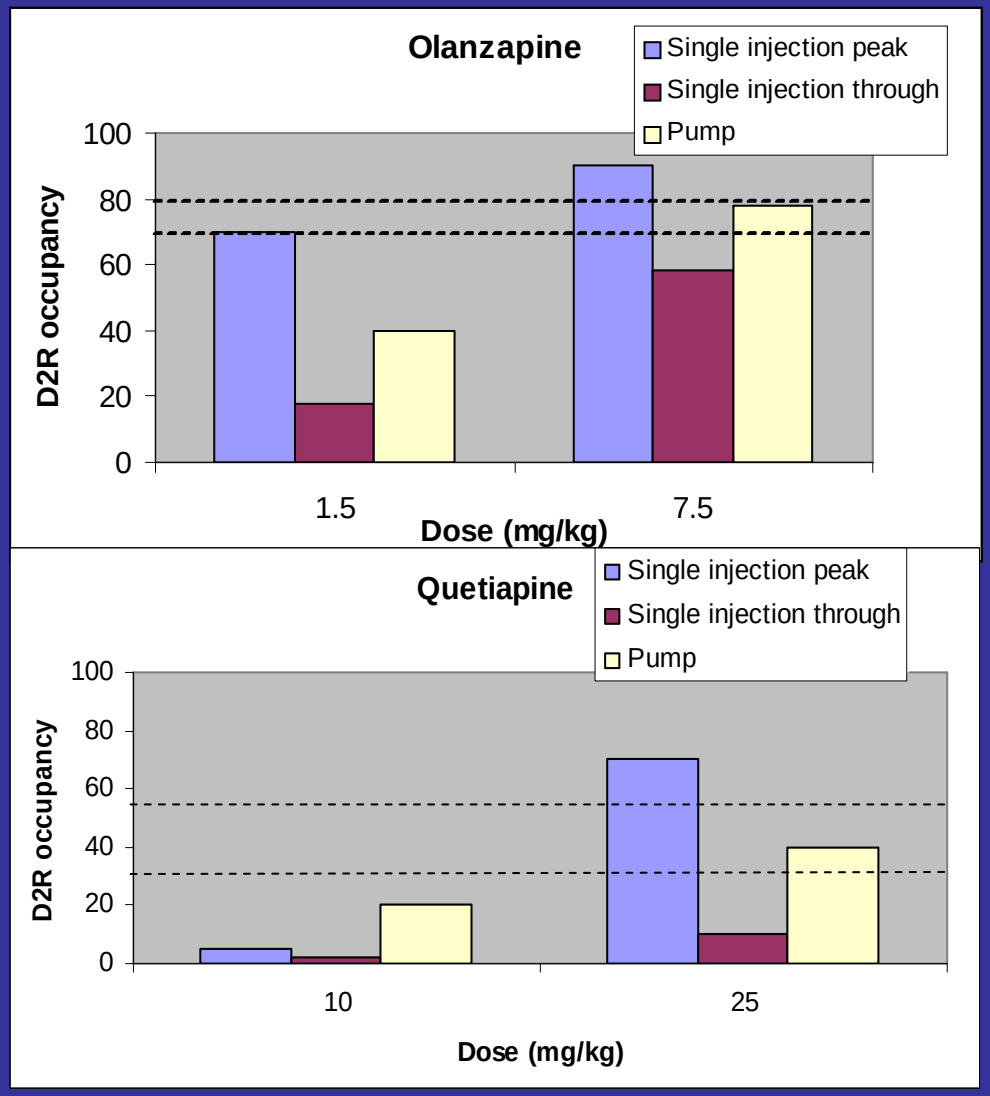




Other examples include
5-HT3, NK1, mGluR5

Hirst 2003

Limitations of animal models
3. Different drug exposure



Increasing use of microPET

Kapur 2003

Limitations of animal models

3. Formation of different active metabolites

Detailed Metabolic Profiles and Species Comparison

AMRI

	Metabolite ID								
	Human metabolites					Unique mammalian metabolites			Parent
	M1	M2	M3	M4	M5	M6	M7	M8	
Δ MW [a]	+32	+16	+2	+16	-14	-10	+2	+16	
ΔRT [b], min	-2.6	-2.2	-0.4	-0.3	<-0.1	-3.2	-0.3	+0.3	
Reaction [c]	oxidation +hydroxyl	oxidation	oxidation +demethyl	hydroxyl	demethyl	unknw	hydroxyl +demethyl	oxidation	none
Liver fractions (HPLC peak area, %)									
Human	2	53	4	11	9	-	-	-	21
Rat		15	2	9	-	23	20	-	31
Guinea Pig	2	18	4	12	-	-	-	3	50
Beagle Dog	-	22	4	5	-	6	-	-	62
Minipig	-	9	4	5	-	-	-	-	69
Cynomolgus Monkey	-	18	2	-	-	-	20	2	60
Rhesus Monkey	0.3	25	4	3	-	-	10	-	55
White Rabbit	1	12	4	9	-	8	4	1	45

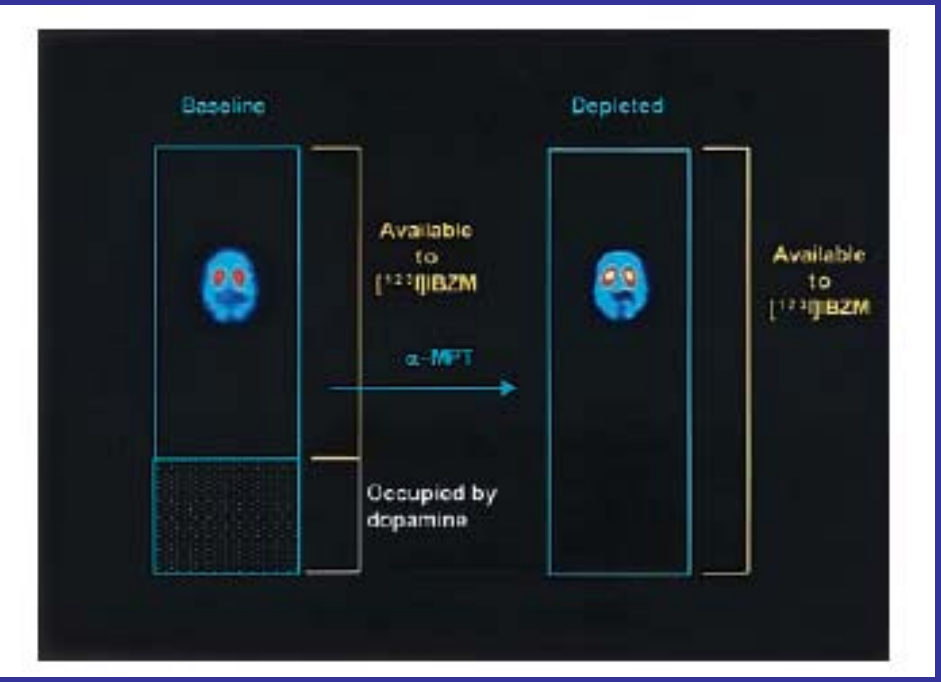
Clinical example : nor-quetiapine (from Seroquel)
is a NET inhibitor and is a metabolite in human but not in rats (Winter 2008)

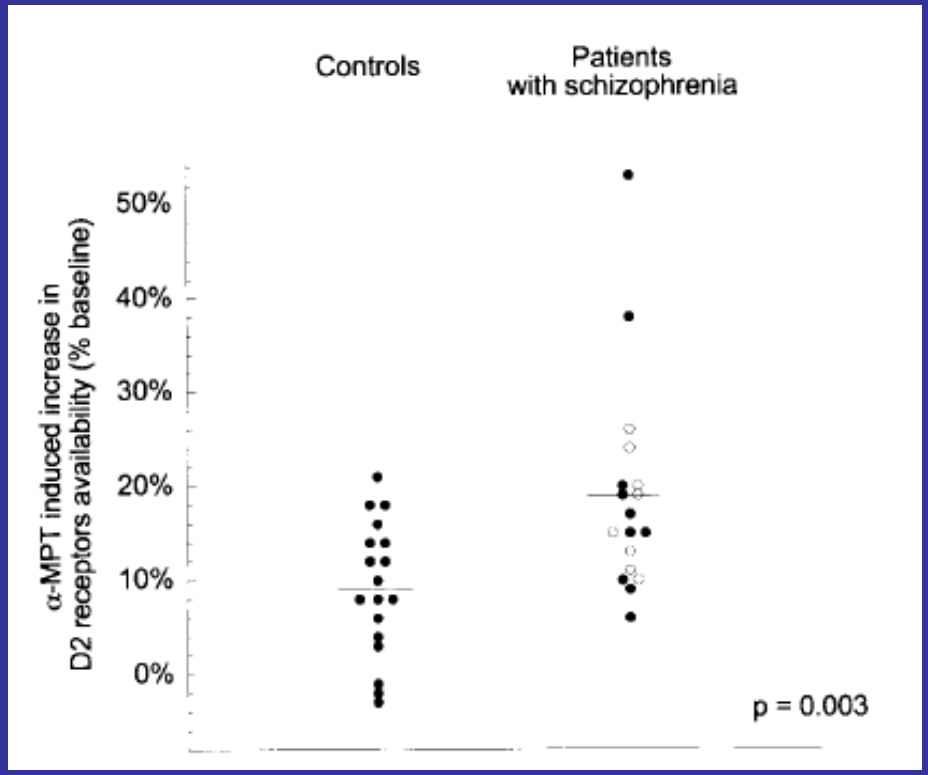
Limitations of animal models
4. Full pathology in animal models

- Many models are based upon ‘lesion’ or genetic manipulation induction
- Advantages
  - Recapitulates part of the (neurochemical) pathology spectrum
  - Great for dissecting the pathological process
- Limitations
  - They don’t capture time-delayed & environmental onset
  - They often don’t display pre-morbid or pre-symptomatic aspects
  - Rodents are nocturnal animals; many CNS diseases have sleep disturbances
- Issues : what animal model to choose?

Limitations of animal models

4. ‘Simple’ pathology can differ between humans and animals





A-methyl-para-tyrosine as Tyrosine Hydroxylase inhibitor, depletes dopamine
Patients experience 2-fold increase in free striatal DA, amphetamine in rats
Results in 4-5 fold increase

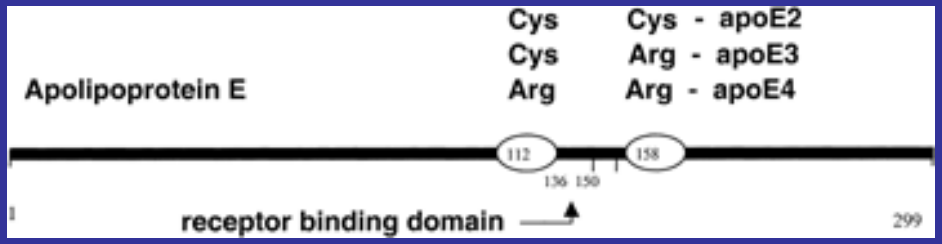
Abi-Darghaam 2000

Limitations of animal models

5. Lack of functional human genotypes

APOE and Alzheimer

Click for Bio



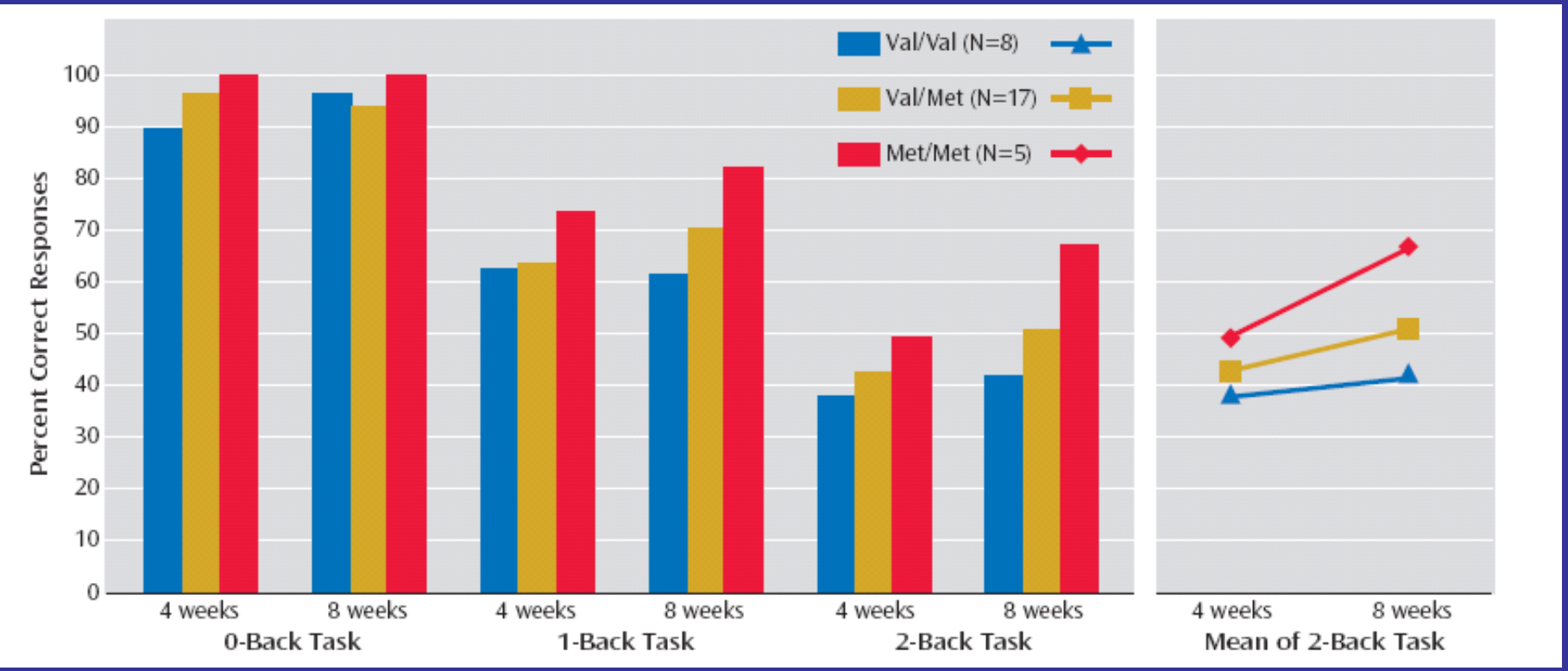
	Distribution of alleles				Comparison of various groups		
Alleles	Early AD	Late AD	Total AD	Controls	Early AD/ Controls (χ^2)	Late AD/Controls (χ^2)	Total AD/Controls (χ^2)
E2	0.06	0.09	0.08	0.09	0.29	0.05	0.19
E3	0.44	0.45	0.45	0.78	7.94*	9.04*	10.54*
E4	0.50	0.46	0.47	0.13	16.67*	14.83*	16.68*

*Significant at $p<0.05$

There is only one ApoE* gene in rodents
Increased interest because of bapineuzumab trial – why should APOE4- subjects respond better ?

Limitations of animal models

5. Lack of functional human genotypes Catechol-O-methyl-Transferase in DA & NE catabolism



Olanzapine treatment in 28 patients : N-back task of working memory
Bertolino 2004

Limitations of animal models

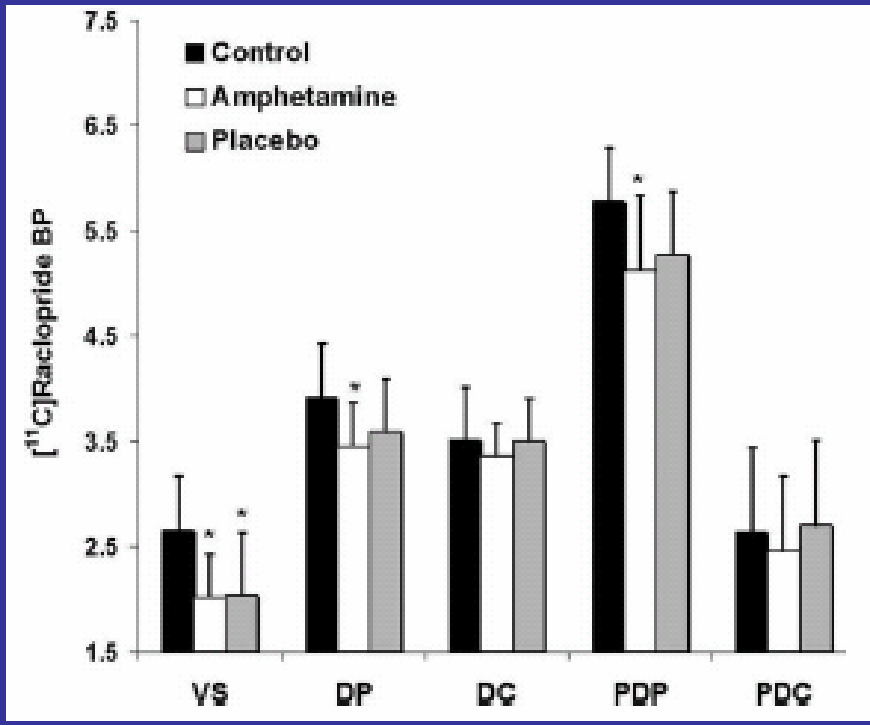
6. No Polypharmacy in preclinical animal models

- In clinical trials AD patients often are allowed to continue on
  - Cholinomimetic medication
  - Insomnia drugs
  - Parkinsonian medication
  - Antidepressant/antipsychotic medication
- Many of these medications act on neurotransmitter pathways involved in cognition and amyloid processing
- Example :
  - muscarinic receptor modulation downstream of standard AChE-I inhibition in patients might modulate APP processing
  - Insomnia drugs work on inhibitory interneuron circuits that affect cognitive clinical scales
- This kind of polypharmacy is rarely tested in preclinical research

Limitations of animal models

7. Placebo activates the dopamine reward system

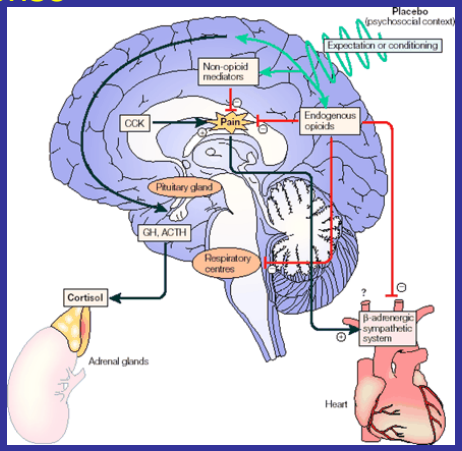
- Placebo effect activates subcortical dopamine reward circuit
- Human imaging & computational modeling gives increasingly more insights on underlying physiology & biological processes

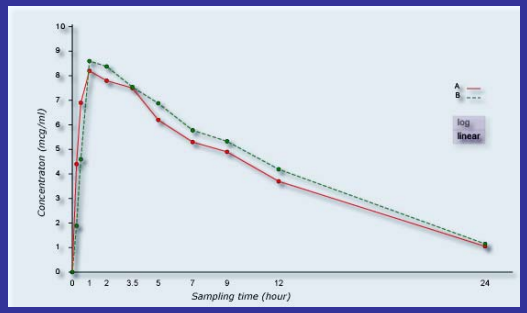


Boileau 2007

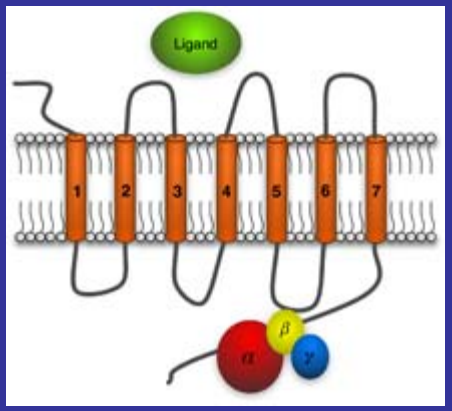
Limitations of animal models

Placebo response

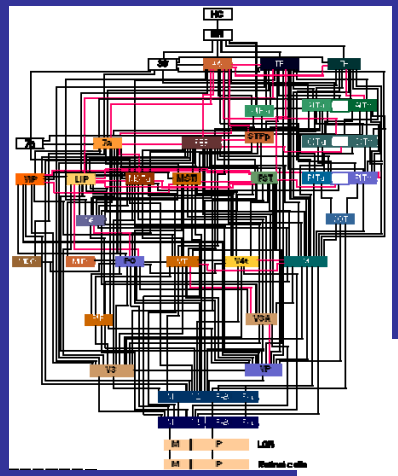




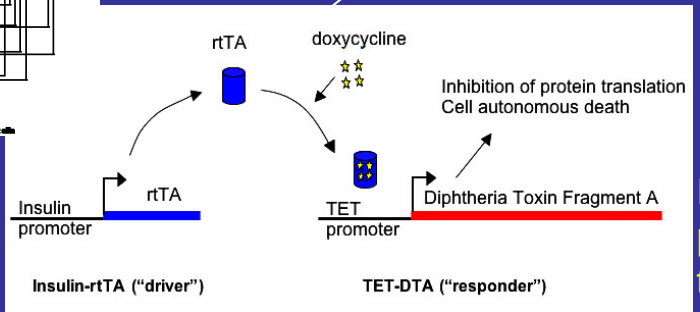
Differences in drug metabolism



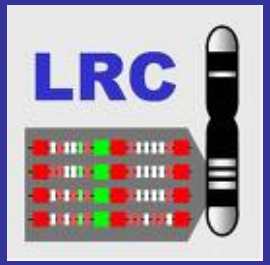
Different drug affinities



Different neurotransmitter wiring



Incomplete pathology in transgenic mice



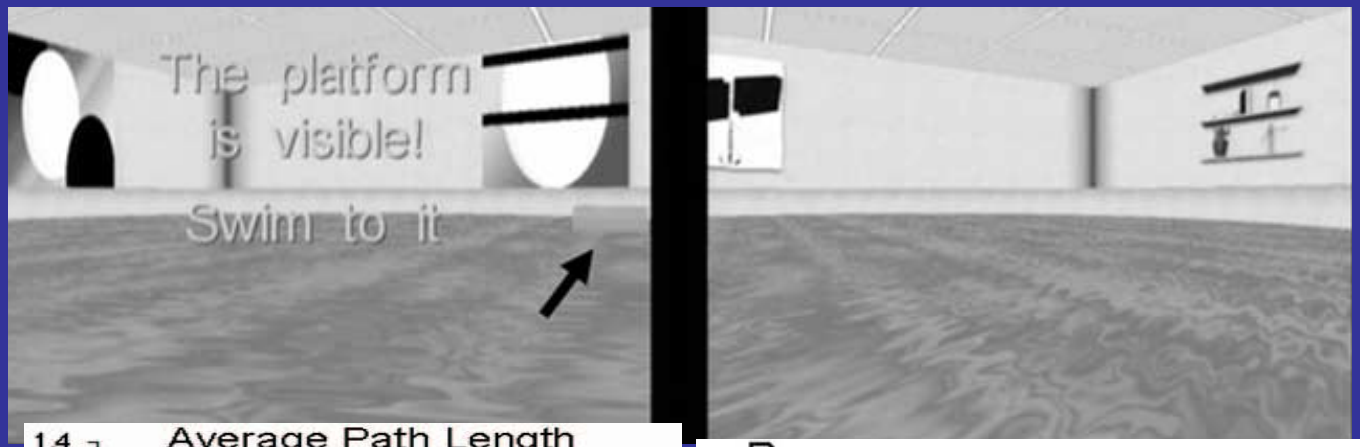
Absence of functional genotypes

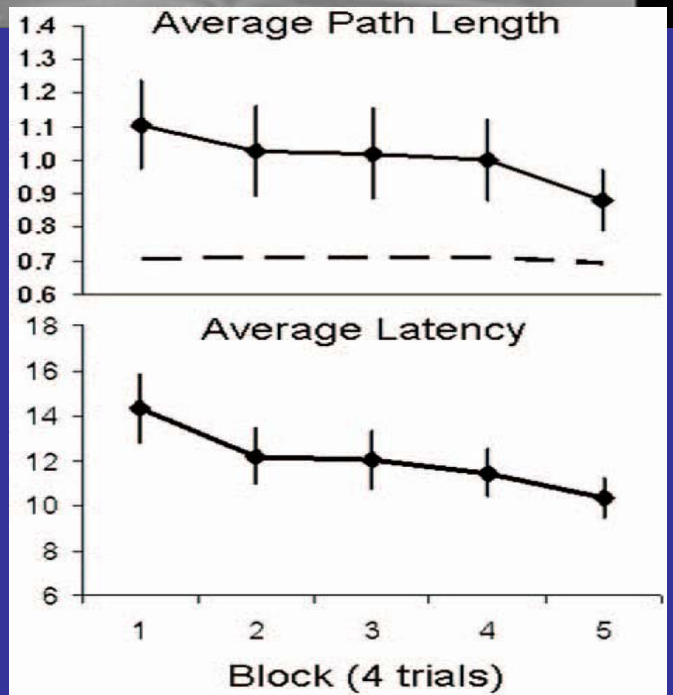
Geerts, CNS Drugs 23,915

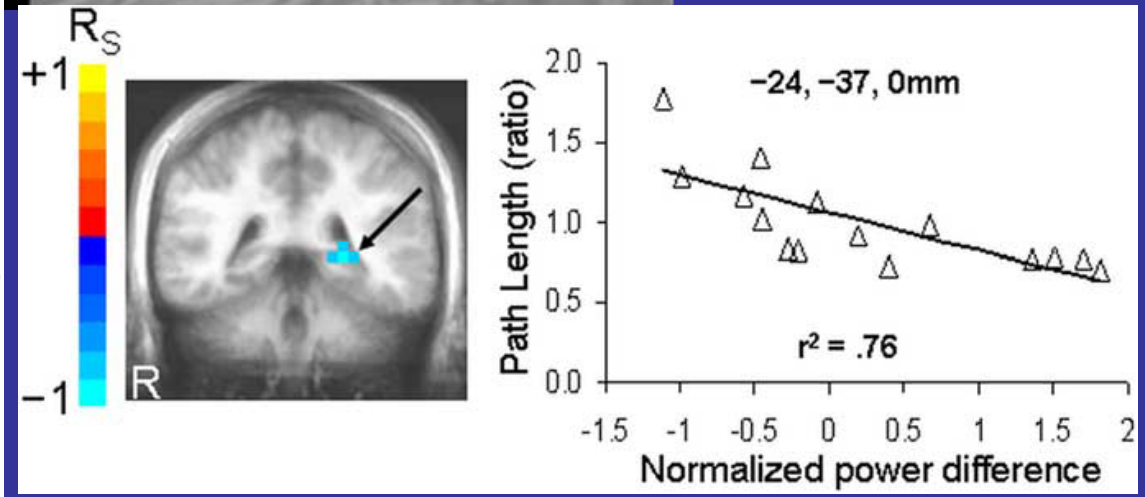
Possible Solutions

1. Better translational Tools

From rodent to human : virtual water maze







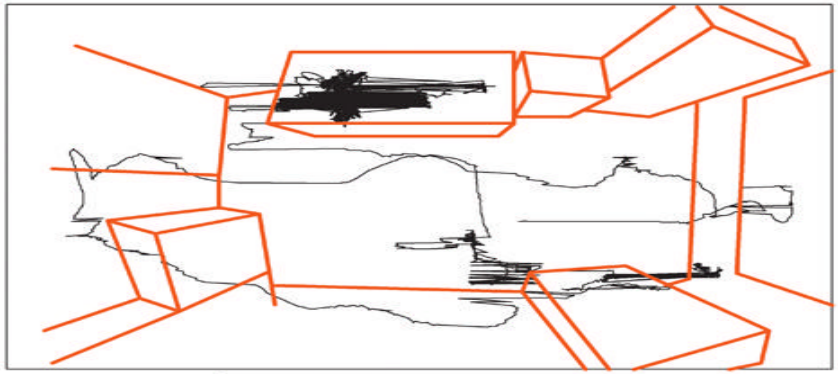
Cornwell 2008

Possible Solutions

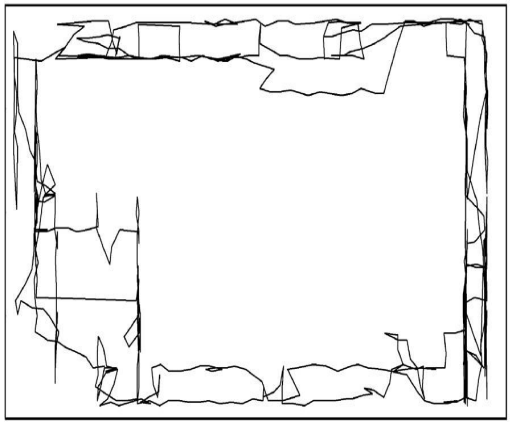
1. Better translational Tools

From human to rodent : Behavioral Pattern Monitor

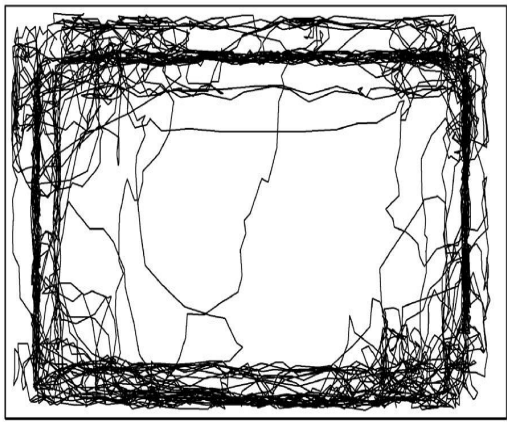
(a)



Acceleration	2.07
Transitions	199
Spatial *d*	1.70
Toy Interactions	7



Transitions	224
Spatial *d*	1.5
Total holepokes	60



Transitions	569
Spatial *d*	1.38
Total holepokes	183

(b)

Acceleration	1.63
Transitions	444
Spatial *d*	1.27
Toy Interactions	19

Bipolar Disorder patients

Young 2008

Possible Solutions
2. Learning from your mistakes

- Micro-electronics
  - 1970's : tunneling was originally seen as nuisance, production process problem
  - Closer look and further development led to the concept of non-volatile memory, launching the cell phone industry
- Child cancer network
  - 1970 : child cancer : 10% survival the first year
  - Decision to set up network, so that every diagnosed child was part of a study with both positive & negative outcomes
  - 40 years later : 90% survival the first year
- US Government mandated ClinTrial website lists over 70,000 trials
  - Only 46% publishes results within 2 years (Ross 2009)
- Barriers
  - 'Move on' philosophy; fatalistic mentality ('nature of our business')
  - Failure seen as personal failure; you want to forget as fast as possible
- Increased interest in Drug Repositioning

Possible Solution

3. Correlate drug effects/phenotypes of animal models with clinical outcome

- Both false positive and false negative predictions from animal model result to clinical outcome
- Barriers to full-scale animal model validation
  - Not perceived as part of the job description or helpful in progressing individual discovery projects
  - Compounds from other companies difficult to acquire
  - Clinical Doses sometimes difficult to match
  - New targets don’t have clinical results
  - Dosing, strain genetics or seasonal influences issues
  - Translational problems with phenotypes

Possible Solution
3. Pre-competitive Consortia

- Third party (i.e. CHA, R&D Biomedical Center for Innovation – MIT) can facilitate global validation testing
- Example : Liver toxicity
  - Cellomics HCS toxicity with human hepatocytes; 10 Pharma companies provide compounds with known human liver liability
  - Selection of the Cellomics parameter which has biggest correlation with human liver toxicity
  - Use this (validated) toxicity test for early selection can save time & money
- Similar initiatives
  - Alzheimer Disease Network
  - Consortium for genetics of schizophrenia
- Set up pre-competitive consortium for systematically testing different animal models in Alzheimer' disease and Schizophrenia
- Consider alternative properties/models : gender, strains, diurnal vs nocturnal animal models

Possible Solution
4. Learn From Other areas
Measurement and Treatment Research to Improve Cognition in Schizophrenia

- NIH-FDA initiated effort to address cognitive deficit in schizophrenia as unmet medical need for treatment
- **Cognition deficit in Schizophrenia is driving the pathology (only 4% of 'successfully' treated patients are back to their professional level after one year)**
- Current Status
  - **FDA approved battery for cognitive enhancers (60 minutes, 7 dimensions)**
  - **TURNS (Treatment Units for Research in Neurocognition in Schizophrenia) has initiated 3 Proof-of-concept trials in schizophrenia (AMPAkine, AL108, nAChR modulator)**

MATRICS

Pharmacological Validation of Animal models (Proposal)

Cognitive Domain	Animal Models/Tests	Clinical Battery (Beta version)
Working memory	Operant or T-maze DNMTP/ DMTP Radial arm maze	BACS WMS-III Spatial Span WAIS-III Letter-Number sequence UoM Letter-Number Span Spatial Delayed Response Task
Attention/vigilance *(pre-attentive processing)*	5-Choice Serial Reaction Time Task *PPI, auditory gating*	3-7 CPT Identical pairs CPT
Verbal learning and memory		NAB- Daily Living Memory HVLT-Revised
Visual learning & memory	Novel Object Recognition	NAB – Shape Learning BVMT-Revised
Speed of processing	5-Choice Serial Reaction Simple Reaction time tasks	Category fluency Trail making A WAIS-III Digit Symbol-Coding BACS – Symbol Coding
Reasoning & problem solving	Attentional set shifting Maze tasks	WAIS-III Block design BACS- Tower of London NAB - Mazes
Social cognition	Social interaction/Social recognition?	MSCEIT – Managing emotions MSCEIT – Perceiving emotions

Possible Solution

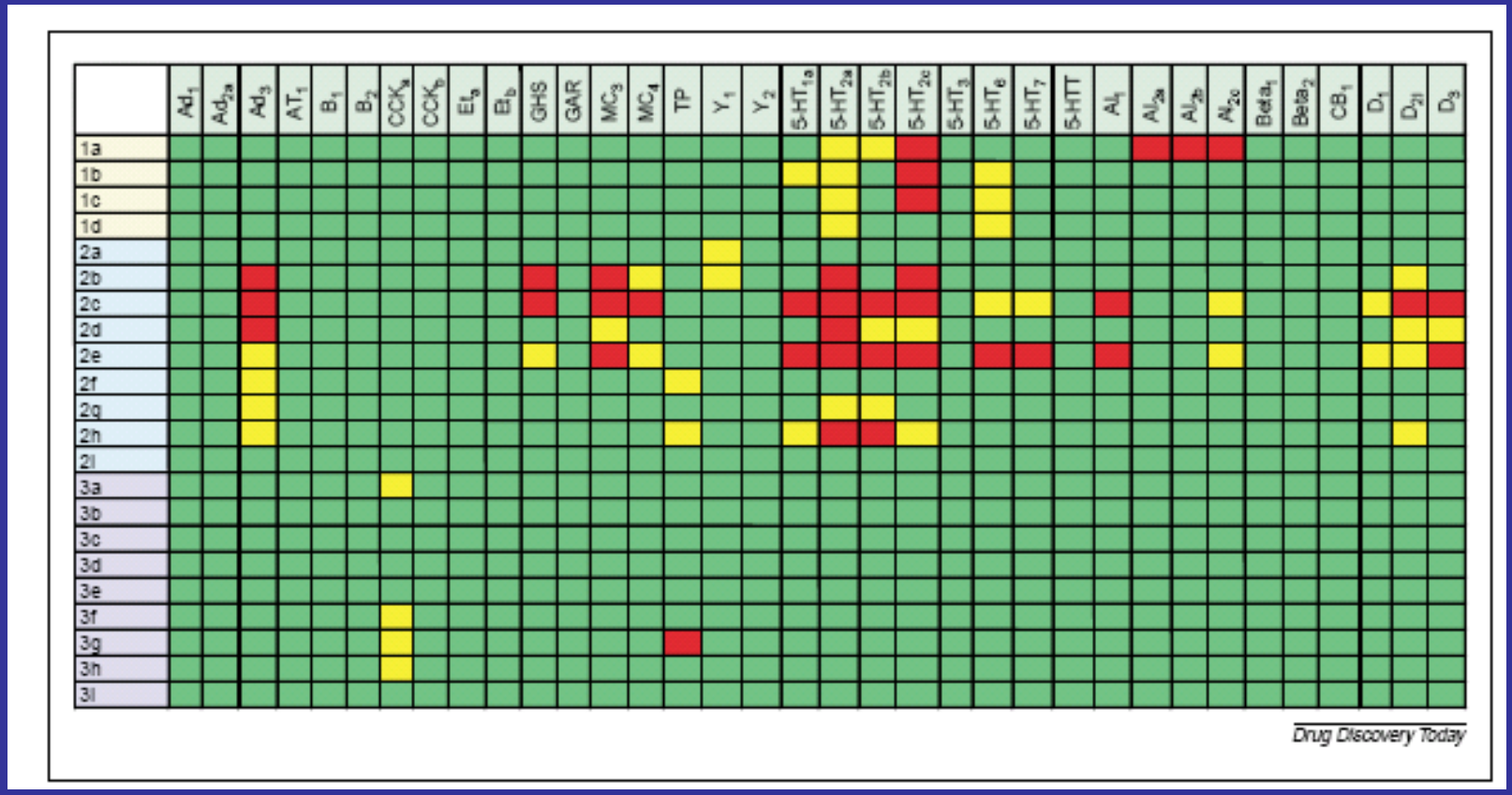
5. Emphasis on Multi-target strategy or polypharmacy

- Polypharmacy : more rule than exception
  - Coctail of drugs is standard in
    - Helicobacter pylori (gastric infection), AIDS treatment, Cancer treatment, Cholesterol-lowering drugs
  - In real-life patients have an average of more than 3 medications at the same time, however, this is not always rationalized
- Complex (CNS) diseases likely need multiple targets to be affected in the right proportion
- New business model (CombinatorX, Lifelike Biomatic)
  - Suboptimal Combinations of existing drugs work synergistically in new indications
- Barriers to adoption
  - MedChem campaign difficult : how ranking different synthesized molecules ?
  - Polypharmacy is rarely tested in preclinical animal models because of costs and complexity

Existing successful antipsychotic drugs found in functional, rather than molecular assays are often very ‘promiscuous’

Receptor

Drugs



Roth 2003

Possible Solution
6. Re-engineer Drug Discovery & Development process

- Look at business model of other successful industries (aerospace, micro-electronics, petrochemistry)
  - Large emphasis on computer simulation and modeling
  - Shorter lifecycles, higher success rate, faster growth
- Barriers to adoption of modeling&simulation
  - Insufficient ‘biological’ knowledge
  - Cultural divide between engineering-mathematics and biology/pharmacology
  - Current extremely reductionist approach driven by molecular biology & genetics – focus on one target, one disease

Possible Solution

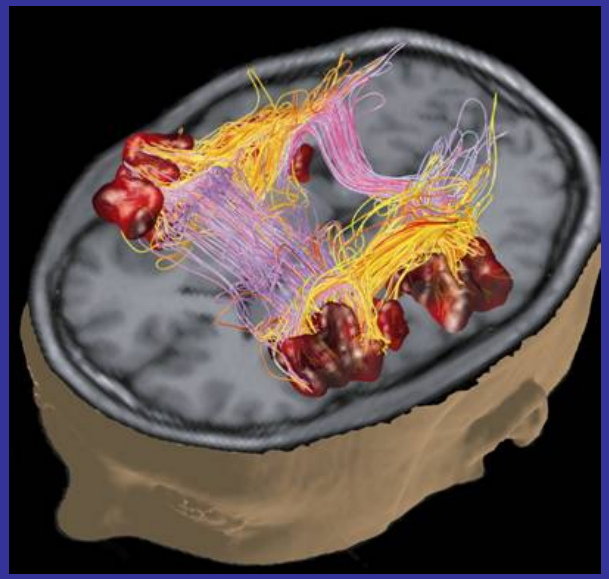
6. Integration of Modeling & Simulation in whole drug R&D process

- M&S currently used peripherally in early and late clinical development
- M&S can improve odds for success
  - End-of-Phase II FDA program
  - Pharmacometrics Dept of FDA sees mechanistic disease modeling and Systems Biology as essential and integrated parts of successful R&D paradigm
- Integrating M&S in Drug Discovery
  - Systems Biology : less applicable to CNS Diseases
  - Mechanistic Disease modeling
    - Based upon computational neuroscience and made actionable to support drug discovery & development
    - Humanizing the rodent brain by combining preclinical animal physiology with human brain imaging and pathology data
    - Building a model with a certain (limited) number of processes that mimic human clinical phenotype

Possible Solutions

6. Humanizing the rodent brain

Human Connectome Project (NIH)



Documenting the connections in the human brain
Functional activation maps
Network analysis

*www.**humanconnectomeproject**.org/*

Possible solutions
6. Increasingly Humanizing rodent models

- Introducing human receptor physiology & drug pharmacology in *in silico* models
  - Implementing ‘primate’ experimental data on striatal dopaminergic processes leads to different predictions for D2 partial agonists and explains clinical failure of certain partial agonists in schizophrenia
- Use *full human pharmacology* to assess off-target effects of a candidate compound
  - Indirect effects through network interactions can reduce the primary pharmacology of a compound
- Introducing PET-imaging based parameters of functional genotypes in *in silico models* of brain circuits, i.e. COMT
  - Assess genotype effect on cholinomimetic medication intended to improve working memory (mAChR, nAChR)
- Explore the biology of clinical responders in combination with PGX data by testing sensitivity of the *in silico* humanized model to the fixed drug pharmacology
  - What is the underlying biology of iloperidone responders?

Possible solutions for limited predictability of animal models

- Better translational biomarkers
  - Explore new types of analyses
- Use pre-competitive collaboration
  - Join forces to improve & validate preclinical models
- Learn from your failures
  - Re-examine why trials failed, drug repositioning
- Learn from other areas
  - Talk to specialists outside your area
- Consider pathology as network in imbalance
  - Embrace polypharmacy/multi-target approaches early on
- Re-engineering drug discovery operation
  - Integrate modeling & simulation organically in CNS Discovery & Development

Of Mice and Men.

Bridging the Translational Disconnect in CNS R&D

Questions & Answers

Hugo Geerts, PhD
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