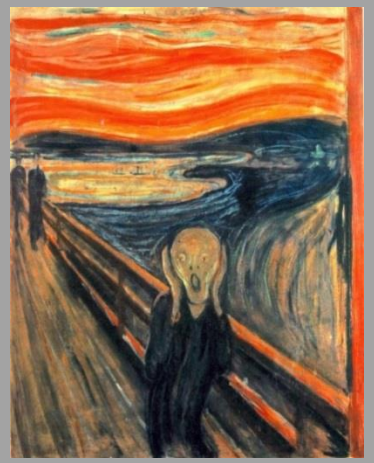
LABORATÓRIO DE FARMACOLOGIA BIOQUÍMICA E MOLECULAR
INSTITUTO DE CIÊNCIAS BIOMÉDICAS – ICB / UFRJ

Ensaios fenotípicos e alvo-dirigidos no processo de desenvolvimento de novos fármacos: aplicação ao caso de um antipsicótico atípico

François Noël



FF-UFRJ, 05/05/2016

Science **287**, 1960 (2000)

DRUG DISCOVERY

REVIEW

Drug Discovery: A Historical Perspective

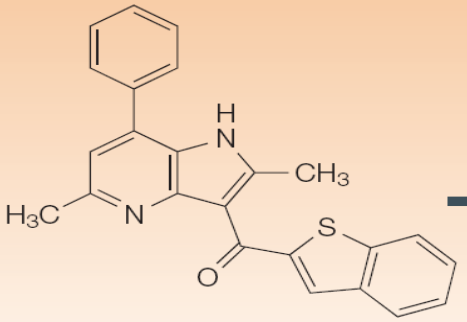
Jürgen Drews

*"Driven by **chemistry** but increasingly guided by **pharmacology** and the clinical sciences, drug research has contributed more to the progress of medicine during the past century than any other scientific factor."*

DESCOBERTA E DESENVOLVIMENTO DE FÁRMACOS

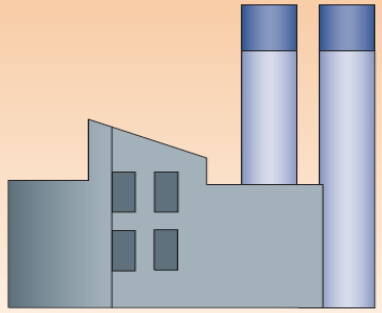
Preclinical studies

Research team formed and objectives set

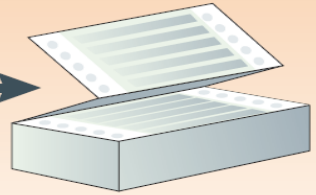


Novel chemicals synthesized

Chemicals tested for efficacy and safety in test tubes and animals. Results used to choose drug candidate.

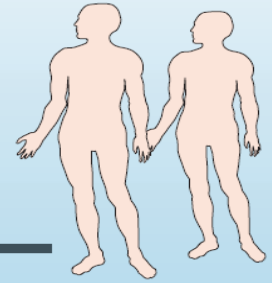


Formulation, stability scale-up synthesis, chronic safety in animals

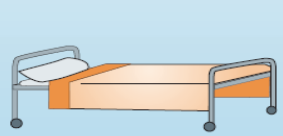


Company files Investigational New Drug (IND) application with FDA

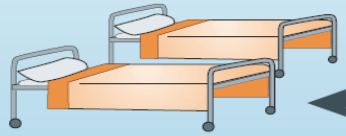
Clinical studies



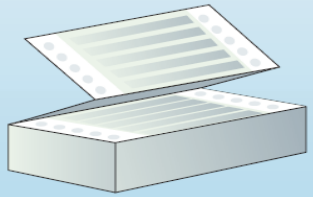
Phase I: studies in healthy humans (toleration)



Phase II: studies in patients (efficacy)



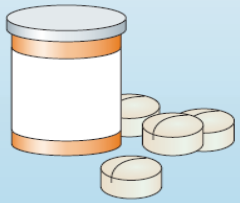
Phase III: large clinical trials in many patients



Company files New Drug Application (NDA)

FDA

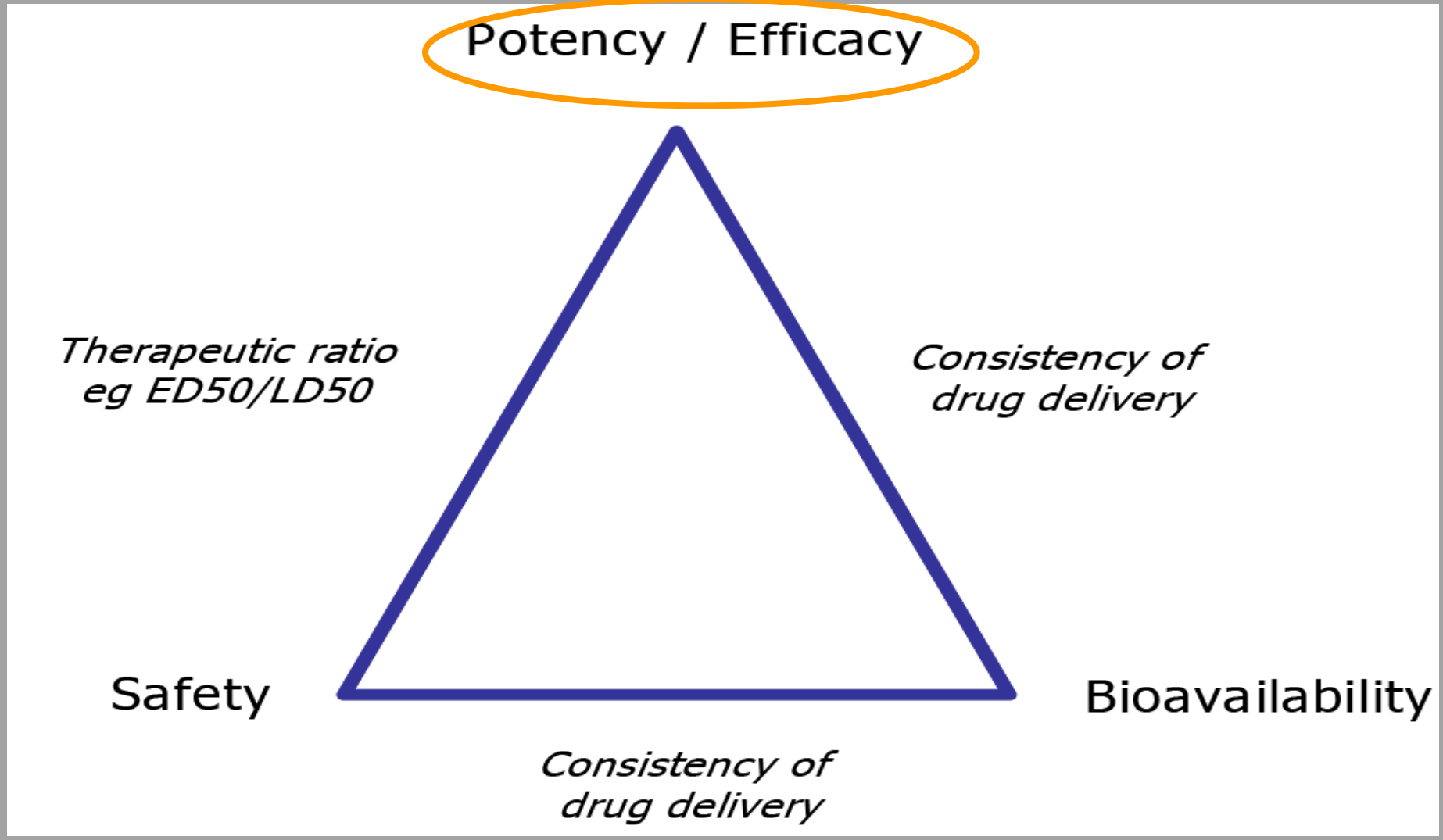
FDA reviews NDA



Drug is approved for marketing

Nature Rev. Drug Discov. 3: 853, 2004

Desenvolvimento de fármacos:
o *Triângulo das Bermudas*

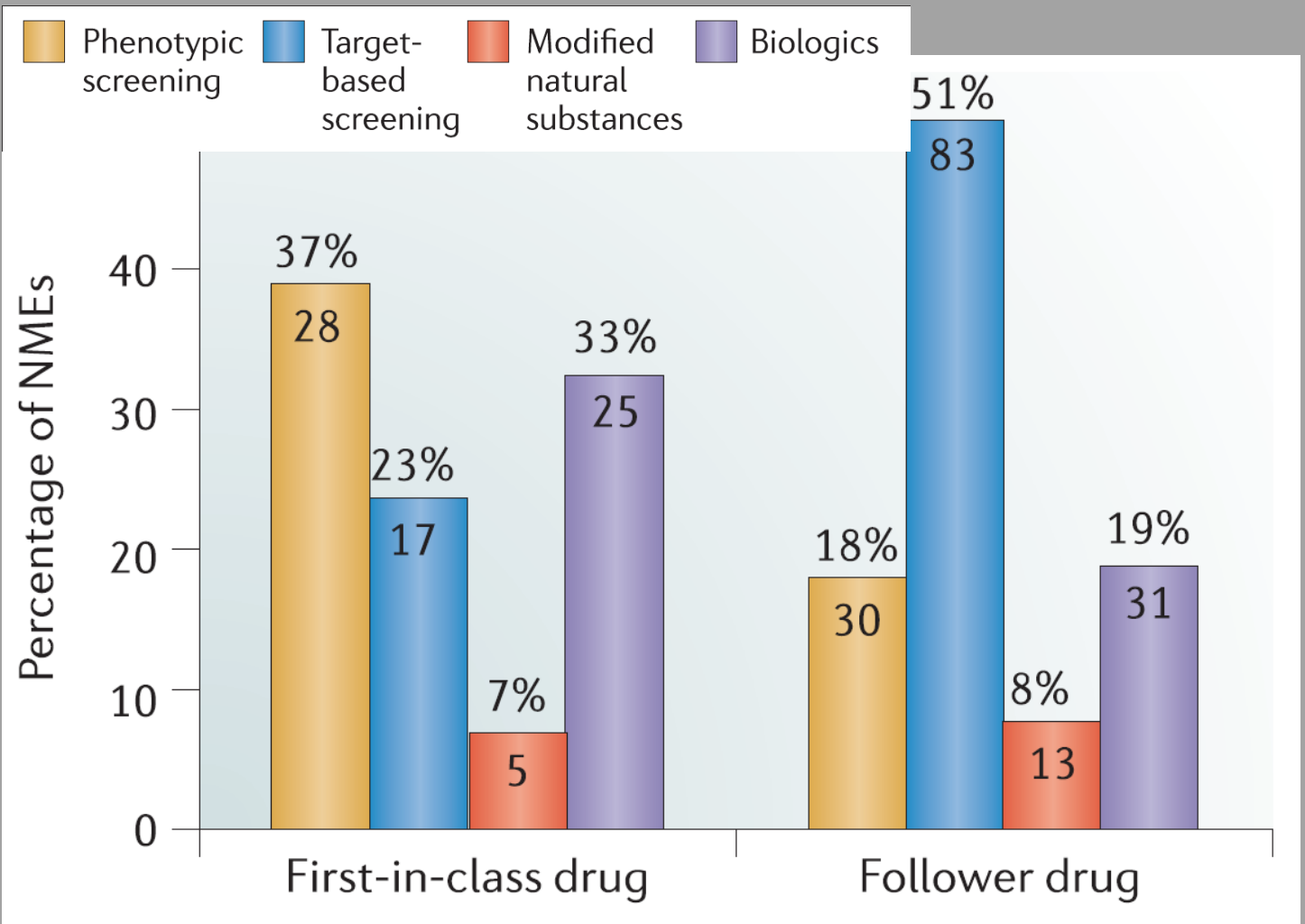


*How Drugs are Developed, P*eter Warne*, 3rd Edition, 2007*

Phenotypic vs. Target-Based Drug Discovery for First-in-Class Medicines

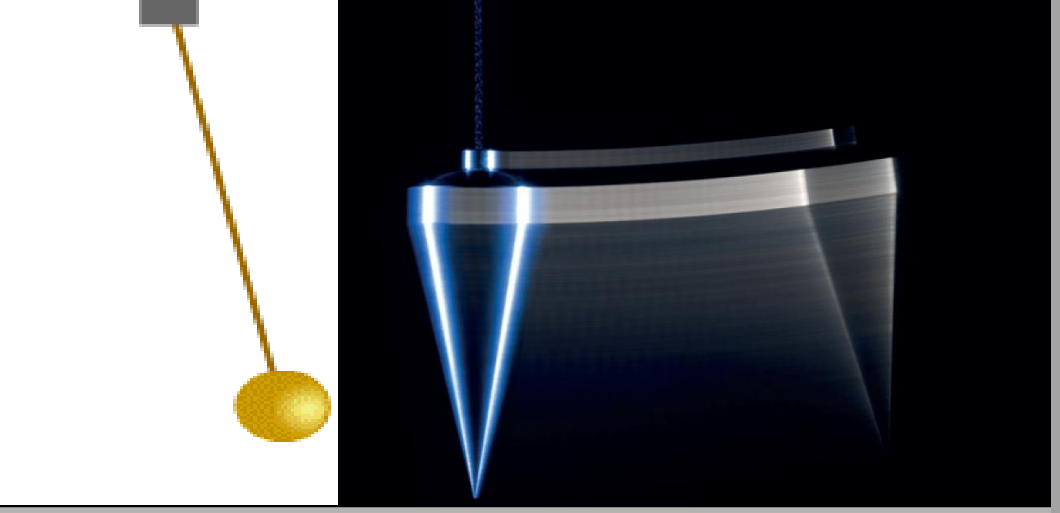
DC Swinney[1]

CLINICAL PHARMACOLOGY & THERAPEUTICS
VOLUME 93 NUMBER 4 | APRIL 2013



" Each of these two approaches has its strengths and weaknesses, and advocates and detractors".

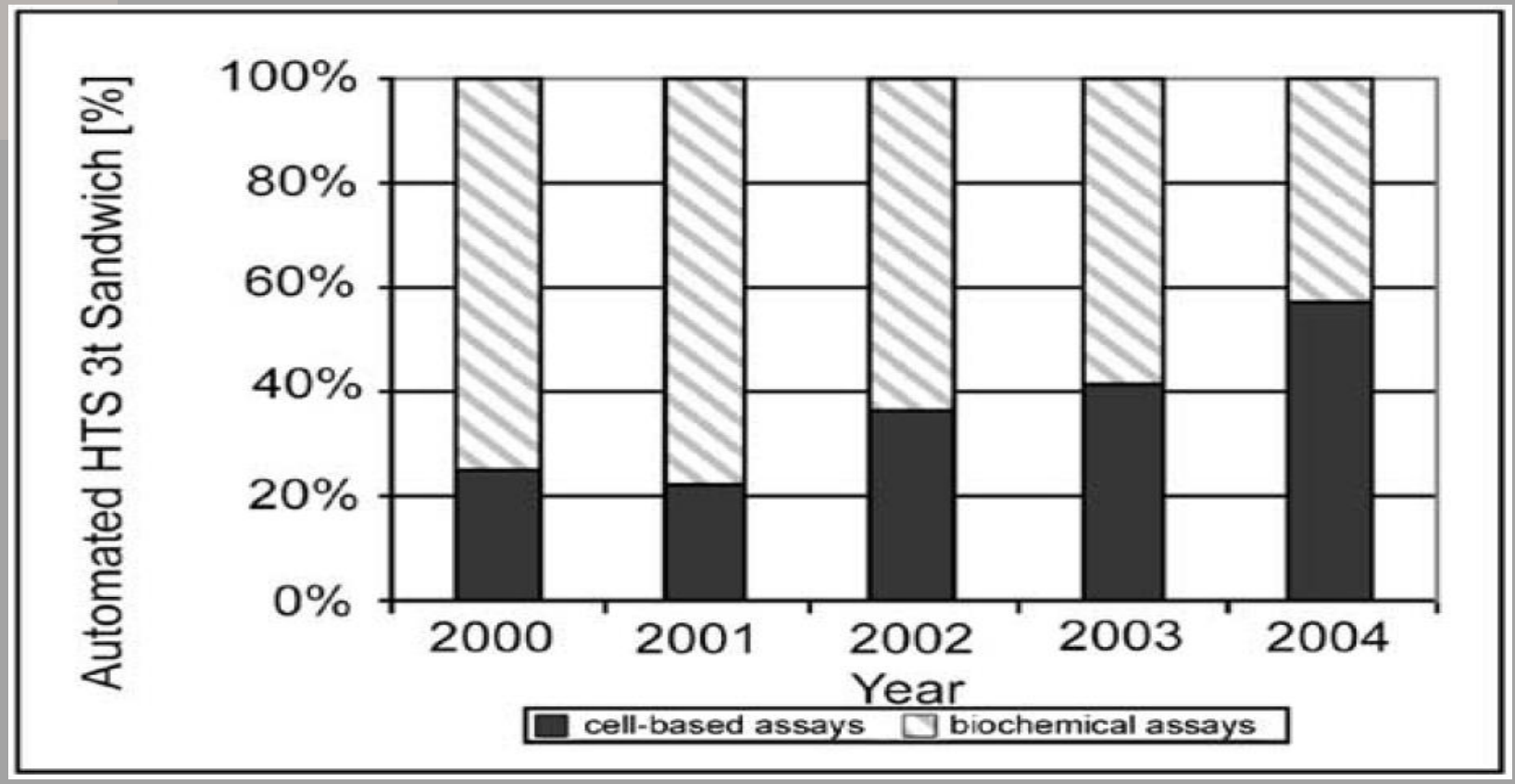
"The challenge is to use an ***appropriate combination of empirical and mechanistic research*** *and development to enable good ideas to successfully move forward"*



The phenotypic screening pendulum swings

Nature Rev. Drug Discov. 14: 807, 2015

Pfizer: a mudança começou em 2002



Combinatorial Chemistry & High Troughput Screening 8: 285, 2005

SPECIAL LEAD ARTICLE

Reflections on drug research

James Black

“Nenhum nível de avaliação é mais informativo do que o outro.

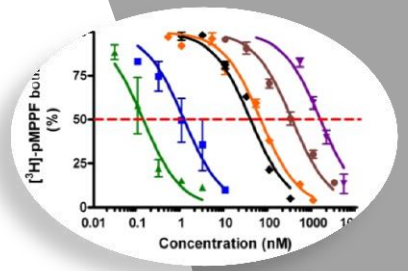
Por isso, acredito fortemente que a farmacologia precisa ser estudado em todos os níveis, sendo que a escolha do nível deve ser ditada pela natureza da questão que é feita”

Br. J. Pharmacol. 161: 1204–1216, 2010

Esquizofrenia

Antipsicóticos: mecanismo, efeitos e necessidades

LASSBio-579: efeitos *in vivo*



LASSBio-579: MMA (*in vitro*)

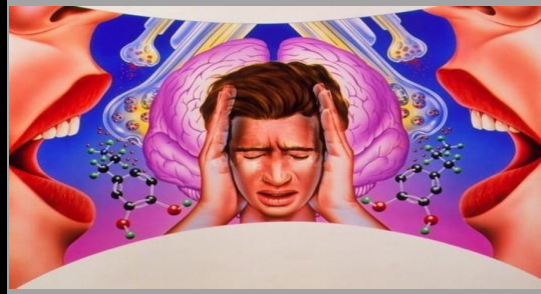
EPIDEMIOLOGIA

- Transtorno psiquiátrico crônico e incapacitante
- 1% da população adulta
- Frequência de suicídio: 5,6 %
- 50% dos esquizofrênicos não recebe tratamento adequado

ESQUIZOFRENIA: sintomas

SINTOMAS POSITIVOS *(psicóticos)*

Delírios
Alucinações (auditivas)
Fala desorganizada
Condutas estereotipadas, agitação motora



SINTOMAS NEGATIVOS

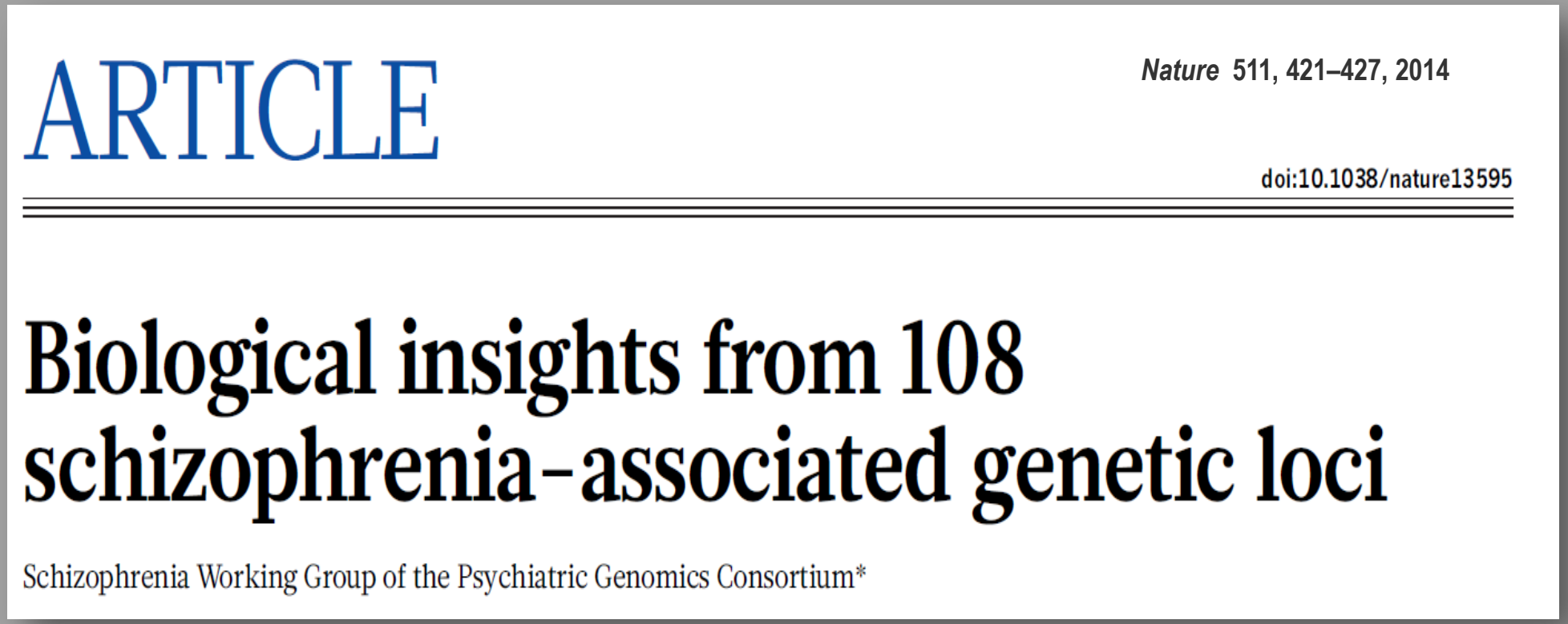
Isolamento social
Perda de motivação e higiene
Abrandamento das respostas emocionais

DÉFICITS COGNITIVOS PERSISTENTES

Déficit de atenção, problemas de memória

ETIOLOGIA: ??

- Desordem do desenvolvimento nervoso com clara contribuição genética mas também interação gene-ambiente



ARTICLE

Nature 511, 421–427, 2014

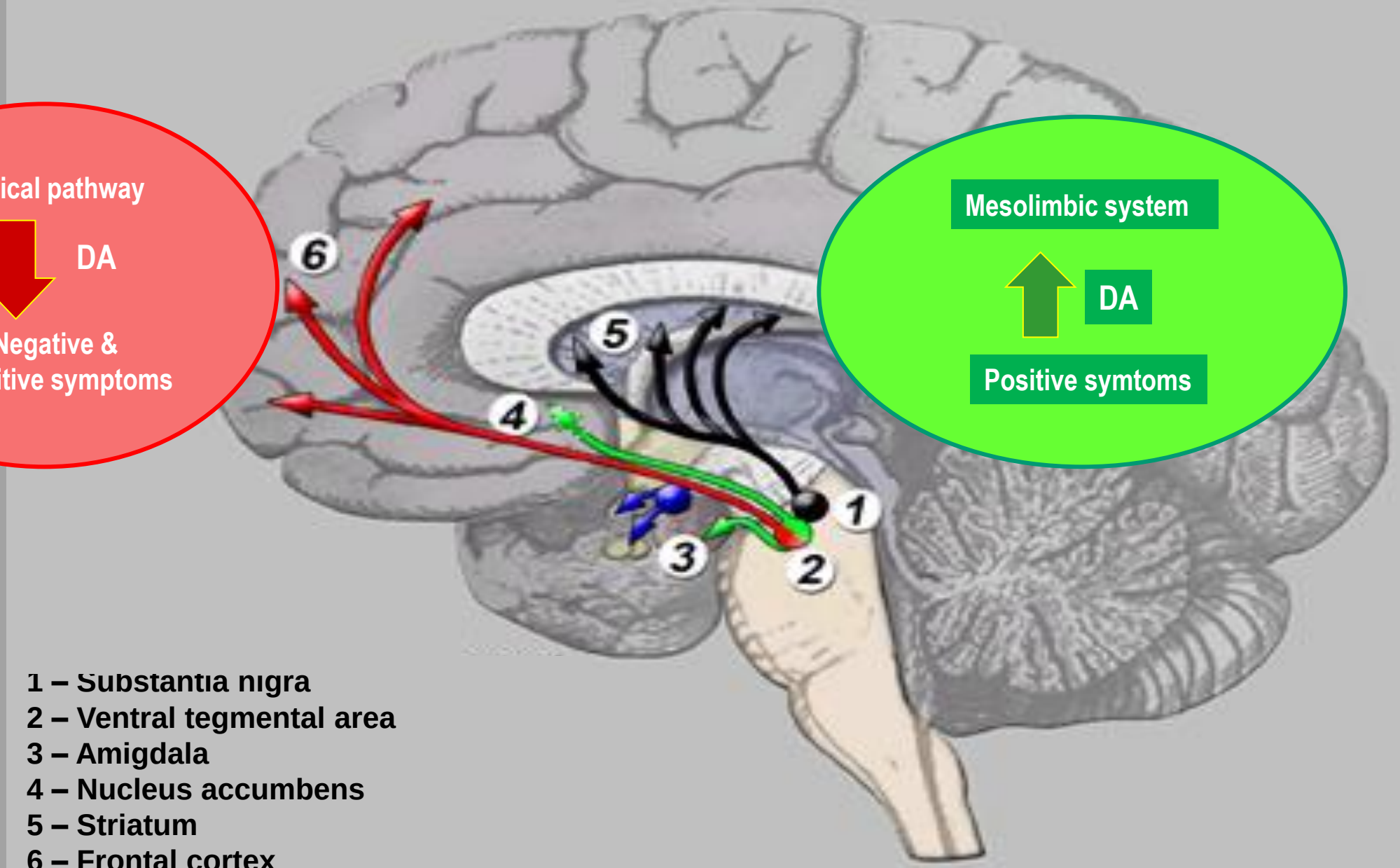
doi:10.1038/nature13595

Biological insights from 108 schizophrenia-associated genetic loci

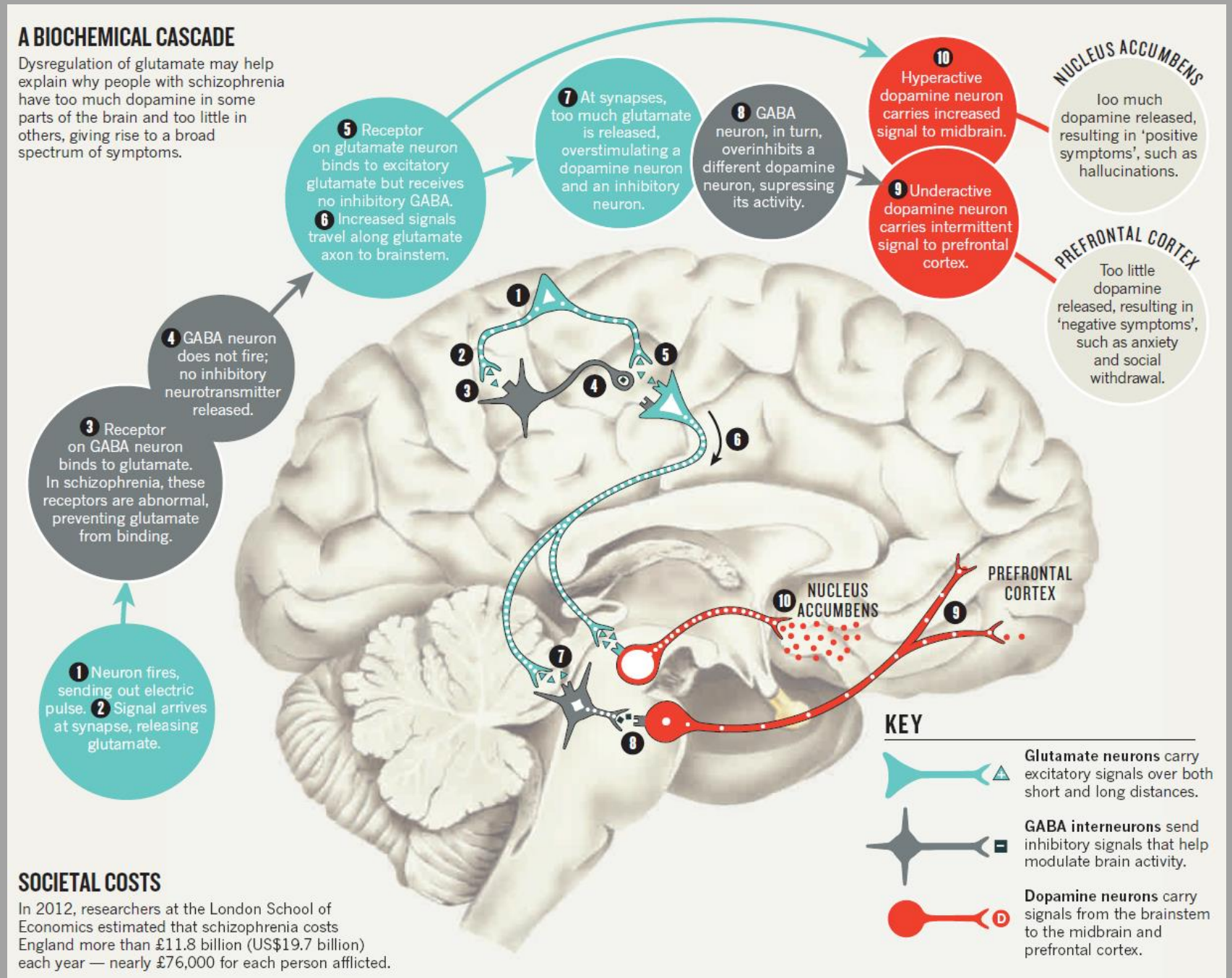
Schizophrenia Working Group of the Psychiatric Genomics Consortium*

HYPOTESE DOPAMINERGICA (*revised - Davis, 1991*)

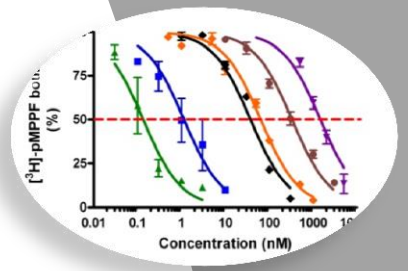
www.inec-usp.org/cursos/cursoV/figuraIV



HIPÓTESE GLUTAMATÉRGICA



Nature 508:S2, 2014

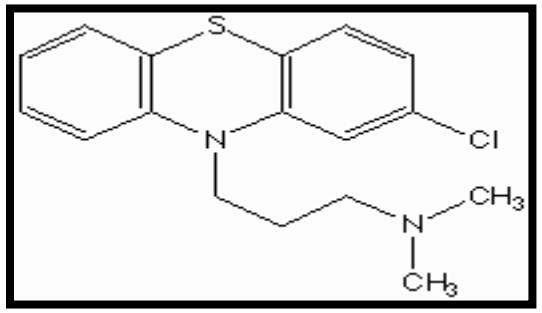


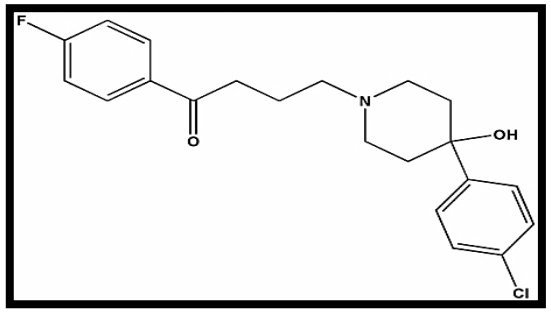
ANTIPSICÓTICOS: mecanismo, efeitos e necessidades

Tratamento Farmacológico da Esquizofrenia

Antipsicóticos de 1ª geração (típicos)

- Clorpromazina e Haloperidol





- Antagonistas D_2
- Eficácia: sintomas positivos
- Efeitos adversos extrapiramidais

X

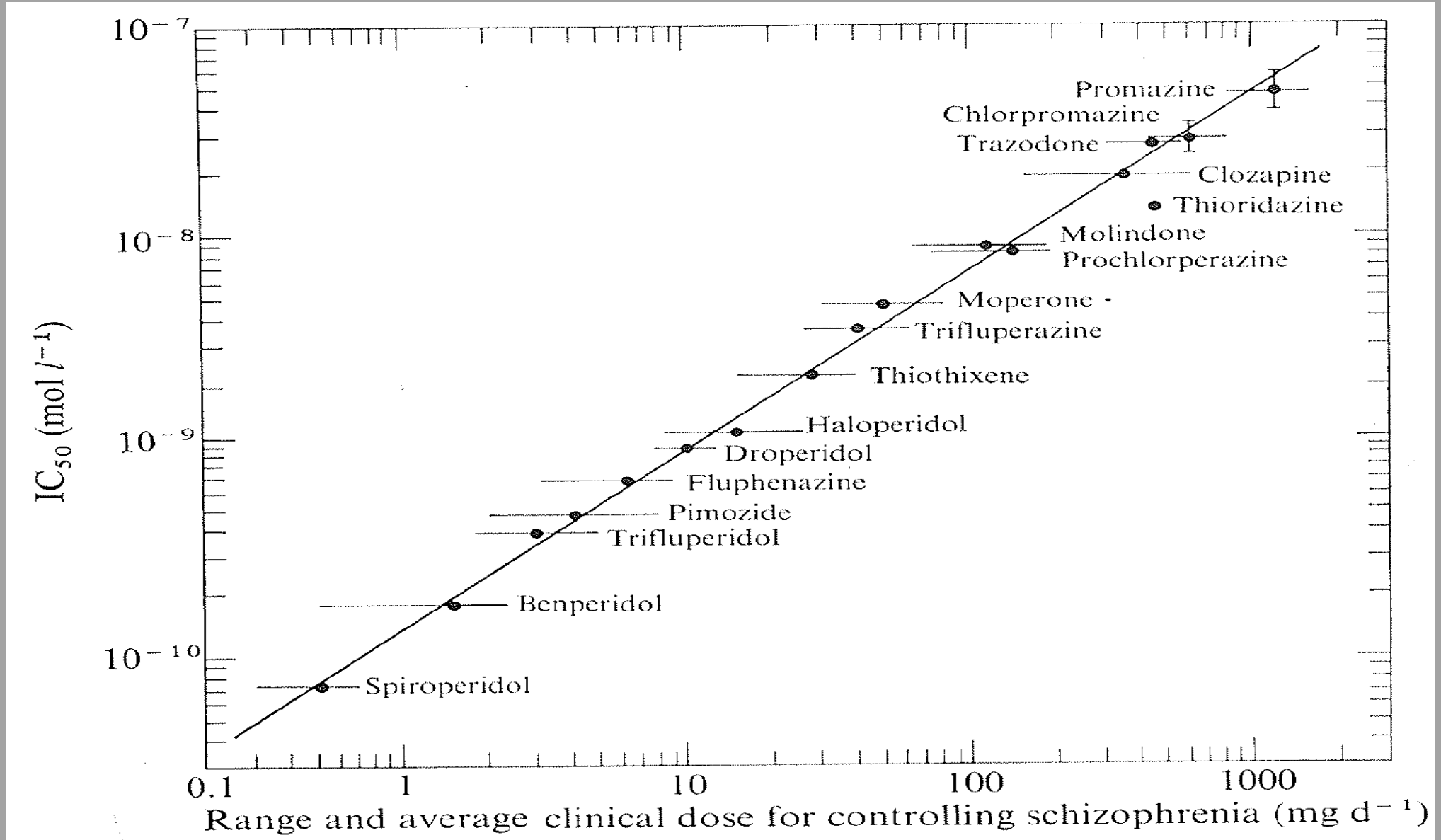
Antipsicóticos de 2ª geração (atípicos)

- Clozapina, amisulprida, olanzapina, risperidona, ziprasidona
- Antagonistas D_2 e 5-HT_{2A}
- *Multi-target drugs*
- Eficácia: sintomas positivos + (negativos, cognitivos)
- ↓Efeitos extrapiramidais
- Efeitos adversos metabólicos

Roth e cols., 2004; Leucht e cols., 2009

RECEPTOR D_2: ALVO DE TODOS OS ANTIPSICÓTICOS

Excelente correlação entre valores de CI_{50} no receptor D2, mas não D1, e doses usadas



Seeman e cols., Nature 261: 717, 1976

Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis

Lancet 2009; 373: 31–41

Stefan Leucht, Caroline Corves, Dieter Arbter, Rolf R Engel, Chunbo Li, John M Davis

1. Better than first-generation for overall efficacy, with small to medium effect sizes: amisulpride − clozapine − olanzapine − risperidone

2. Fewer extrapyramidal side-effects than did haloperidol (but: only a few have fewer EPS than low-potency first-generation antipsychotic drugs)

3. With the exception of aripiprazole and ziprasidone, second-generation APS drugs induced more weight gain than did haloperidol but not than low-potency first-generation drugs

4. The second-generation drugs also differed in their sedating properties

Interpretation Second-generation antipsychotic drugs differ in many properties and are not a homogeneous class This meta-analysis provides data for individualised treatment based on efficacy, side-effects, and cost.

NECESSIDADE DE NOVOS ANTIPSICÓTICOS

EFICÁCIA:

Pouca eficácia sobre sintomas negativos e déficits cognitivos

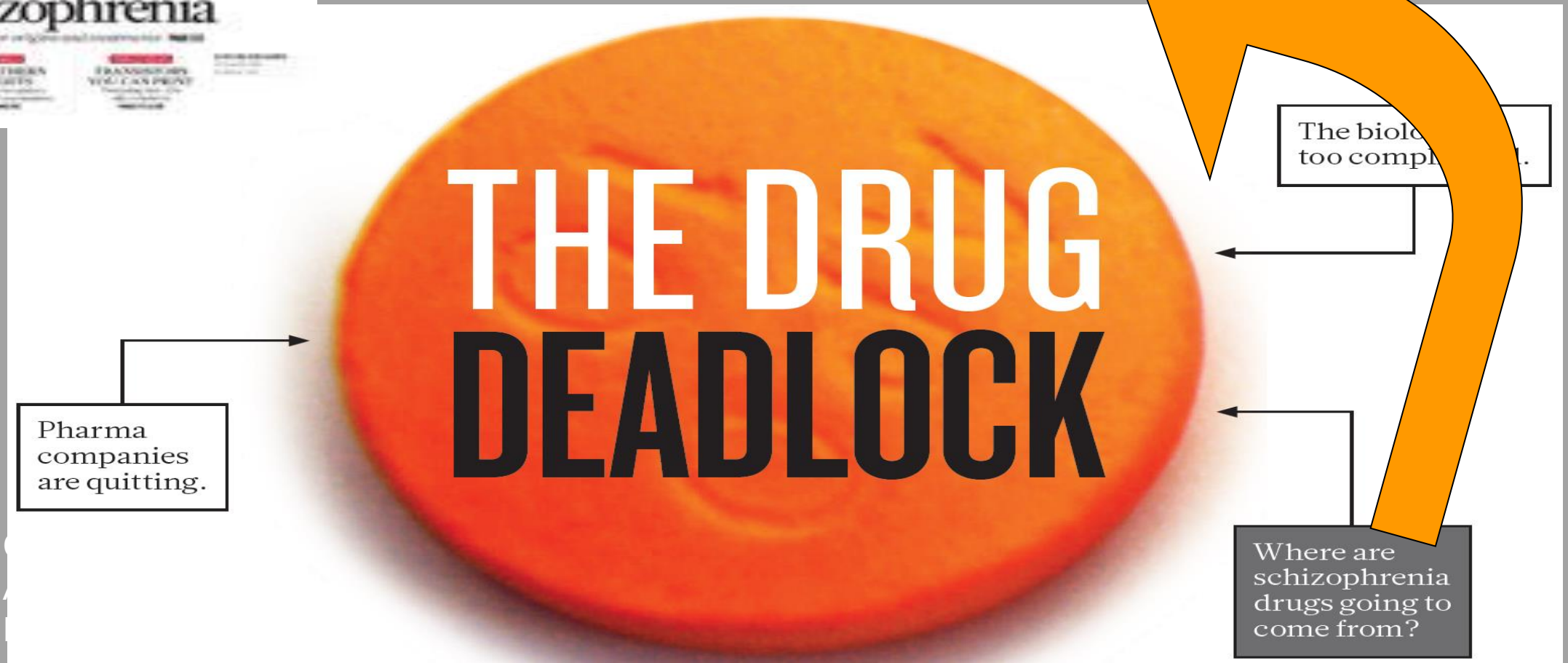
EFEITOS ADVERSOS

ADESÃO: CATIE-NIH (***C****linical* ***A****ntipsychotic* ***T****rials of* ***I****ntervention* ***E****ffectiveness)*

Alto índice de descontinuação ! 74% dos pacientes abandonam o tratamento em 18 meses < baixa tolerabilidade ou eficácia incompleta

NATURE 468 (7321):133-340, 2010

Academic-Industry collaboration ??
(NEWMEDS:Lundbeck – Kings College London)



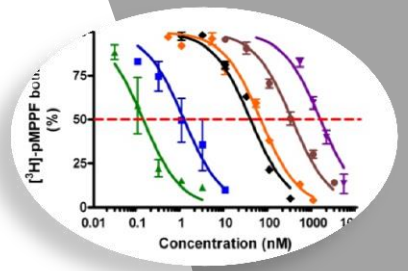
Building a Better Antipsychotic: Receptor Targets for the Treatment of Multiple Symptom Dimensions of Schizophrenia

Dennis H. Kim,* Matthew J. Maneen,* and Stephen M. Stahl†

If an antipsychotic were to be "built" from scratch, what features would be desirable?

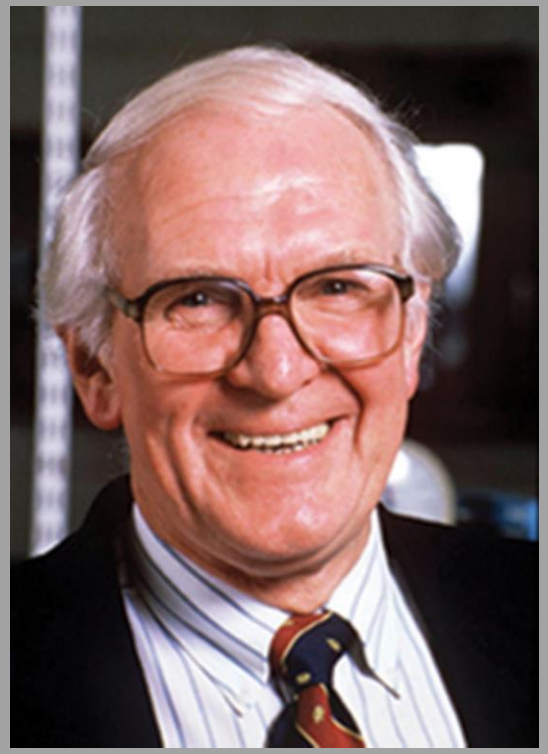
D_2 or not D_2 (D_3, D_4)?
Tuning Dopamine Output With 5-HT_{2A}
5-HT_{1A}: Full or Partial Agonism ?
5-HT_{2c}: Agonist or Antagonist ? / 5-HT_7: ?
α_2 adrenergic Antagonist ?
Glutamatergic / Glycine targets

Neurotherapeutics 6: 78–85, 2009



LASSBio-579: efeitos *in vivo*

"The most fruitful basis of the discovery of a new drug is to start with an old drug"



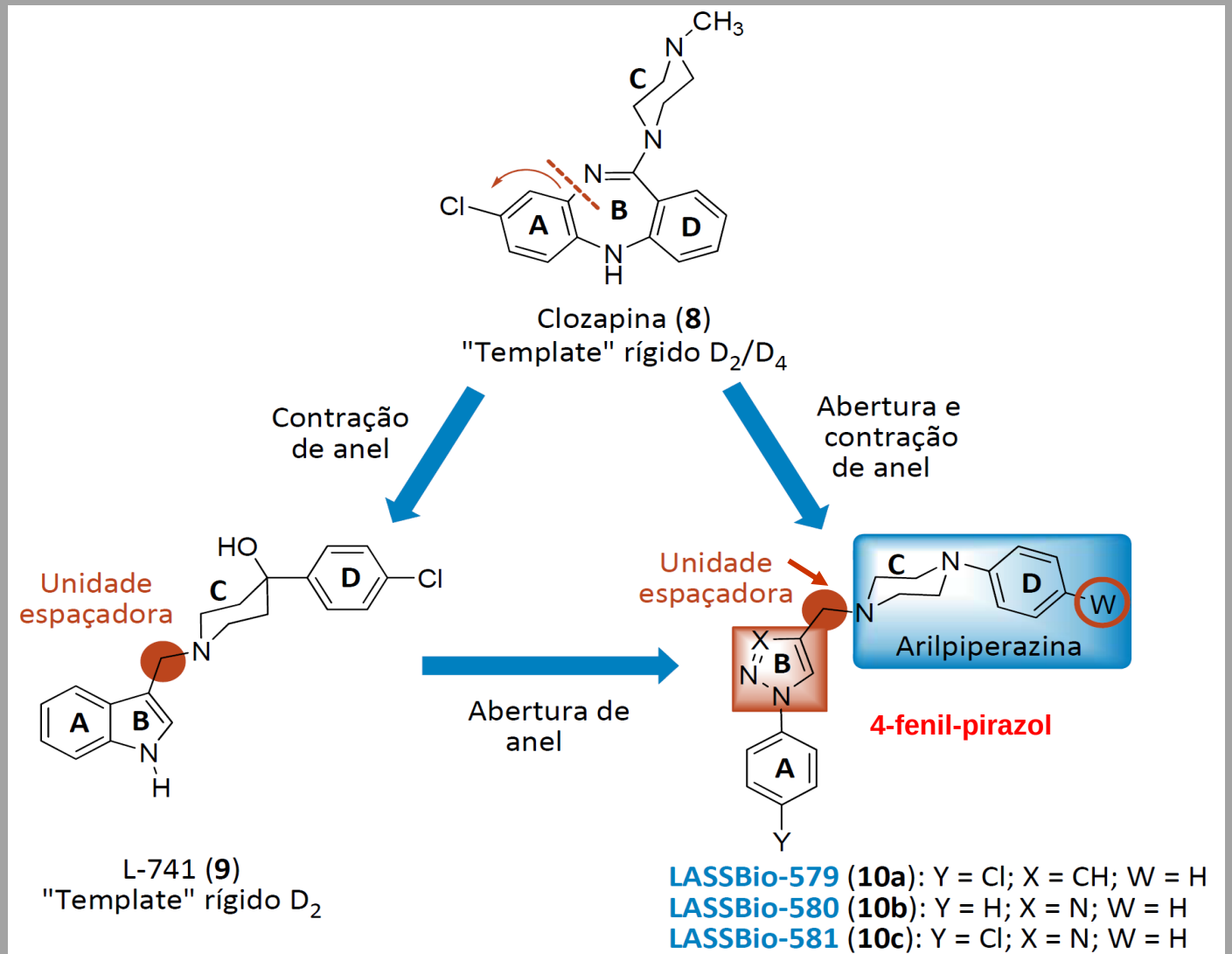
Sir James Blake

Nature Rev. Drug Discov. 2: 259, 2003

Bioorganic & Medicinal Chemistry 11 (2003) 4807–4813

Design, Synthesis and Pharmacological Profile of Novel Dopamine D2 Receptor Ligands

Ricardo Menegatti,[a,b] Anna C. Cunha,[c] Vítor F. Ferreira,[c] Edna F. R. Perreira,[d] Ahmed El-Nabawi,[d] Amira T. Eldefrawi,[d] Edson X. Albuquerque,[d,e] Gilda Neves,[f] Stela M. K. Rates,[f] Carlos A. M. Fraga[a,b] and Eliezer J. Barreiro[a,b,*]



Rev Virtual Quim 2(1):28-37, 2010

Brazilian Journal of Medical and Biological Research (2003) 36: 625-629

Dopaminergic profile of new heterocyclic N-phenylpiperazine derivatives

G. Neves, R. Fenner, A.P. Heckler, A.F. Viana, L. Tasso, R. Menegatti, C.A.M. Fraga, E.J. Barreiro, T. Dalla-Costa and S.M.K. Rates

LASSBio-579 (i.p.) was active in some tests predictive of TYPICAL antipsychotic activity:

- **Discrete** catalepsy in mice

- Inhibitory effect on amphetamine-induced stereotypy in rats

Behavioural Brain Research 237 (2013) 86–95

Contents lists available at SciVerse ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Research report

New insights into pharmacological profile of LASSBio-579, a multi-target *N*-phenylpiperazine derivative active on animal models of schizophrenia

Gilda Neves[a,b,1], Camila B. Antonio[a,1], Andresa H. Betti[a], Mariana A. Pranke[a], Carlos A.M. Fraga[c], Eliezer J. Barreiro[c], François Noël[b], Stela M.K. Rates[a,*]

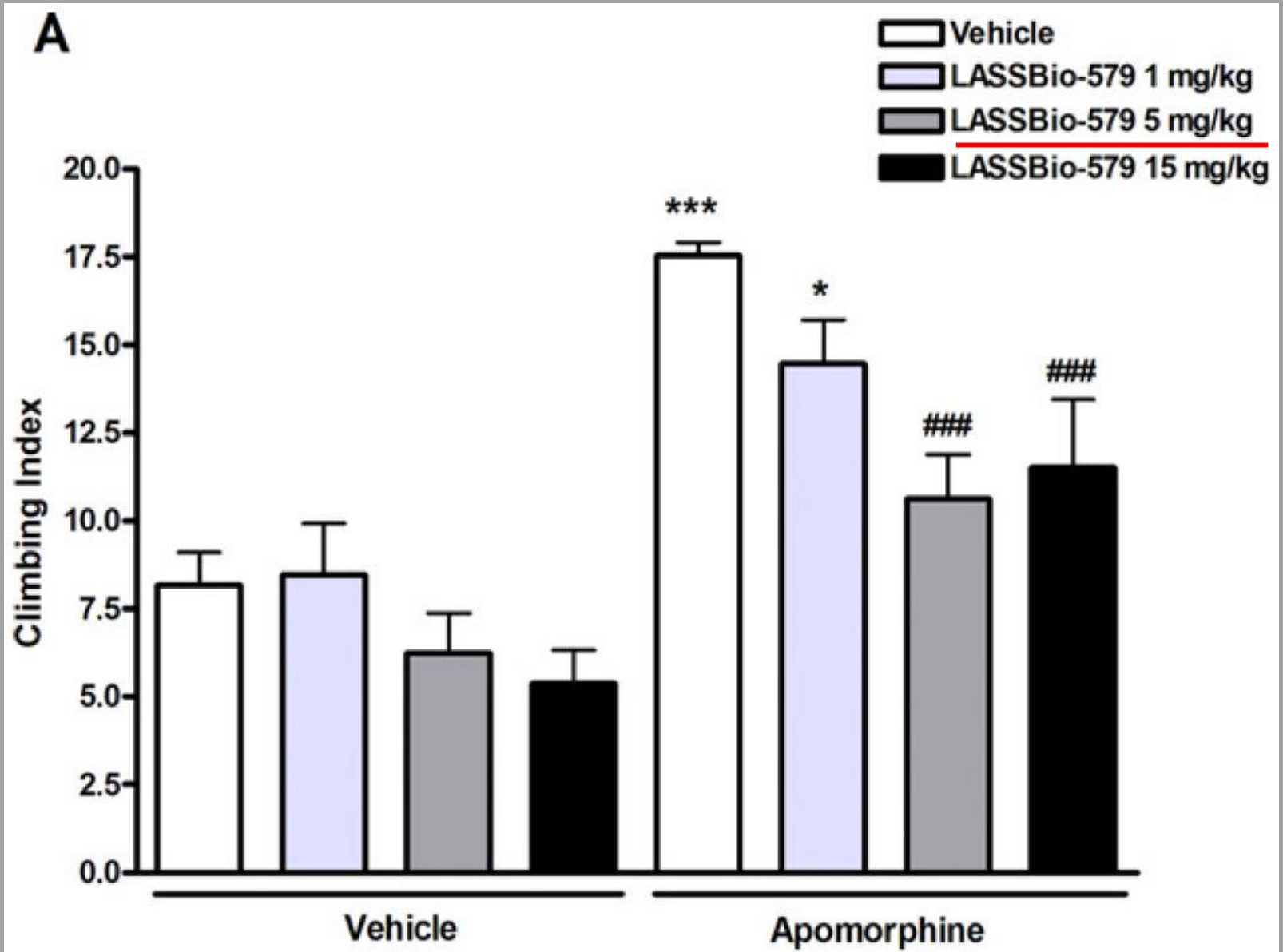
[a] Programa de Pós-Graduação em Ciências Farmacêuticas, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil
[b] Laboratório de Farmacologia Bioquímica e Molecular, Instituto de Ciências Biomédicas, Centro de Ciências da Saúde, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil
[c] Laboratório de Avaliação e Síntese de Substâncias Bioativas, Faculdade de Farmácia, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil

1. Modelos roedores preditivos de sintomas positivos da esquizofrenia

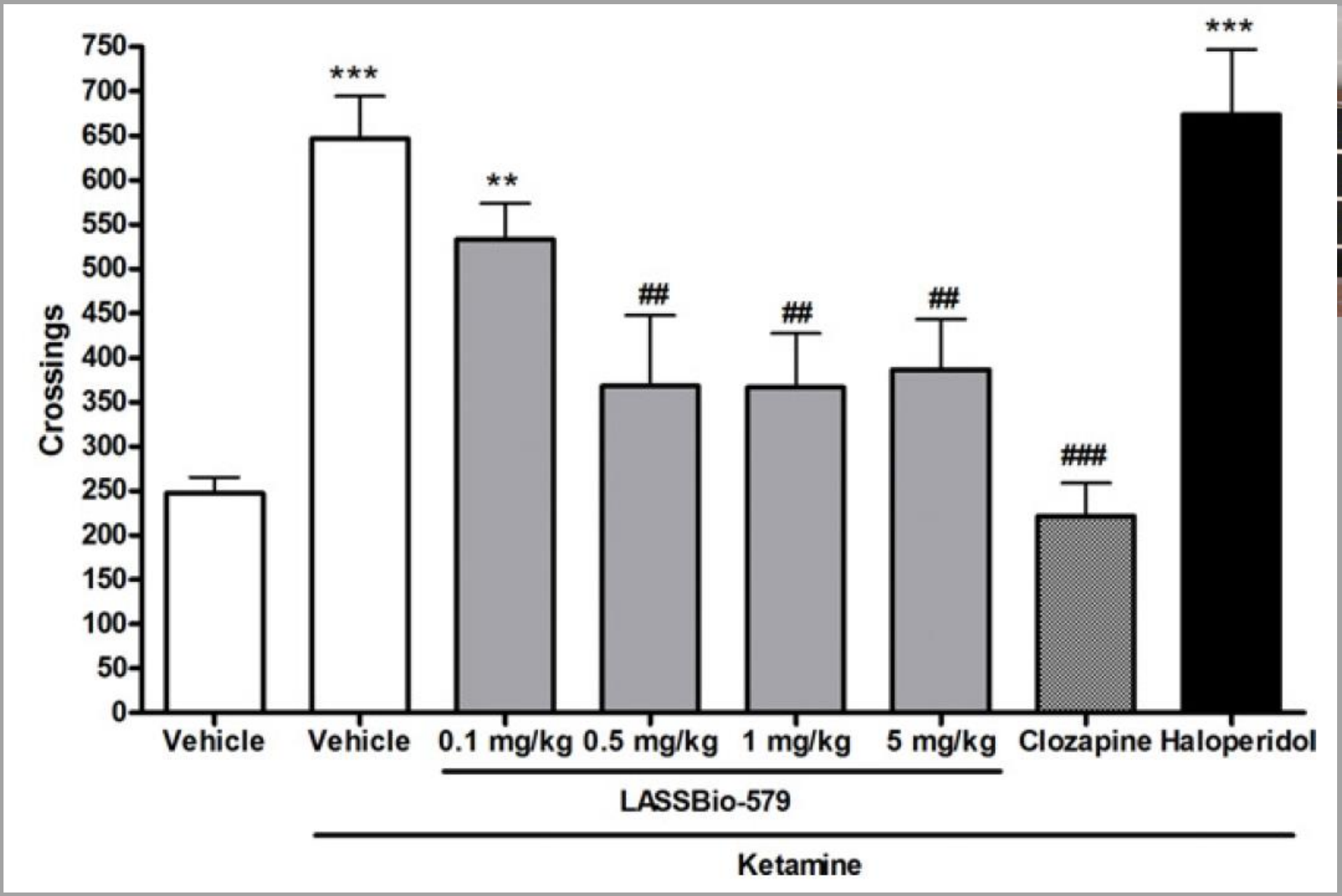
- Escalada induzida por apomorfina (5 mg/kg, p.o.)

- Hiperlocomoção induzida por cetamina (0.5 mg/kg, p.o.)

Escalada induzida por apomorfina (camundongo – p.o. – 30 min LB)



Hiperlocomoção induzida por cetamina (p.o. – 30 min LB)



2. Modelos roedores de processos pré-atencionais

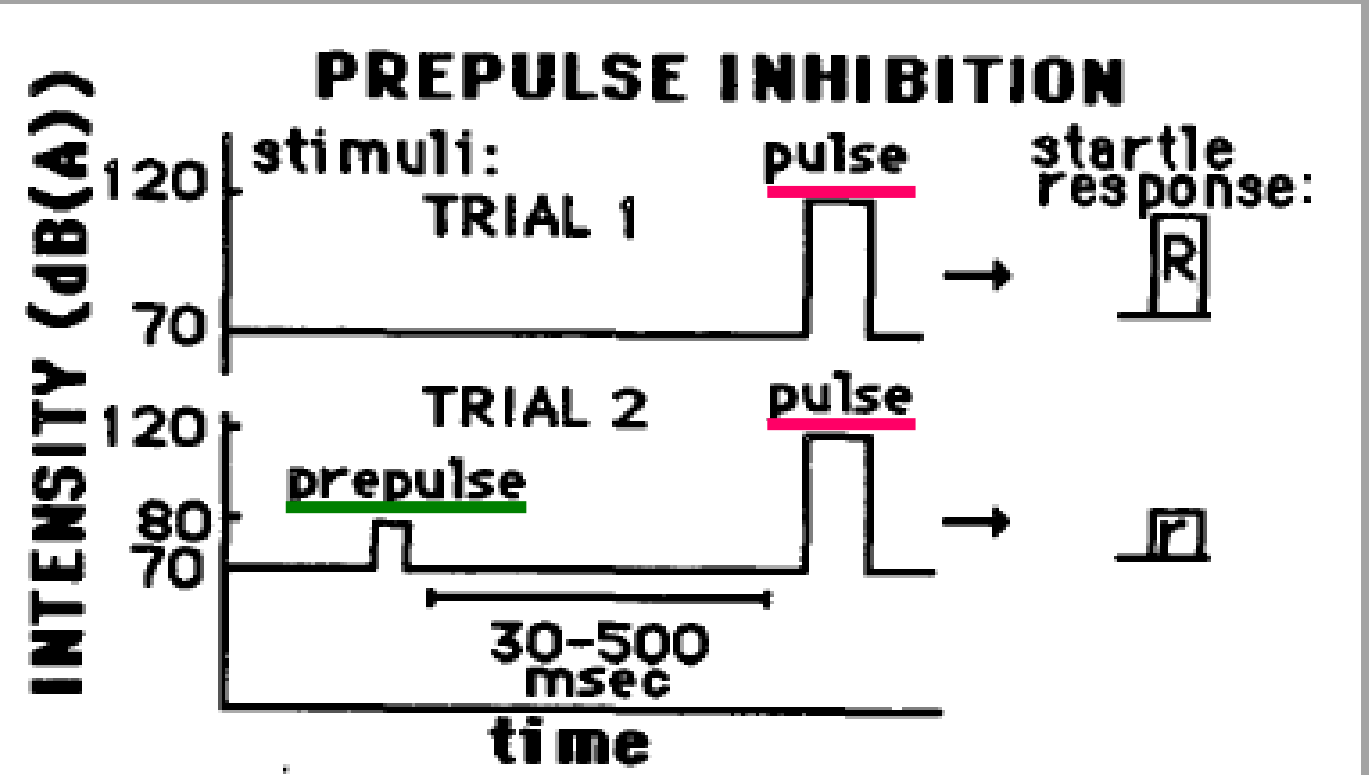
O LASSBio-579 foi efetivo em três condições diferentes do modelo padrão para se avaliar processos pré-atencionais:

Inibição do reflexo de sobressalto por pré-pulso (PPI)

INIBIÇÃO DO REFLEXO DE SOBRESSALTO ACÚSTICO POR PRÉ-PULSO
(prepulse inhibition of acoustic startle reflex – PPI: mice)

Startle chamber: um alto-falante produz um barulho de fundo contínuo de 65 dB assim como um pulso de maior intensidade (115 dB - 50 ms) desencadeador de reação (pulo)

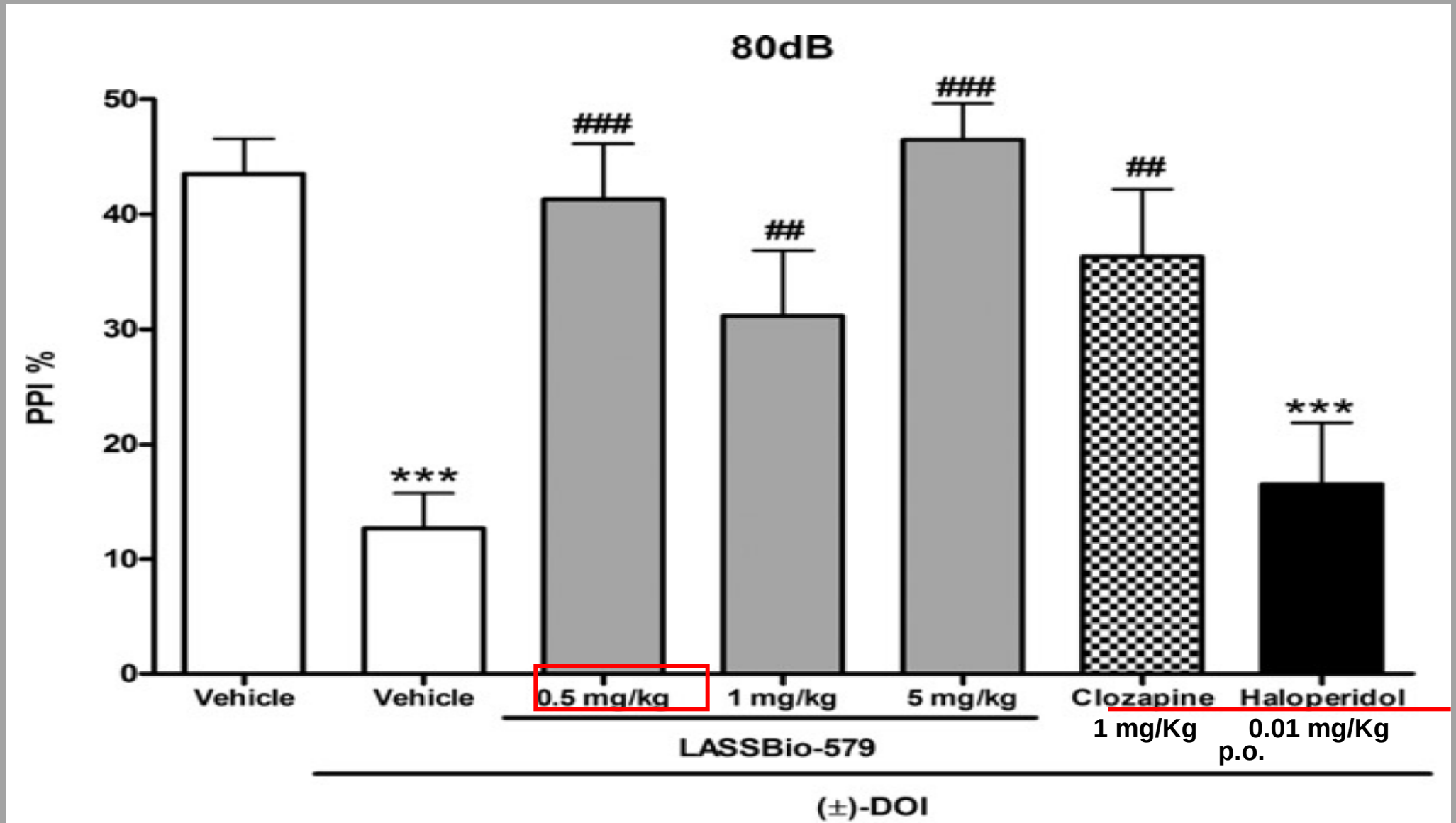
Startle chamber



Quando se aplica um estímulo prévio de menor intensidade (80- 90 dB, 20 ms), observa-se uma diminuição da resposta.

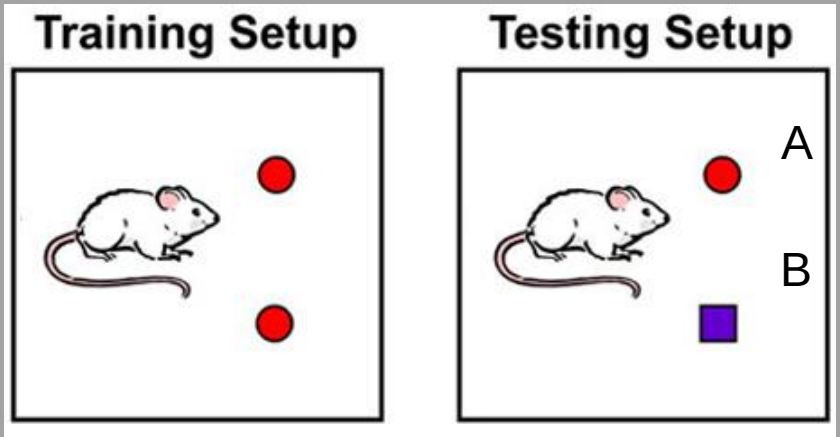
= medida comum da capacidade de filtrar as informações externas, que é deficitária na esquizofrenia

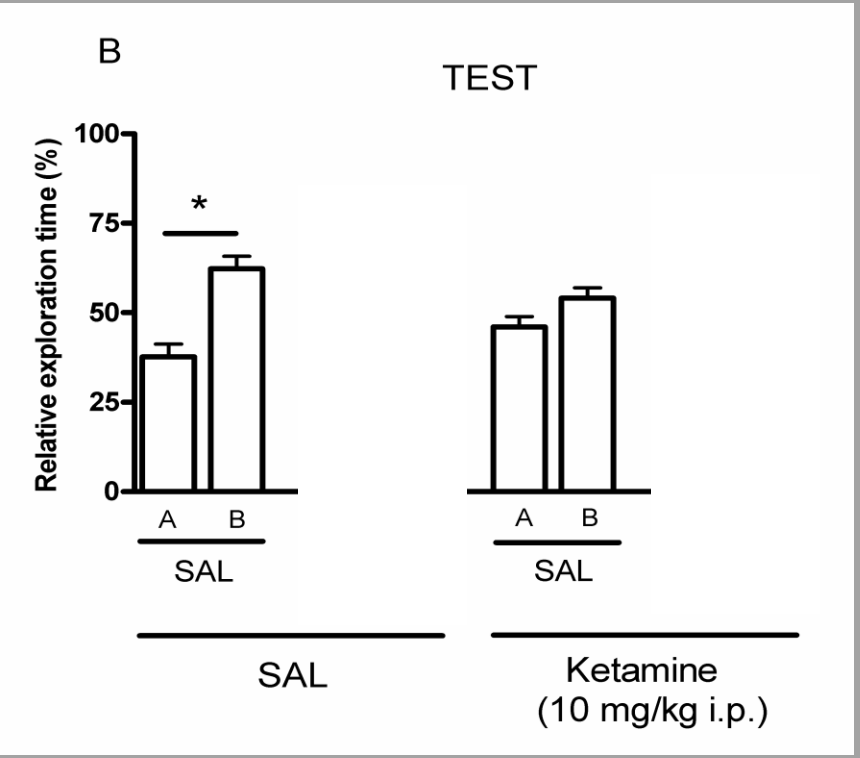
PREJUIZO NO PPI INDUZIDO POR (±)-DOI (0.5 mg/kg s.c. - camundongo)
(também por apomorfina e cetamina):
padrão de efeito muito semelhante ao da clozapina e diferente do haloperidol

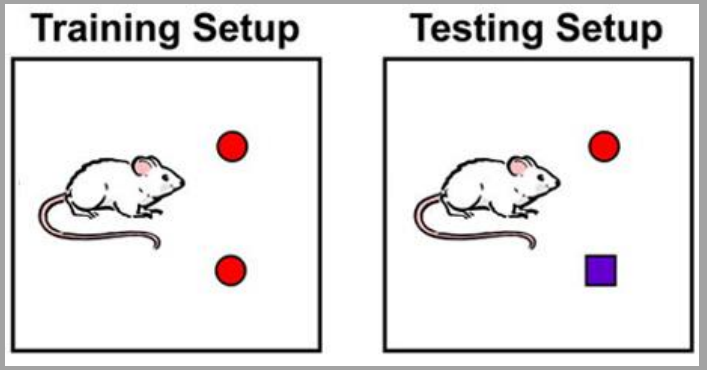


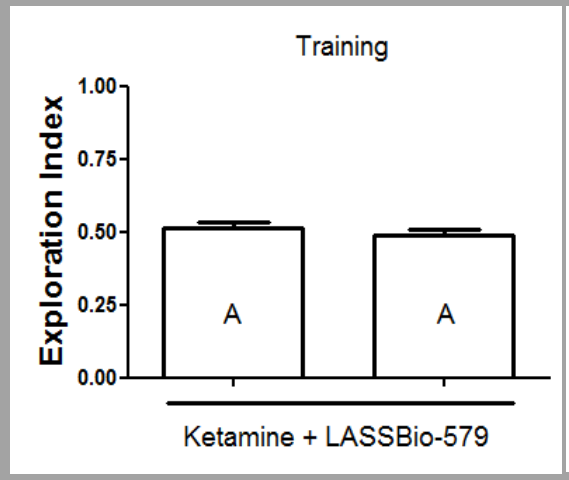
3. MODELOS ROEDORES DE MEMÓRIA

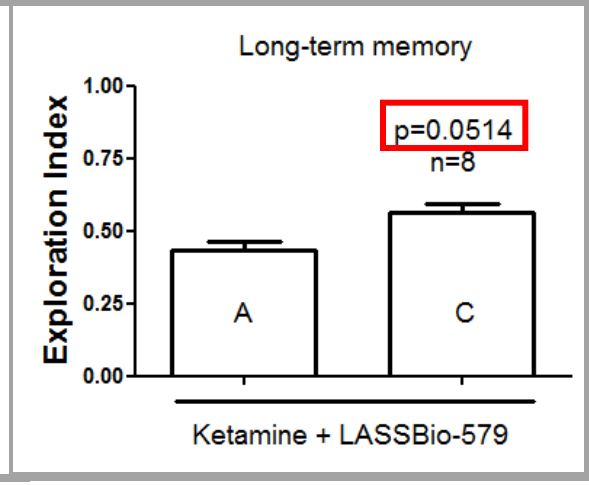
- Reconhecimento de Objeto Novo (5 mg/kg, p.o.):
  Indução de prejuízo de memória induzido por cetamina:





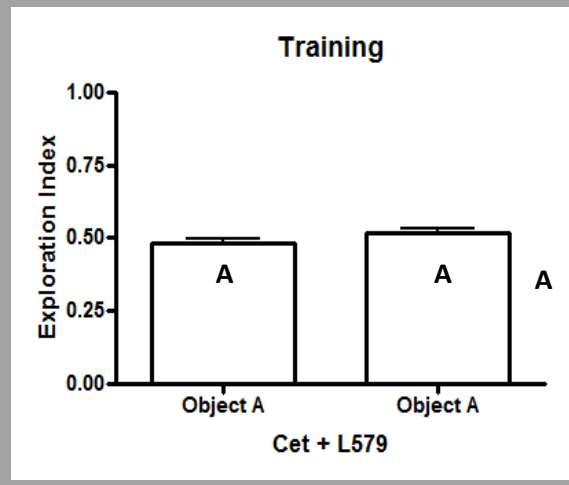


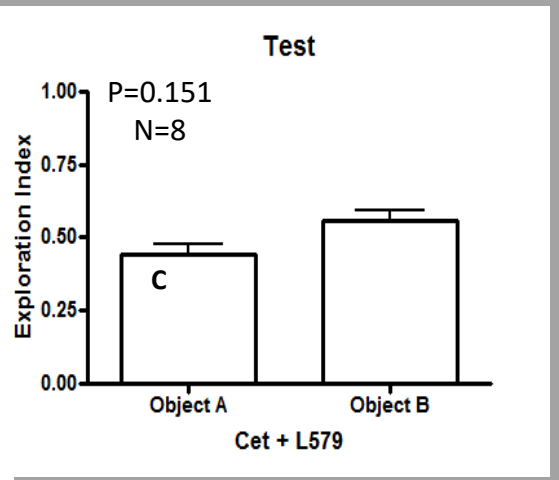




Aquisition

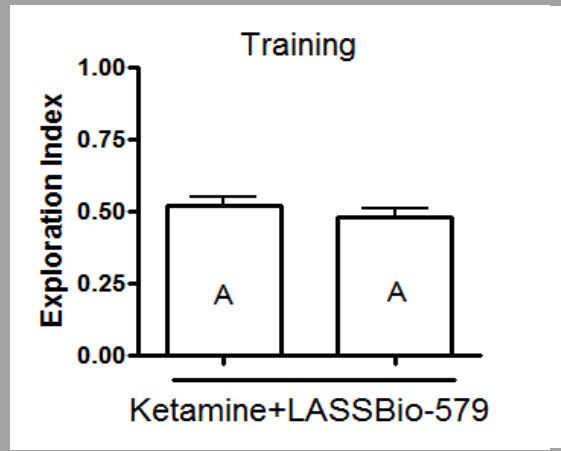
Ketamine and LASSBio-579
1h before training

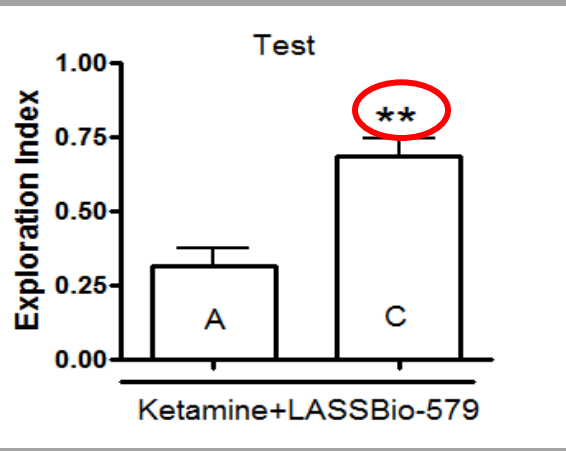




Consolidation

Ketamine 1h before training
LASSBio-579 post-training





Evocation

Ketamine 1h before training
LASSBio-579 1h before testing

o LASSBio-579 foi efetivo na fase de **aquisição** e também de **evocação**

Behav. Pharmacol., 2016

Pharmacokinetic evaluation of LASSBio-579: an *N*-phenylpiperazine antipsychotic prototype

Daniela J. Conrado, Hugo Verli, Gilda Neves, Carlos Alberto Manssour Fraga, Eliezer J. Barreiro, Stela Maris Kuze Rates and Teresa Dalla Costa

Journal of **Pharmacy and Pharmacology** 2008, 60: 1–9

Table 2 Pharmacokinetic parameters obtained after single intraperitoneal and oral administration of LASSBio-579 to Wistar rats

Parameter	30 mg kg^{-1} i.p.		60 mg kg^{-1} i.p.		60 mg kg^{-1} oral
	Model-independent (G2A)	Two-compartment (G2B)	Model-independent (G3A)	Two-compartment (G3B)	Model-independent (G4)
t½ β (h)	—	9.5 ± 5.8	—	17.9 ± 10.1	—
t½ (h)	6.2 ± 1.2	—	9.7 ± 3.2[a]	—	11.5 ± 4.2
$AUC_{0-\infty}$ (μg/mL^{-1}/h^{-1})	2.1 ± 0.8	2.3 ± 1.1	4.7 ± 1.3[a]	5.5 ± 1.5[b]	1.5 ± 0.5
CL_{tot} (L h^{-1} kg^{-1})	0.26 ± 0.10	0.25 ± 0.13	0.24 ± 0.08	0.20 ± 0.05	0.25 ± 0.11
Vd_{ss} (L kg^{-1})	1.9 ± 0.9	2.6 ± 1.1	3.5 ± 1.6[a]	4.6 ± 2.1[b]	—
MRT (h)	8.2 ± 1.5	12.7 ± 7.7	15.5 ± 6.5[a]	24.3 ± 13.7	18.9 ± 5.0
a (μg mL^{-1})	—	1.4 ± 1.3	—	4.07 ± 3.03[b]	—
b (μg mL^{-1})	—	0.17 ± 0.06	—	0.26 ± 0.14	—
α (h^{-1})	—	2.53 ± 0.68	—	2.70 ± 1.98	—
β (h^{-1})	—	0.10 ± 0.05	—	0.05 ± 0.03	—
k_a (h^{-1})	—	8.96 ± 7.61	—	3.80 ± 2.04	—
t_0 (h)	—	0.16 ± 0.12	—	0.15 ± 0.10	—
f (%)	1.6	—	1.8	—	0.6

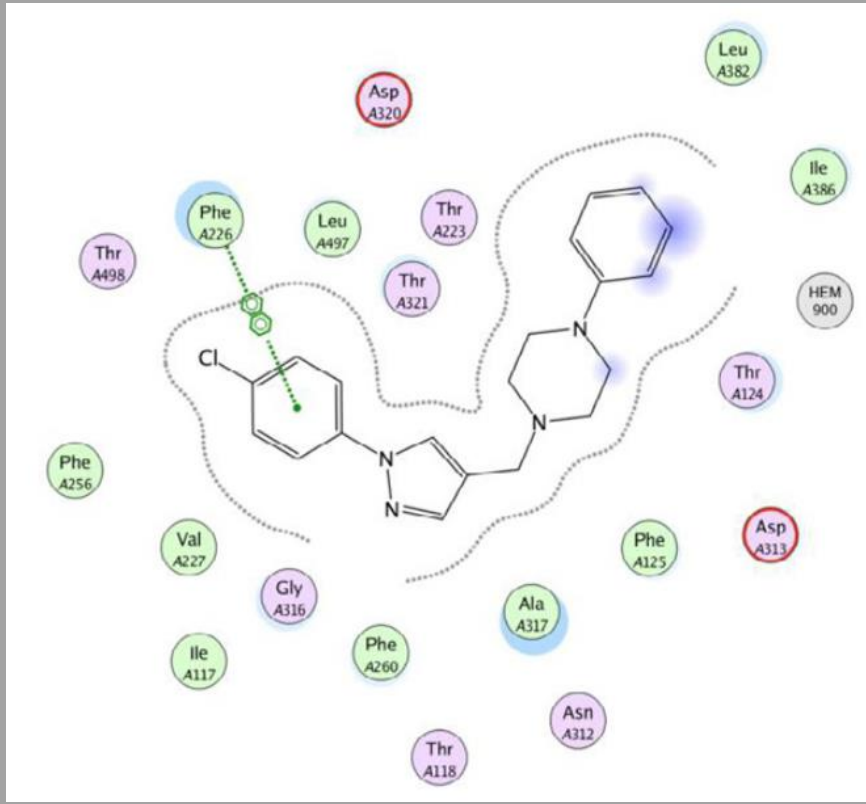
Baixa biodisponibilidade (ratos)

Baixa permeabilidade cerebral (ratos): 6,3%

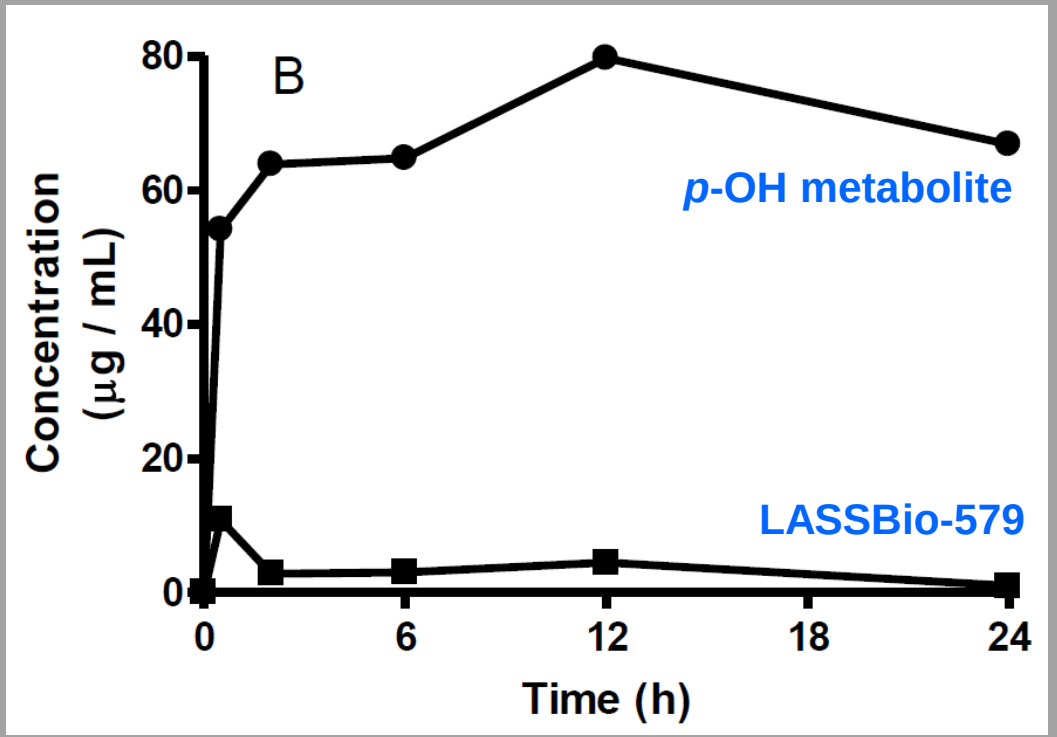
Biotransformation of LASSBio-579 and pharmacological evaluation of *p*-hydroxylated metabolite a *N*-phenylpiperazine antipsychotic lead compound

Tatiana F. Gomes [a], Thais E.T. Pompeu [b], Daniel A. Rodrigues [a], François Noël [b], Ricardo Menegatti [a], Carolina H. Andrade [a], José R. Sabino [c], Eric S. Gil [a], Teresa Dalla Costa [d], Andresa H. Betti [d], Camila B. Antonio [d], Stela M.K. Rates [d], Carlos A.M. Fraga [e], Eliezer J. Barreiro [e], Valéria de Oliveira [a,*]

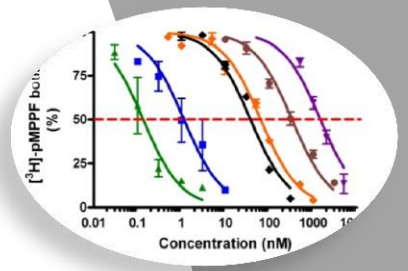
European Journal of Medicinal Chemistry 62 (2013) 214–221



Binding pose of LASSBio-579 in the active site of CYP1A2, as predicted by docking



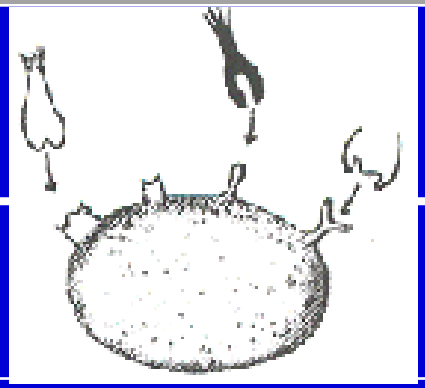
Plasma level-time curve for LASSBio-579 (■) and its *p*-OH metabolite (●) after *i.p.* administration in rat.



LASSBio-579: Mecanismo de ação molecular (*in vitro*)

1. AFINIDADE PARA RECEPTORES AMINÉRGICOS

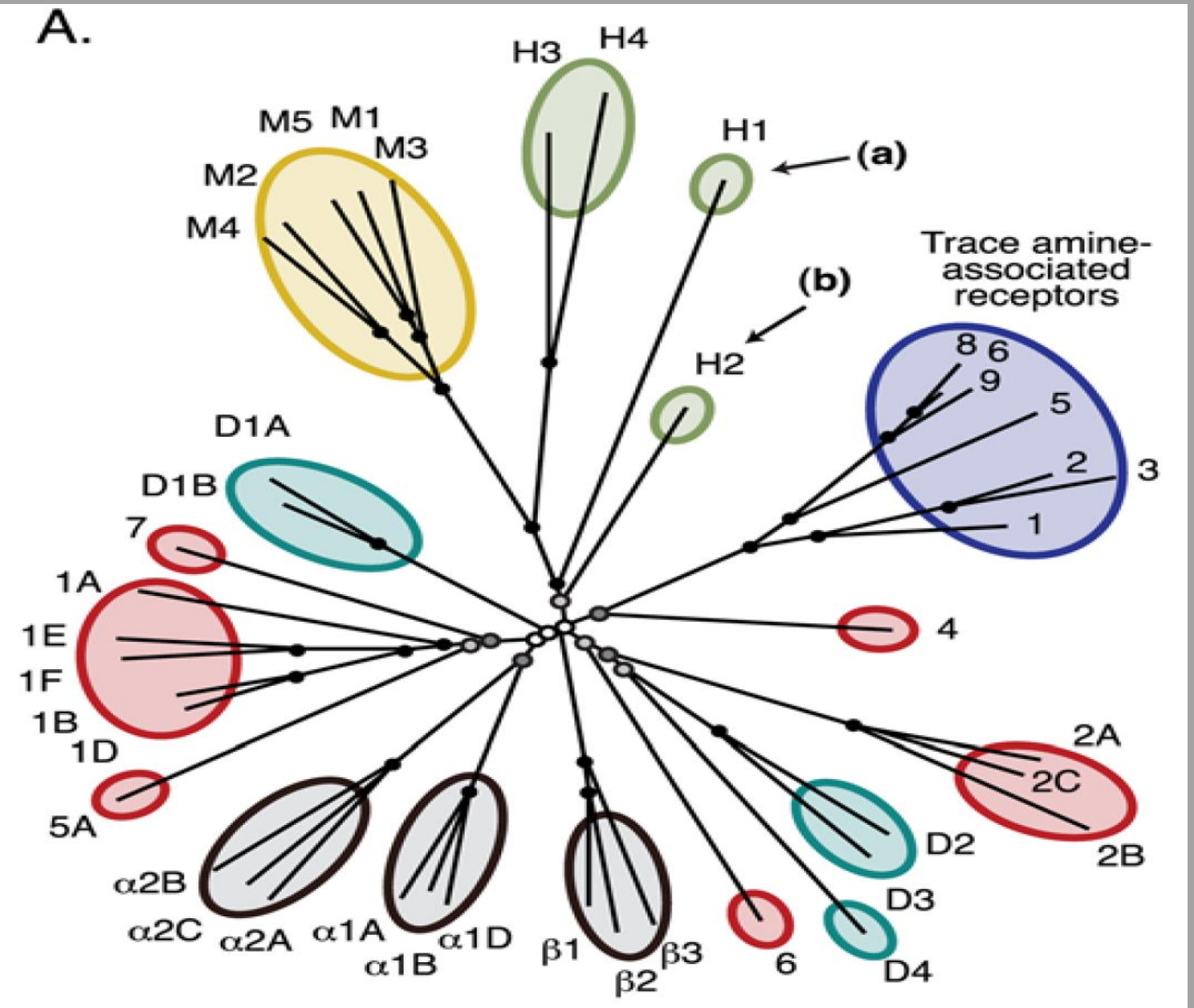
O **LASSBio-579** é um **ligante multi-alvo dos receptores D2-like, D4 e 5-HT1A,** com afinidade menor para o receptor **5-HT2A**



	K_i (μM)								
	D2-like	D3	D4	5-HT1A	5-HT2A	5-HT2C	α2	α1B	musc.
Clozapine	0,14	1,43	0,06	0,26	0,021	0,023	0,10	0,025	0,022
LASSBio-579	0,39	1,89	0,18	0,22	6,91	8,63	2,5	2,6	>30
Metabólito p-OH do LASSBio-579	0,53	-	0,034	5,87	8,22	12,3	6,45	1,15	>30

Eur. J. Med. Chem. 62: 214-221, 2013

Relações entre os dominios ligantes de aminas em 42 GPCRs humanos

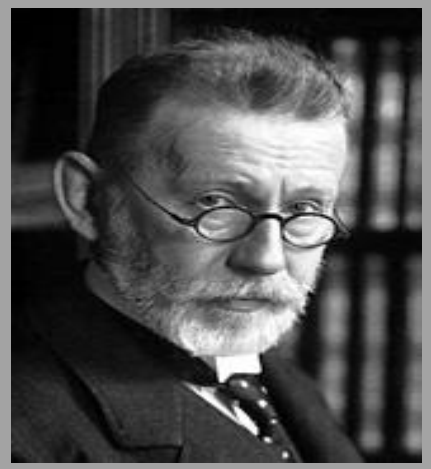


- Histamine
- Muscarinic Acetylcholine
- Dopamine
- Adrenoceptors
- Serotonin
- Amine (general)

PlosOne 4 (2):, e4345, 2009

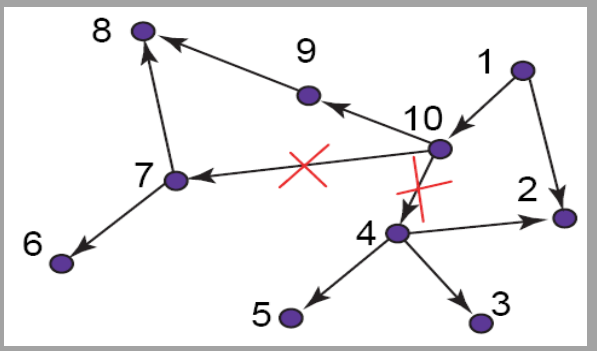
FÁRMACO SELETIVO *vs* MULTI-ALVO

Magic bullet



X

visão holística:
redes e circuitos neurais



Magic shotguns versus magic bullets: selectively non-selective drugs for mood disorders and schizophrenia

Bryan L. Roth, Douglas J. Sheffler and Wesley K. Kroeze

Nature Drug Discov. 3: 352-359, 2004

The efficiency of multi-target drugs: the network approach might help drug design

Péter Csermely[1], Vilmos Ágoston[2] and Sándor Pongor[2,3]

TIPS 26: 178-182, 2005

2. ATIVIDADE INTRÍNSECA PARA RECEPTORES AMINÉRGICOS

Ensaios de *binding* funcional mostram que o LASSBio-579 se comporta como:

- **1. Antagonista dos receptores 5-HT_{2A}**
- **2. Agonista parcial fraco do receptor 5-HT_{1A}**
- **3. Agonista parcial fraco dos receptores D_2**

o que poderia contribuir para sua atipicalidade

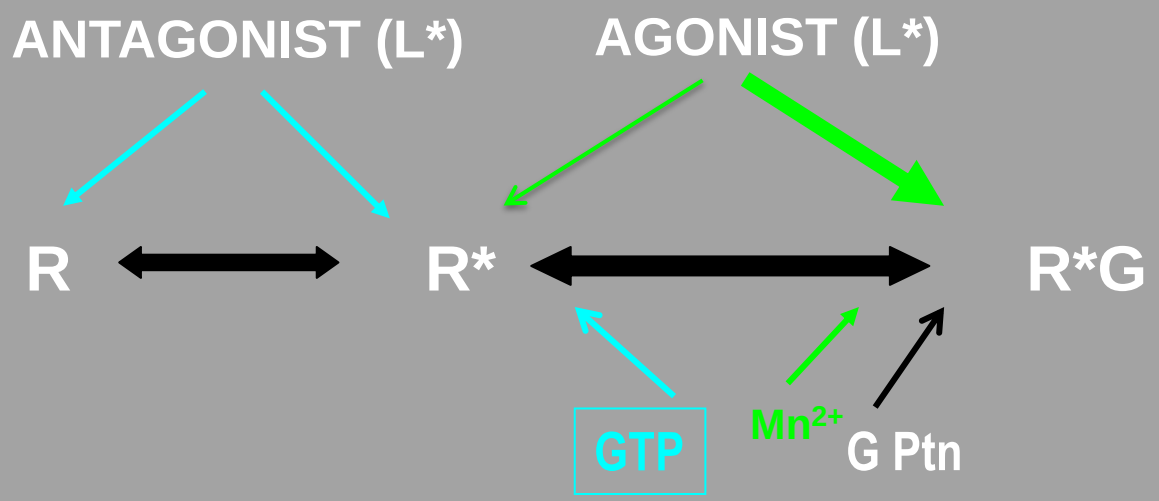
Eur. J. Med. Chem. 62: 214-221, 2013

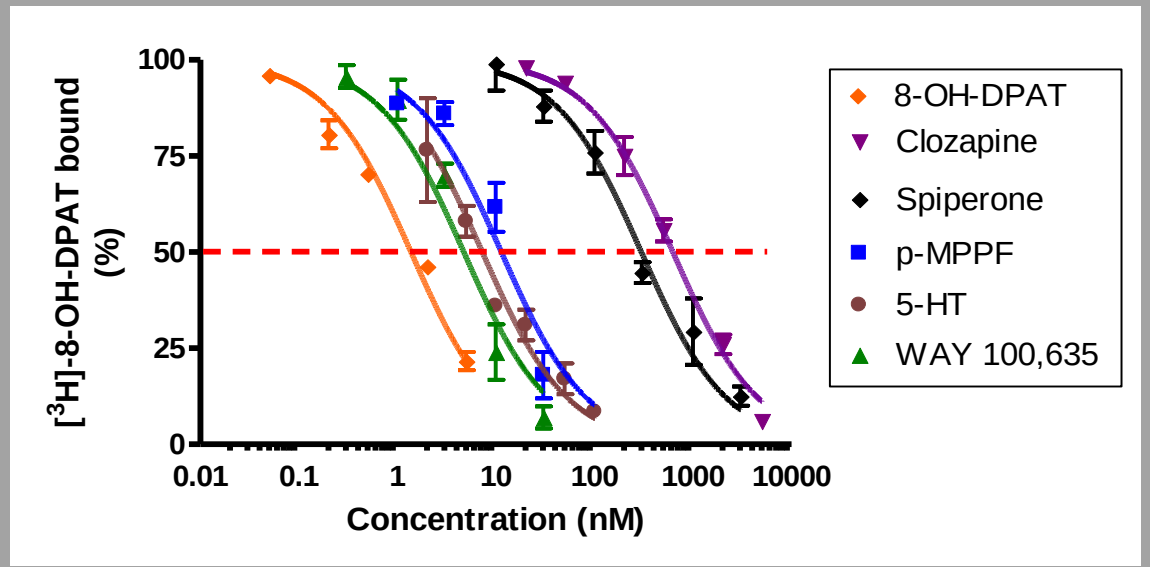
Functional binding assays for estimation of the intrinsic efficacy of ligands at the 5-HT_{1A} receptor: Application for screening drug candidates

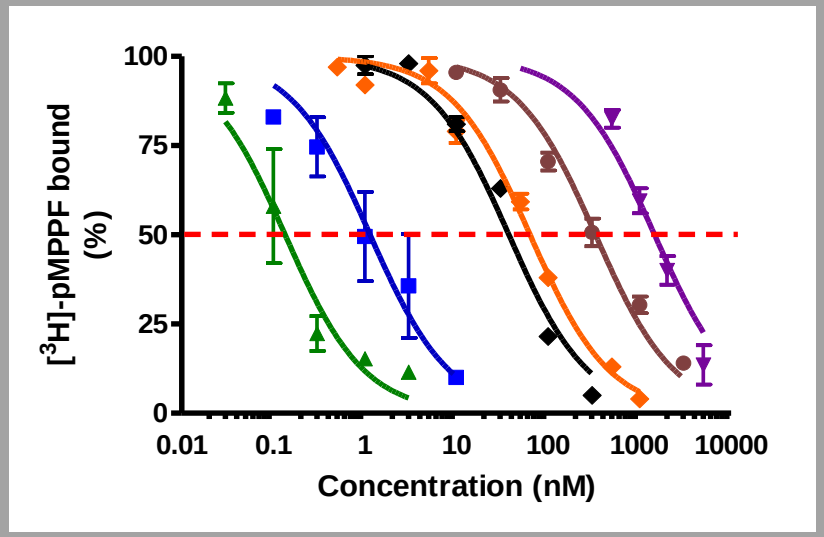
François Noël *, Thais E.T. Pompeu, Bruna C. Moura

Extended ternary complex model

Journal of Pharmacological and Toxicological Methods 70 (2014) 12–18







2.1. RECEPTOR 5-HT$_{1A}$: AVALIAÇÃO DA ATIVIDADE INTRÍNSECA (RAZÃO DE *KI*)

	K_i (nM) (1) [^{3}H] *p*-MPPF	K_i (nM) (2) [^{3}H]-8-OH-DPAT	*Ratio* (1) / (2)
5-HT	189 [6] (125 - 282)	2.46 [3] (0.99 – 5.87)	**76.6** (40.4 – 145)
8-OH-DPAT	29.1 [6] (17.8 - 46.9)	0.517 [3] (0.365 - 0.732)	51.0 (26.4 – 98.9)
Buspirone	111 [4] (49.2 – 242)	19,2 [4] (8,38 – 42,2)	5.81 (2.43 – 13.9)
Clozapine	847 [5] (542 – 2606)	259 [3] (132 - 508)	**3.29** (1.83 – 5.9)
***p*-MPPF**	1.20 [5] (0.97 – 1.46)	4.65 [3] (3.61- 5.99)	**0.250** (0.196 – 0.330)
Spiperone	11.8 [6] (4.15 – 31.8)	117 [3] (57.3 - 237)	0.100 (0.025 – 0.400)
WAY 100,635	0.18 [6] (0.087- 0.35)	2.0 [3] (1.10 – 3.68)	**0.088** (0.033 – 0.230)
LASSBio-579	753 [4] (430 - 1311)	218 [5] (145 – 326)	**3.45** (1.21 – 9.77)

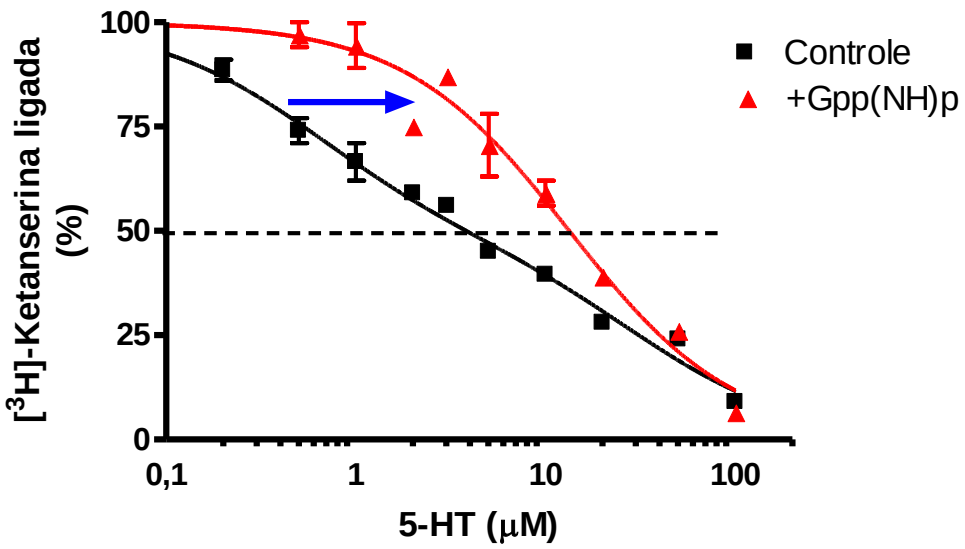
Agonist (>>1)

Neutral Antagonist (1)

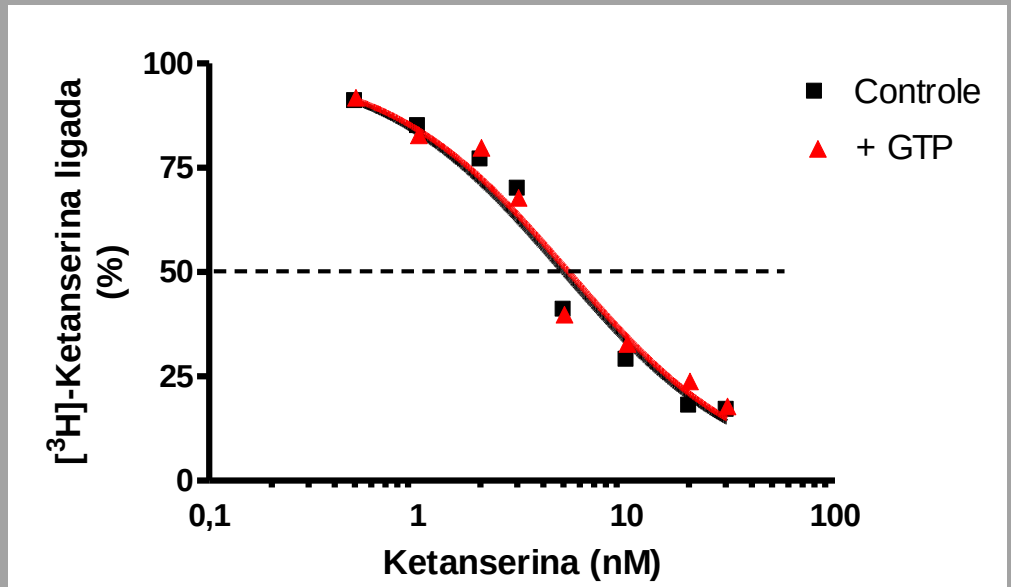
Inverse agonist (<1)

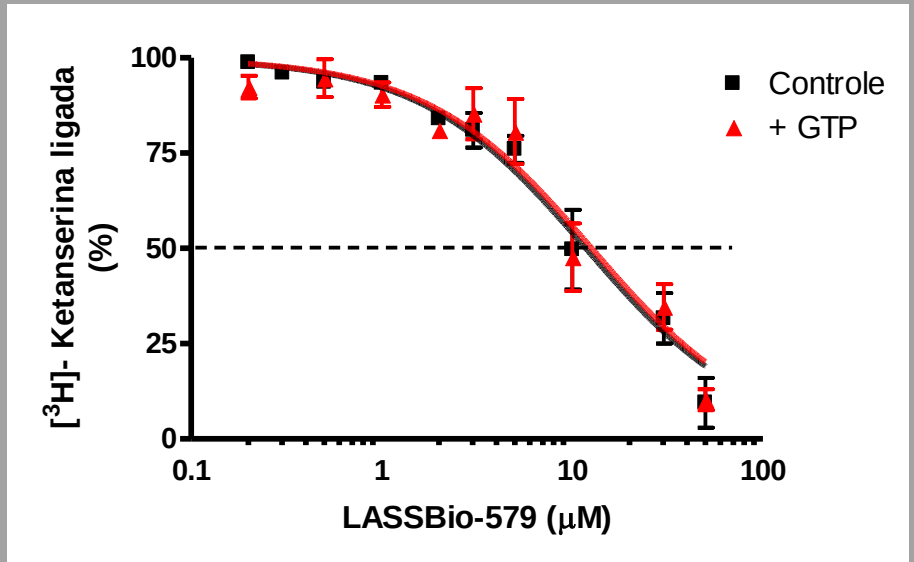
2.2. RECEPTOR 5-HT$_{2A}$: AVALIAÇÃO DA ATIVIDADE INTRÍNSECA: GTP-SHIFT

Agonista



Antagonista



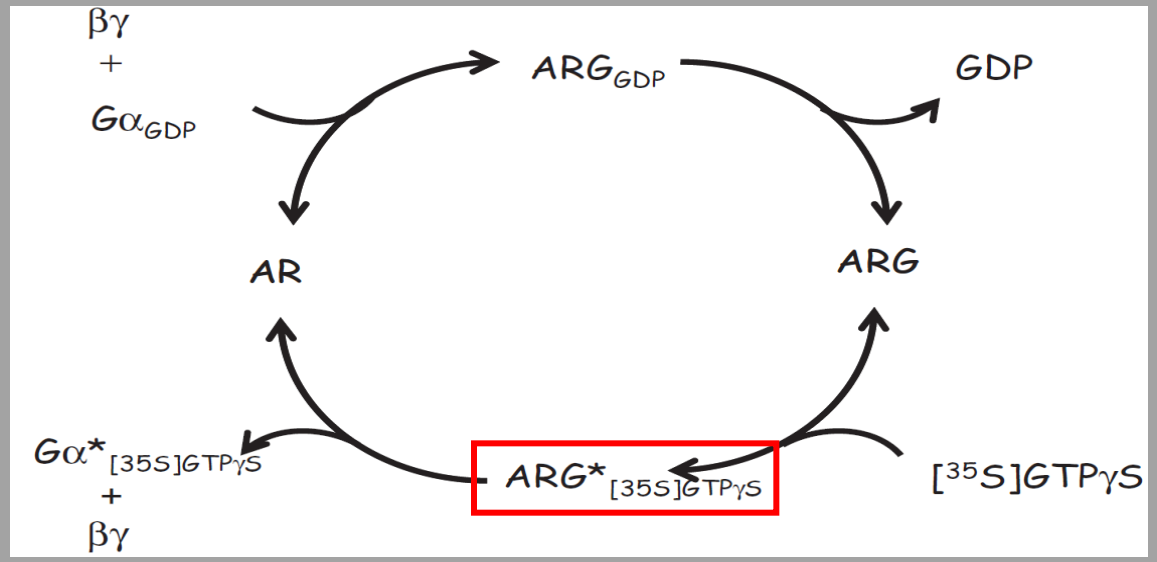


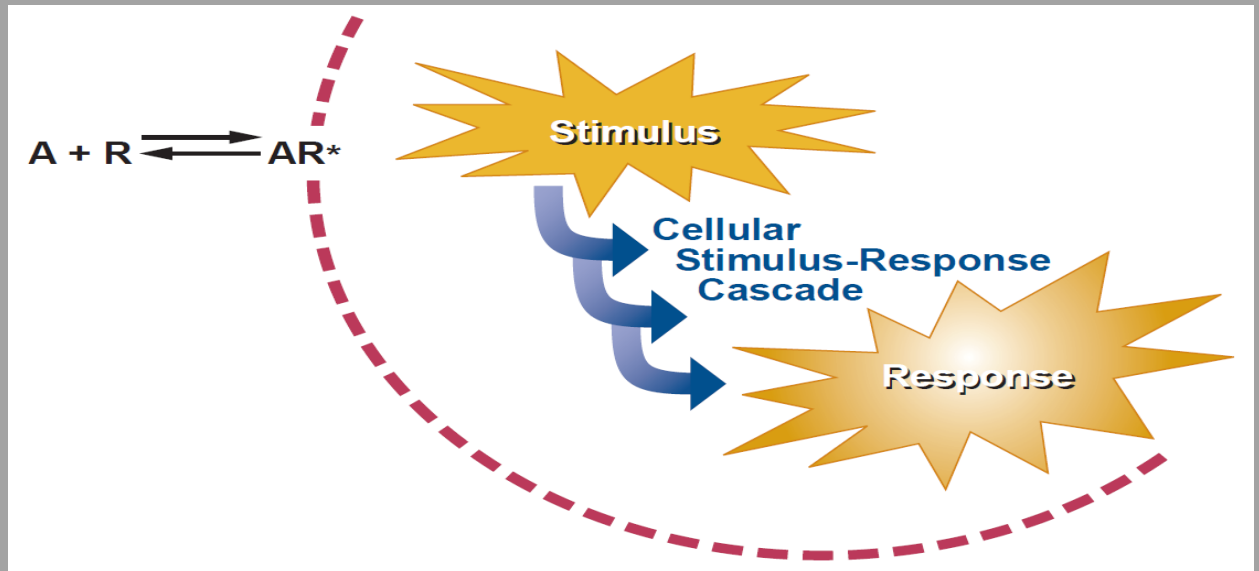
→ LASSBIO-579
= ANTAGONISTA

2.3. RECEPTOR D_2: AVALIAÇÃO DA ATIVIDADE INTRÍNSECA: ENSAIO DE LIGAÇÃO DO [^{35}S]-GTPγS

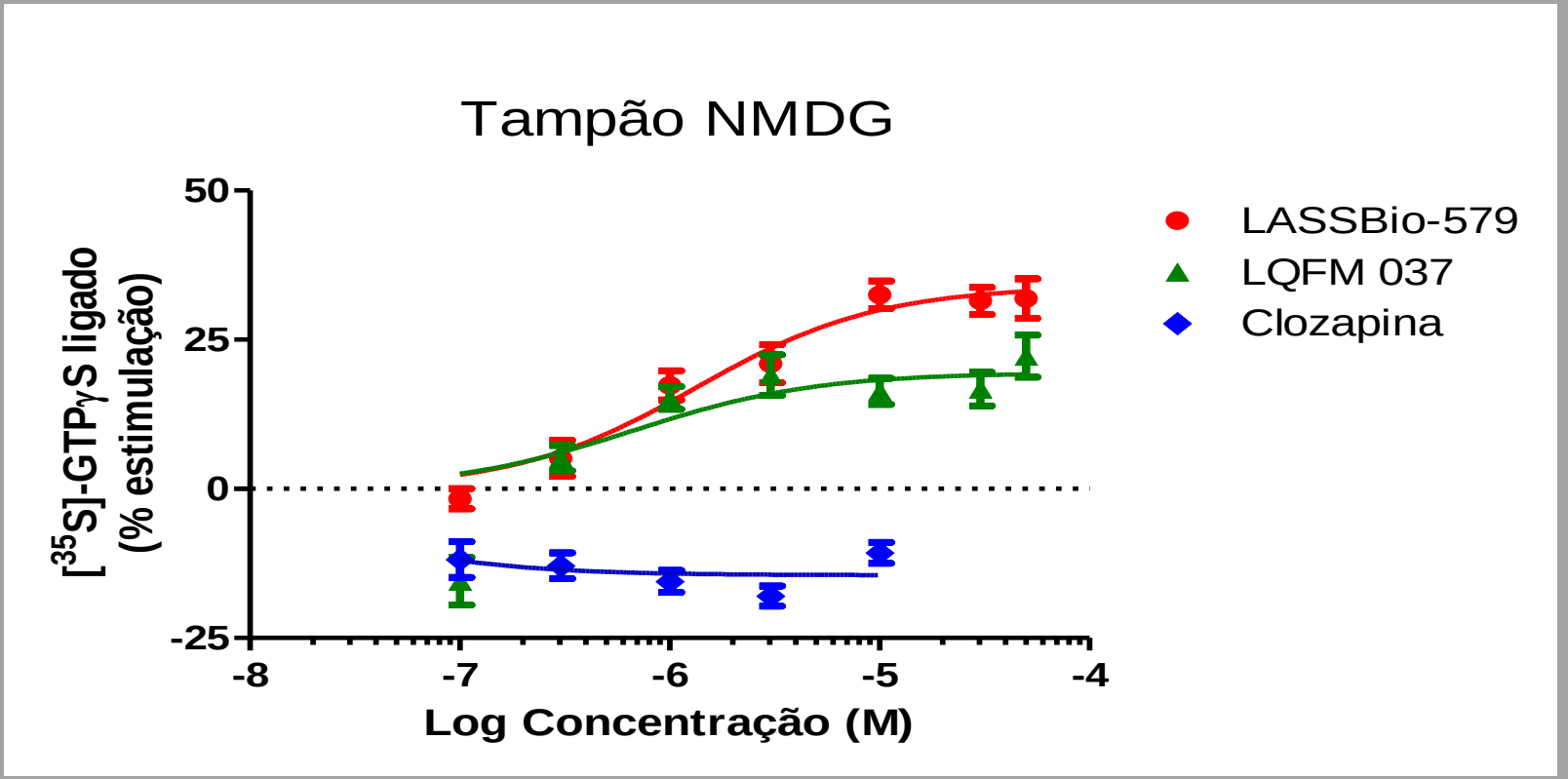
Use of the GTPγS ([^{35}S]GTPγS and Eu-GTPγS) binding assay for analysis of ligand potency and efficacy at G protein-coupled receptors

Strange PG
Brit. J. Pharmacol. 161:1238–1249, 2010





Células Hela Tet-On-pTRE com superexpressão de receptor D_{2L} de rato



LASSBio-579 (n=4)	LQFM 037 (n=4)
E_{max}: 34 ± 2,1 %	E_{max}: 19.4 ± 2,1 %
Log EC_{50} (M) = -5,87 ± 0,12	Log EC_{50} (M) = -6,18 ± 0,24

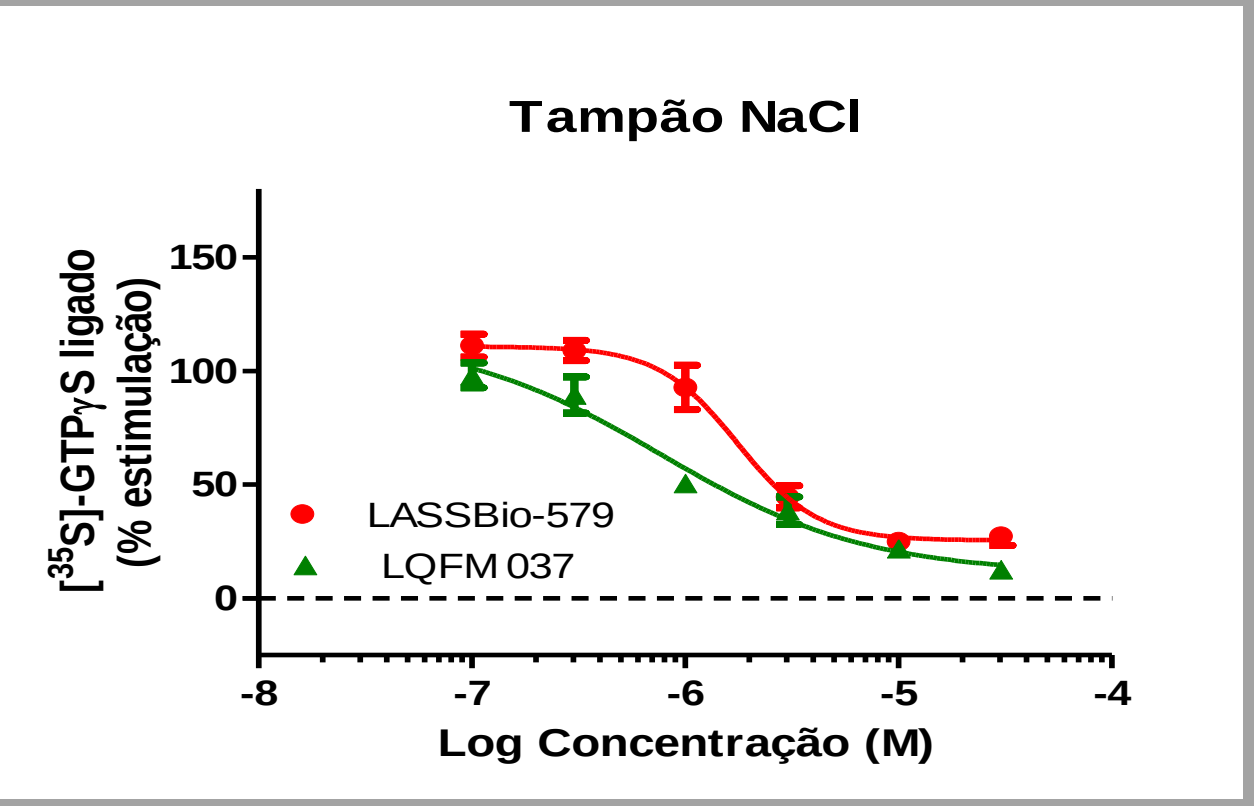
Dopamina 1µM
E_{max}= 162%

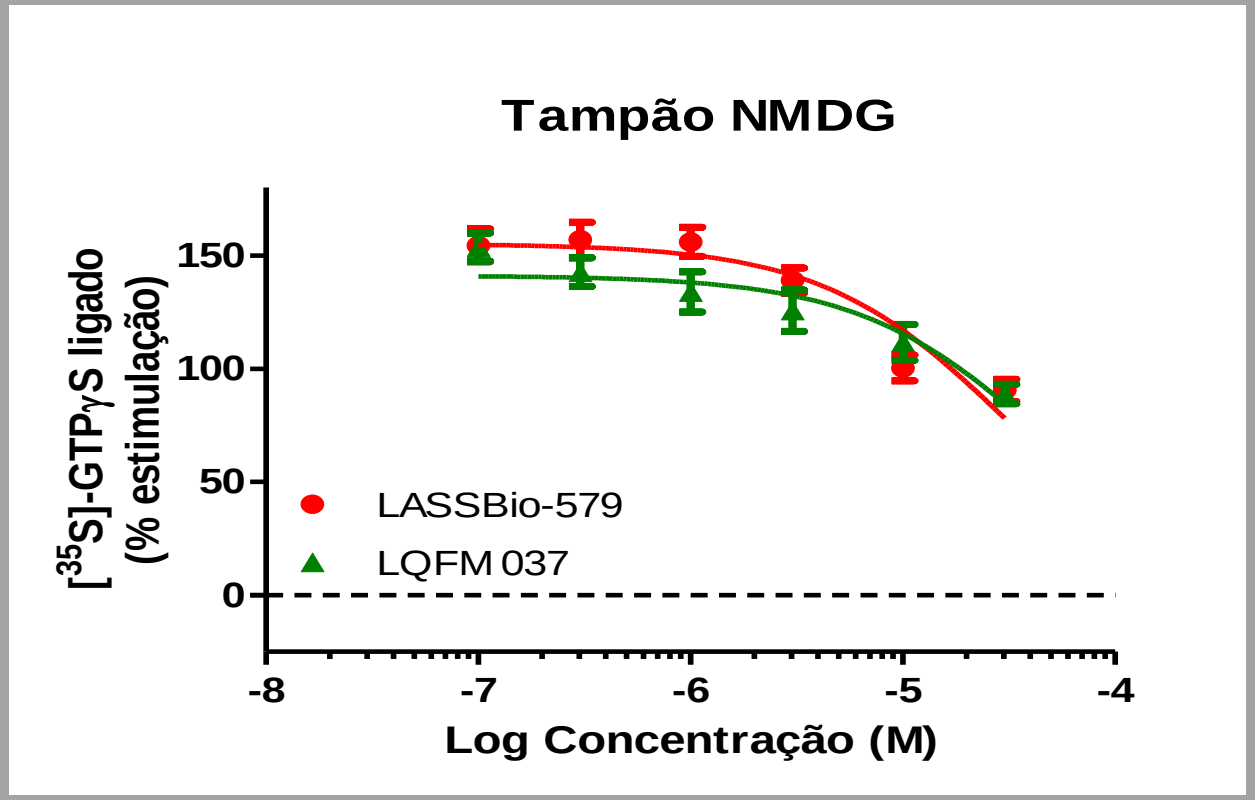
Progress Neuro-Psychopharmacol. Biol. Psychiatry 62: 1-6, 2015

Compound	E_{max} (% of stimulation relative to dopamine)
	NMDG
Dopamine 100 µM	**100** (261*)
Apomorphine 10 µM	84
3-PPP 100 µM	65
Aripiprazole 1 µM	**20.7**
LASSBio-579 10 µM	**14**
LQFM 037 10 µM	12.5
Clozapine 10 µM	-7.1
Domperidone 0.1 µM	-6.7

Progress Neuro-Psychopharmacol. Biol. Psychiatry 62: 1-6, 2015

Efeito antagônico de LASSBio-579 e LQFM 037 sobre a estimulação da ligação do [^{35}S]-GTPγS induzida por 1μM de dopamina





Progress Neuro-Psychopharmacol. Biol. Psychiatry 62: 1-6, 2015

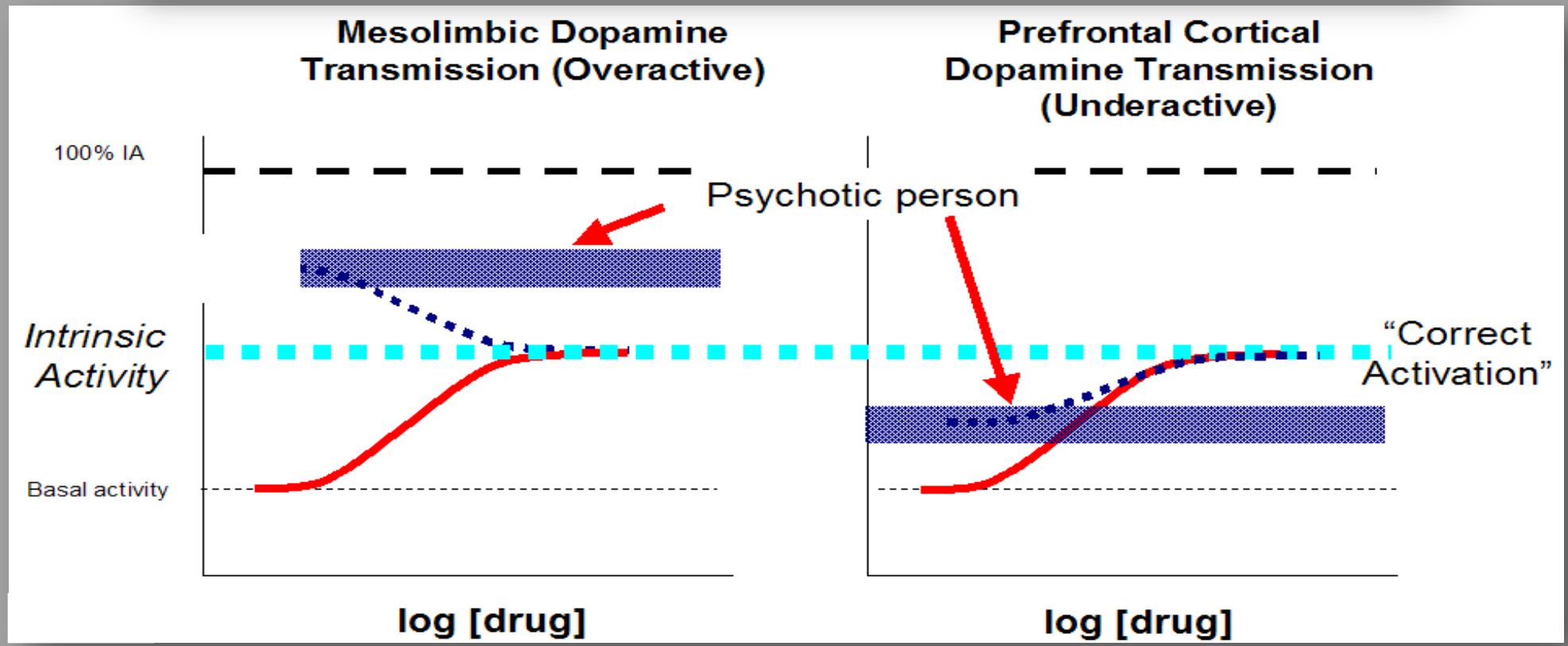
0022-3565/02/3021-381–389$7.00
THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS
JPET 302:381–389, 2002
Vol. 302, No. 1
33175/990838
Printed in U.S.A.

Aripiprazole, a Novel Antipsychotic, Is a High-Affinity Partial Agonist at Human Dopamine D2 Receptors

KEVIN D. BURRIS,[1] THADDEUS F. MOLSKI, CEN XU, ELAINE RYAN, KATSURA TOTTORI, TETSURO KIKUCHI, FRANK D. YOCCA, AND PERRY B. MOLINOFF[1]

Neuroscience Drug Discovery, Bristol-Myers Squibb Pharmaceutical Research Institute, Wallingford, Connecticut (K.D.B., T.F.M., C.X., E.R., F.D.Y., P.B.M.); and CNS Research Group, Research Institute of Pharmacological and Therapeutic Development, Otsuka Pharmaceutical Co. Ltd., Tokushima, Japan (K.T., T.K.)

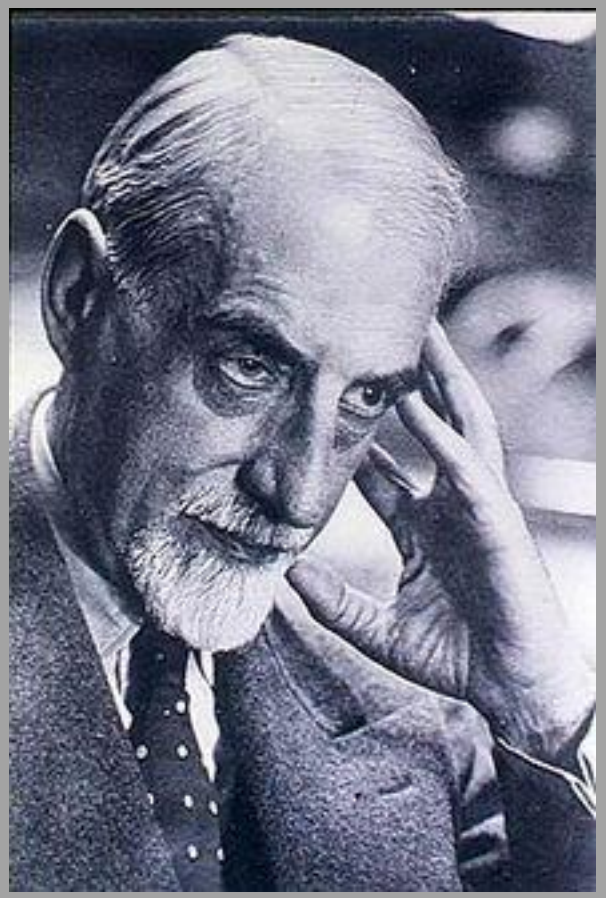
Received January 15, 2002; accepted March 27, 2002



Curr Pharm Des. 16(5): 488–501, 2010

“*Quand on est tombé sur um bom produit il n´a jamais fini d´être intéressant*”

Quando se tem um bom produto, ele nunca deixa de ser interessante



Ernest Fourneau
(1872-1949)

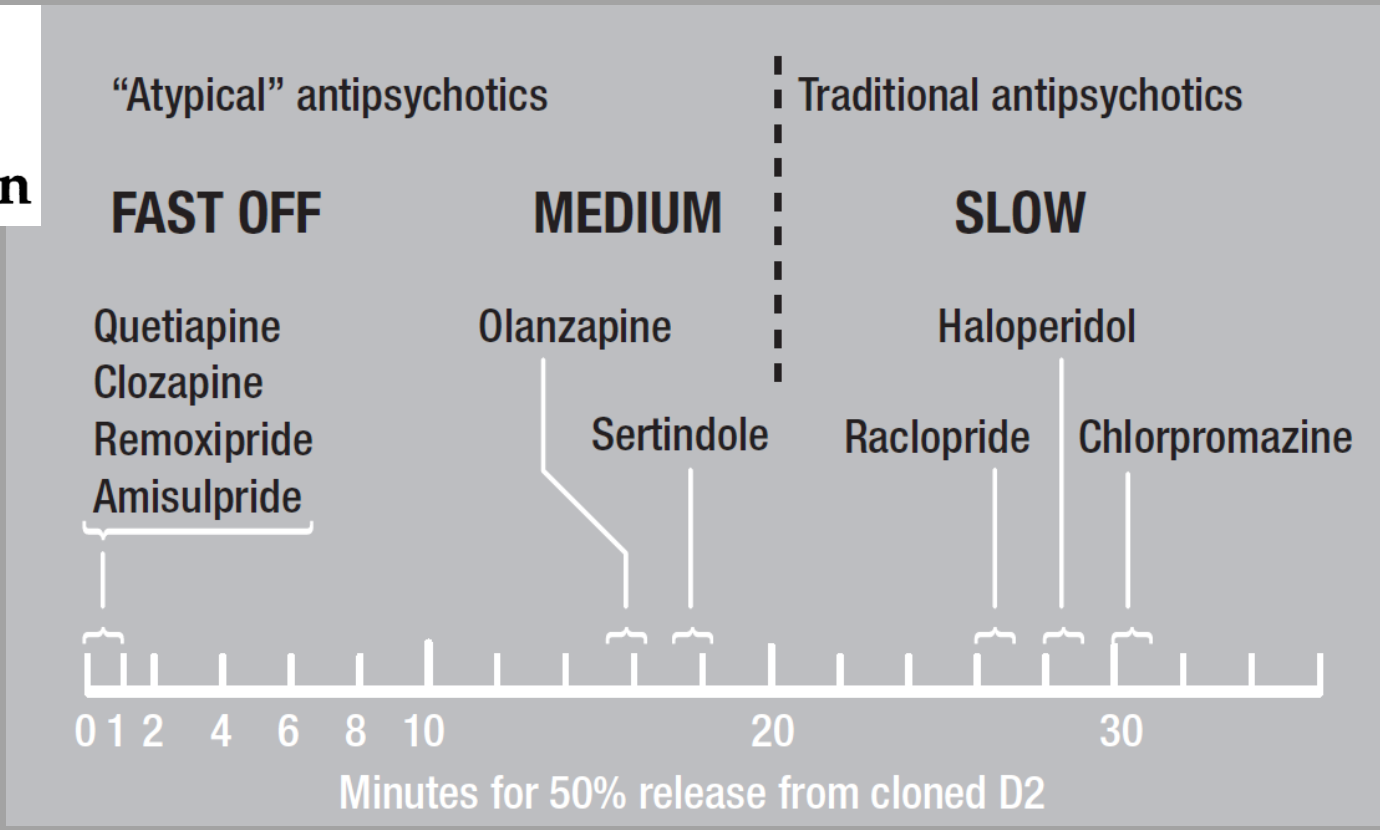
3. Busca por outro MMA que poderia contribuir para atipicalidade: Cinética de ligação ao receptor D_2

Teoria da rápida dissociação (*Fast-off theory*)

Antipsychotic agents differ in how fast they come off the dopamine D_2 receptors. Implications for atypical antipsychotic action

Shitij Kapur, MD, PhD; Philip Seeman, MD, PhD

J Psychiatry Neurosci 2000;25(2):161-6.



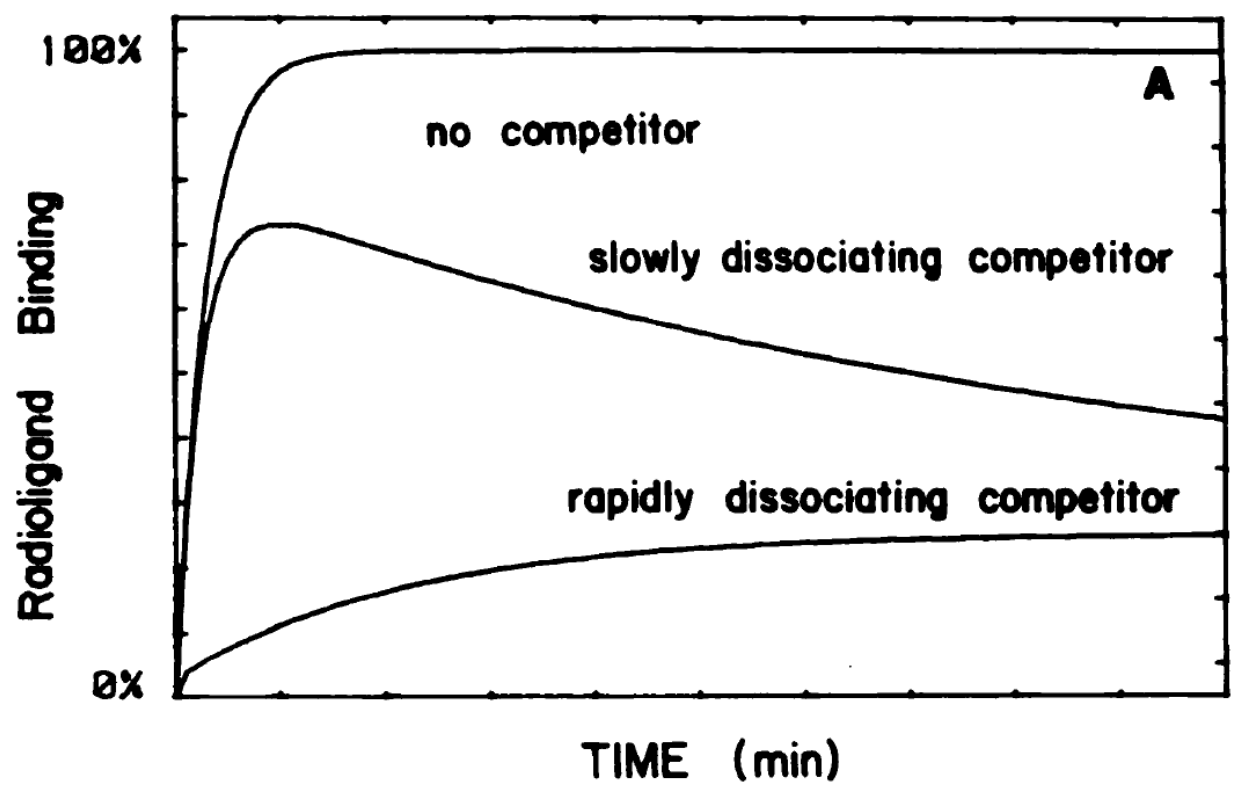
Canadian Journal of Psychiatry 2002; 47:27–38

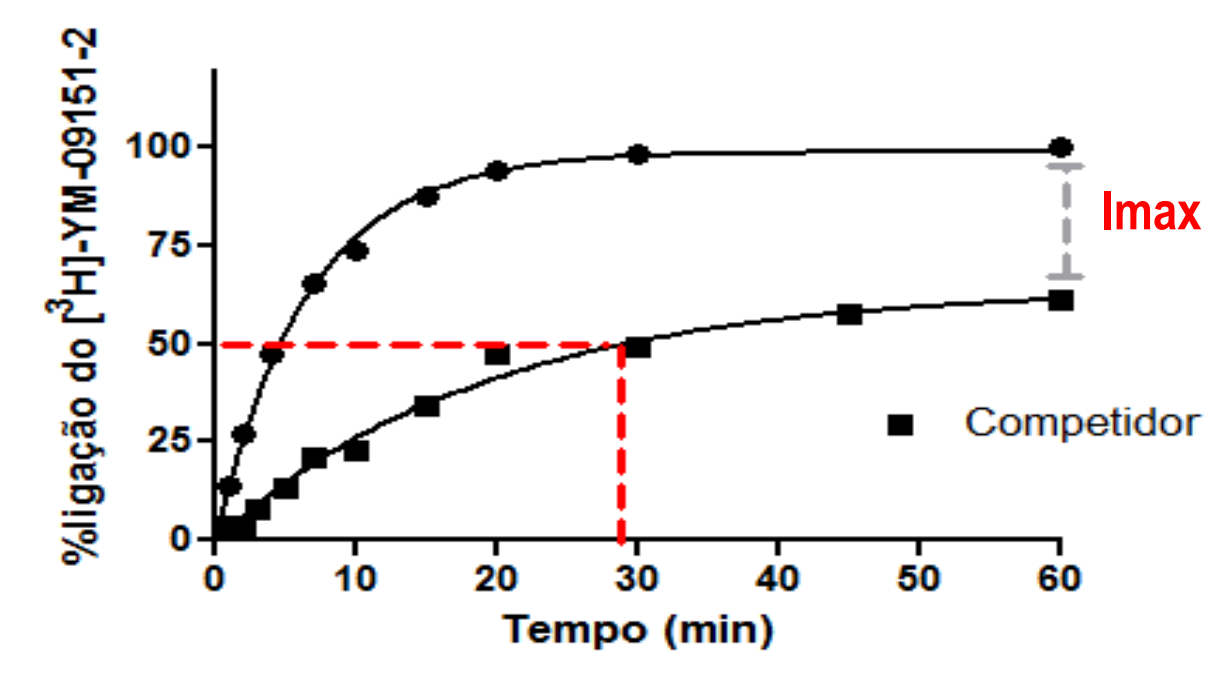
The Kinetics of Competitive Radioligand Binding Predicted by the Law of Mass Action

HARVEY J. MOTULSKY[1] AND LAWRENCE C. MAHAN[2]

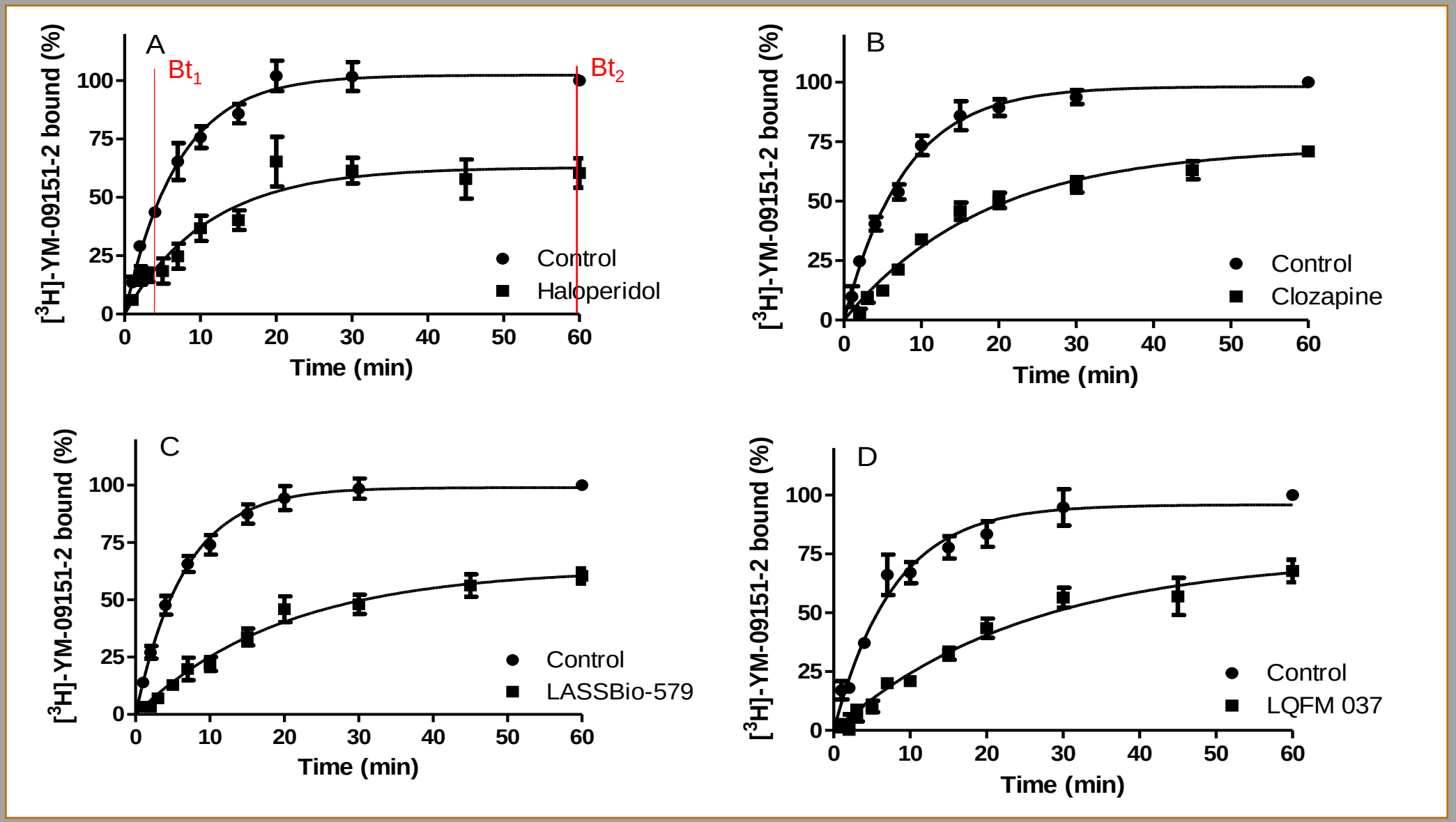
MOLECULAR PHARMACOLOGY, 25:1-9, 1983

Ensaio de Competição de Associação





Cinética da ligação de [^{3}H]-YM09151-2 aos receptores D_2 de estriado de rato



Progress Neuro-Psychopharmacol. Biol. Psychiatry 62: 1-6, 2015

Compound	% Inhibition (at equilibrium)	Half-life (min)	Kinetic rate index (Bt_1/Bt_2)
Control	-	5.10 ± 0.27	0.510 ± 0.020
Haloperidol (5 nM)	38.6 ± 6.4	7.70 ± 0.63	0.360 ± 0.024**
Clozapine (0.3 µM)	26.5 ± 2.3	12.6 ± 0.96***#	0.250 ± 0.015***#
LASSBio-579 (0.3 µM)	33.2 ± 3.5	16.2 ± 2.3***###	0.230 ± 0.028***#
LQFM 037 (0.3 µM)	22.3 ± 1.6	17.9 ± 1.8***###	0.190 ± 0.012***#

Progress Neuro-Psychopharmacol. Biol. Psychiatry 62: 1-6, 2015

TEMPO DE RESIDÊNCIA

NATURE REVIEWS | DRUG DISCOVERY

Drug–target residence time and its implications for lead optimization

*Robert A. Copeland**, *David L. Pompliano*‡ *and Thomas D. Meek*§

The drug–target residence time model: a 10-year retrospective

Robert A. Copeland

Epizyme

Drug-Target Residence Time

An Alternative Approach to Drug Optimization

Robert A. Copeland, Ph.D.

CONCLUSÕES

1. LASSBio-579: ativo em modelos animais de esquizofrenia (atípico) + efeito pró-cognitivo

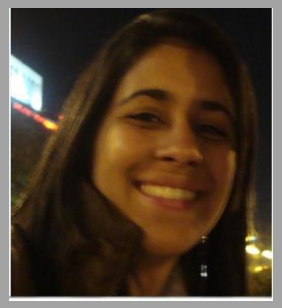
2. LASSBio-579: ligante multi-alvo (D_2, D_4, 5-HT_{1A} > 5-HT_{2A})
   D_2 : agonista parcial fraco ; rápida dissociação

3. Metabólito ativo !

4. Desenvolvimento de fármaco: interdisciplinaridade !!

AGRADECIMENTOS

ICB-UFRJ (LFBM)



Dr. Thais E. T. Pompeu

Bruna Cunto de Moura

Carolina Drummond M. Figueiredo

Fernando Monteiro do Monte

ICB-UFRJ (LASSBio)

Prof. Carlos Alberto Manssour Fraga

FF- UFRGS

Profa. Stela Maris Kuze Rates

DESDOBRAMENTOS DO PROJETO: PERSPECTIVAS

1. LASSBio-579 (e metabólito): MMA

1.a. Afinidade para receptor 5-HT_7? (efeito pró-cognitivo)

Binding

1.b. Seletividade funcional ? (Gi/AMPc *vs* β-arrestina2)

BRET (HEK293T) < Claudio M. da Costa Neto /USP-RP

1.c. Efeito sobre a via Akt/GSK-3β, *in vivo ?*

Western blot

1.d. ↑Níveis de glutamato, D-serina e/ou glicina no cérebro ?

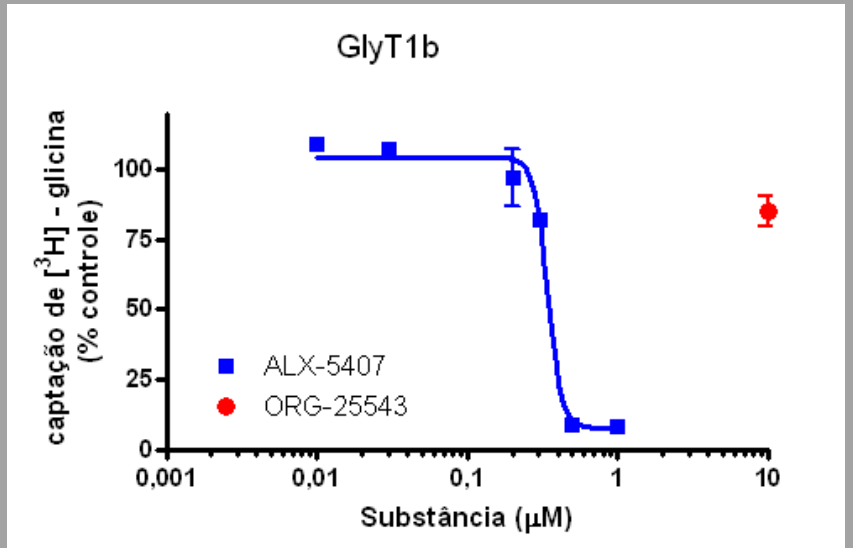
Microdiálise < Rogério A. Panizzutti / ICB

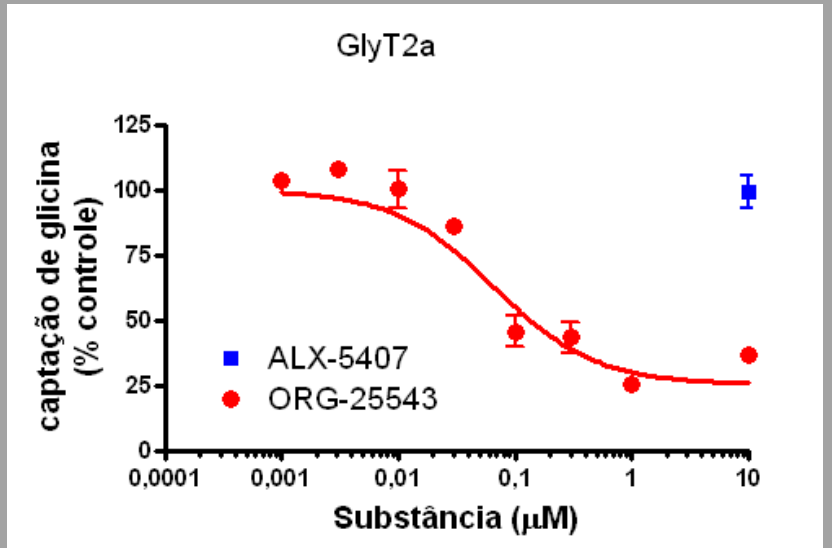
DESDOBRAMENTOS DO PROJETO E PERSPECTIVAS

2. Inibidores seletivos do transportador de glicina GlyT1:

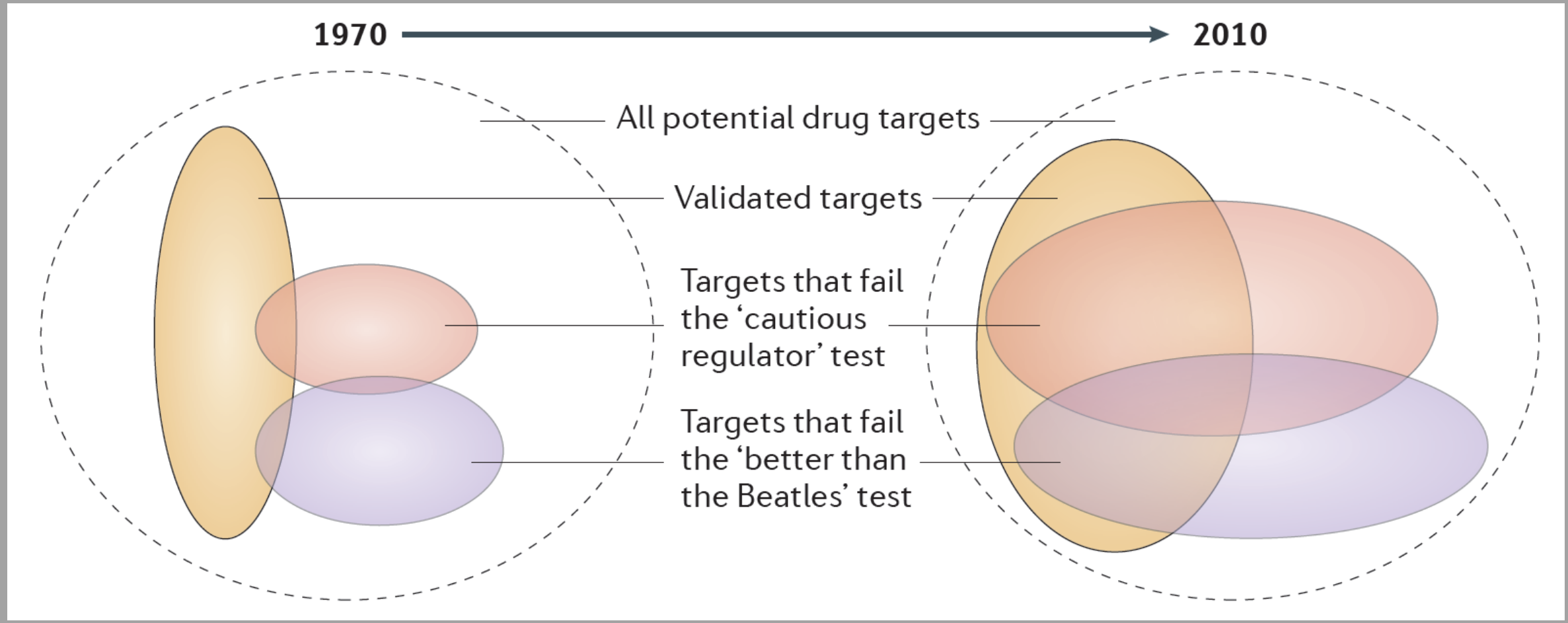
Racional: De acordo com a hipótese glutamatérgica, desenvolver inibidores seletivos do transportador de glicina do tipo GlyT1 análogos a *bitopertina (Roche®)*, visando efeito sobre os **sintomas negativos e déficits cognitivos** da Esquizofrenia e que poderiam também ser benéficos em outras doenças (Alzheimer)

Metodologia: células transfectadas com plasmídeos recombinantes GlyT1b e GlyT2a humanos

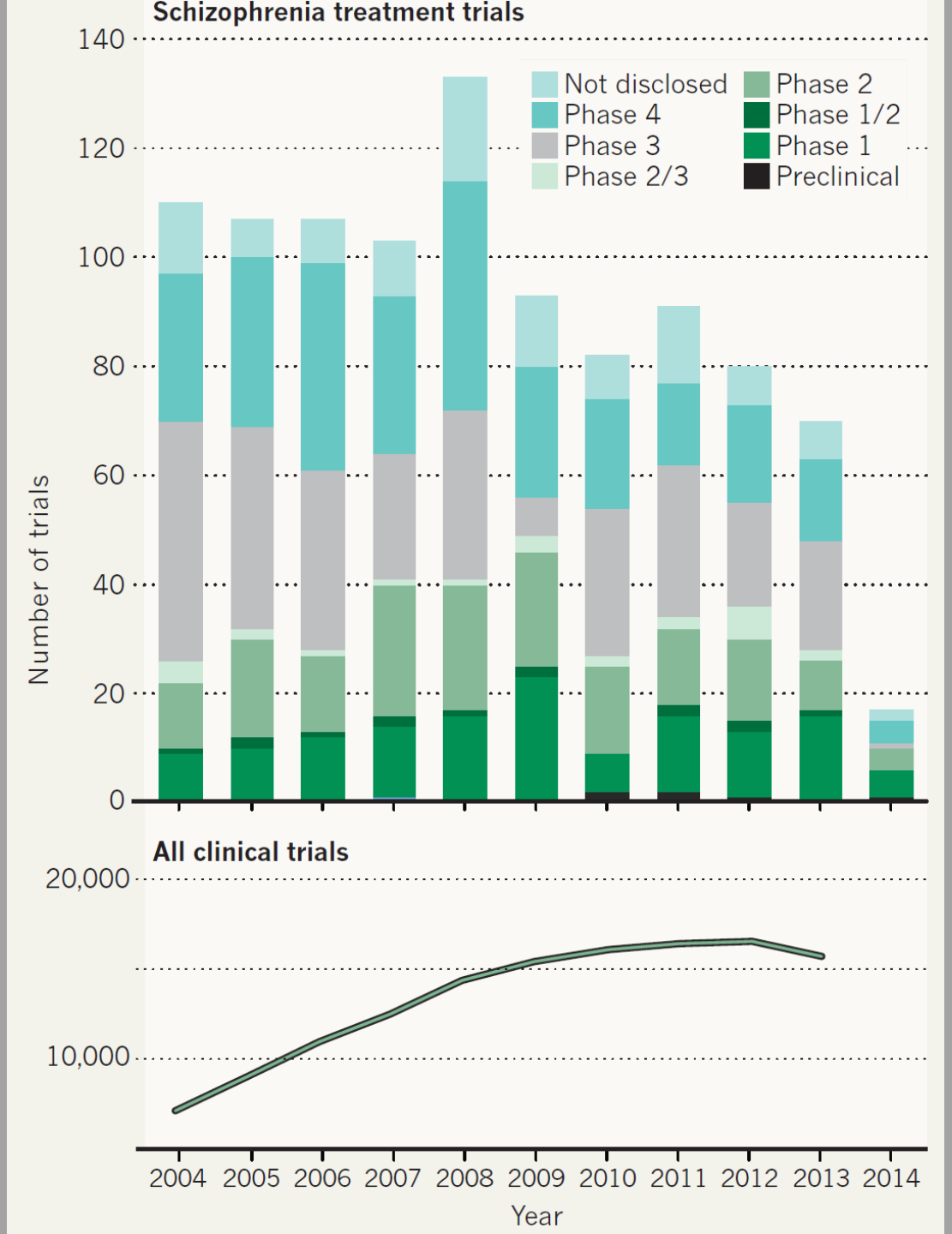




“The increase in the number of validated targets between 1970 and 2010 is outweighed by increasing regulatory caution and an improving catalogue of approved drugs”



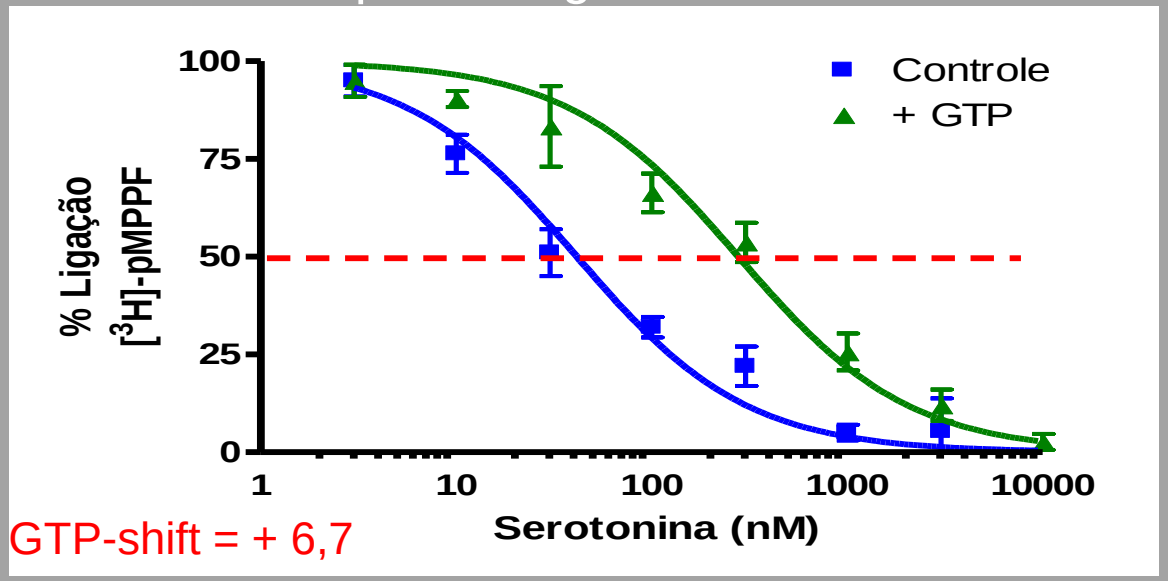
Nature Rev. Drug Discov. 11:198, 2012



Nature 508:S2, 2014

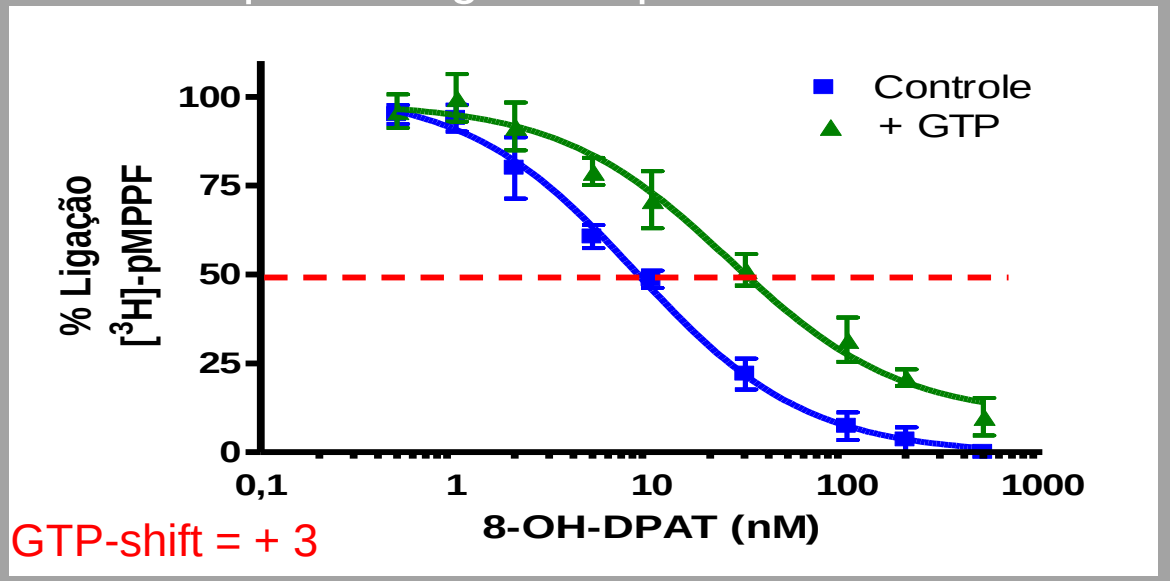
I. GTP-shift (*radioligante antagonista*)

Competidor agonista



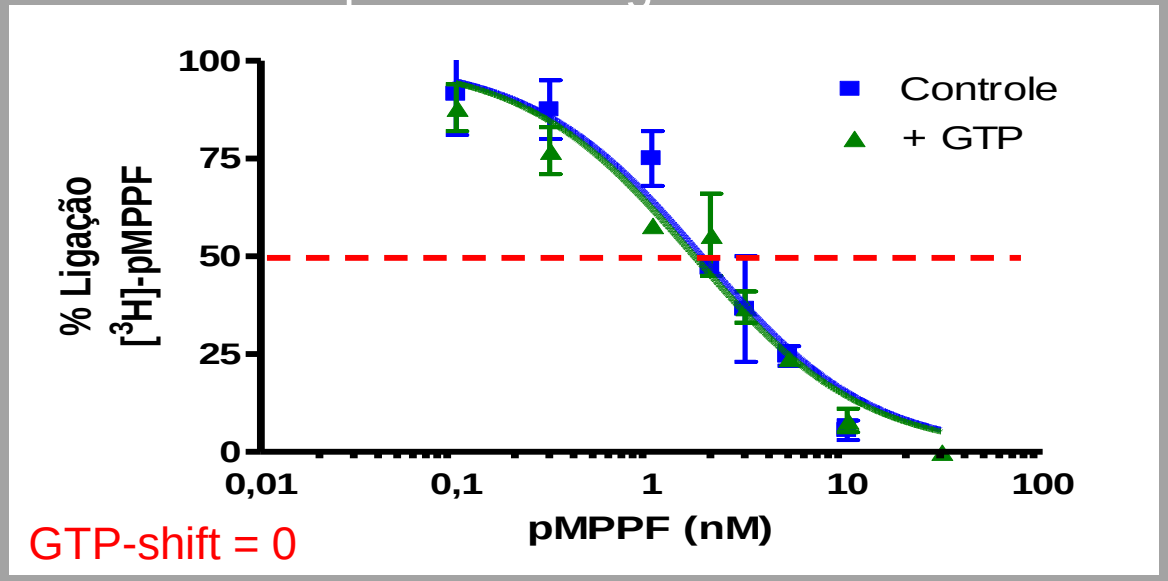
GTP-shift = + 6,7

Competidor agonista parcial



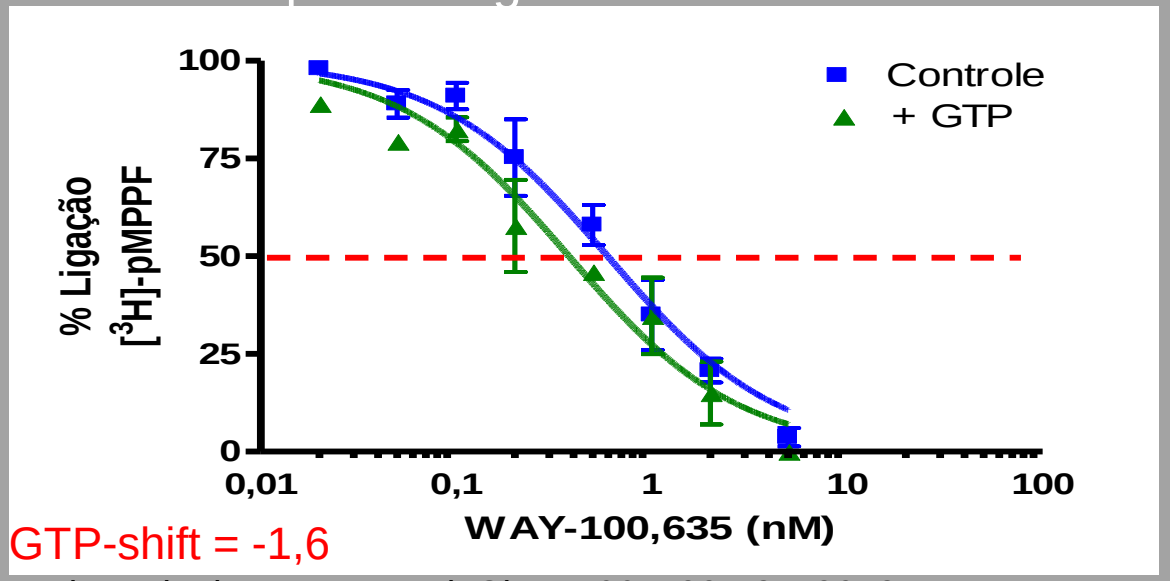
GTP-shift = + 3

Competidor antagonista



GTP-shift = 0

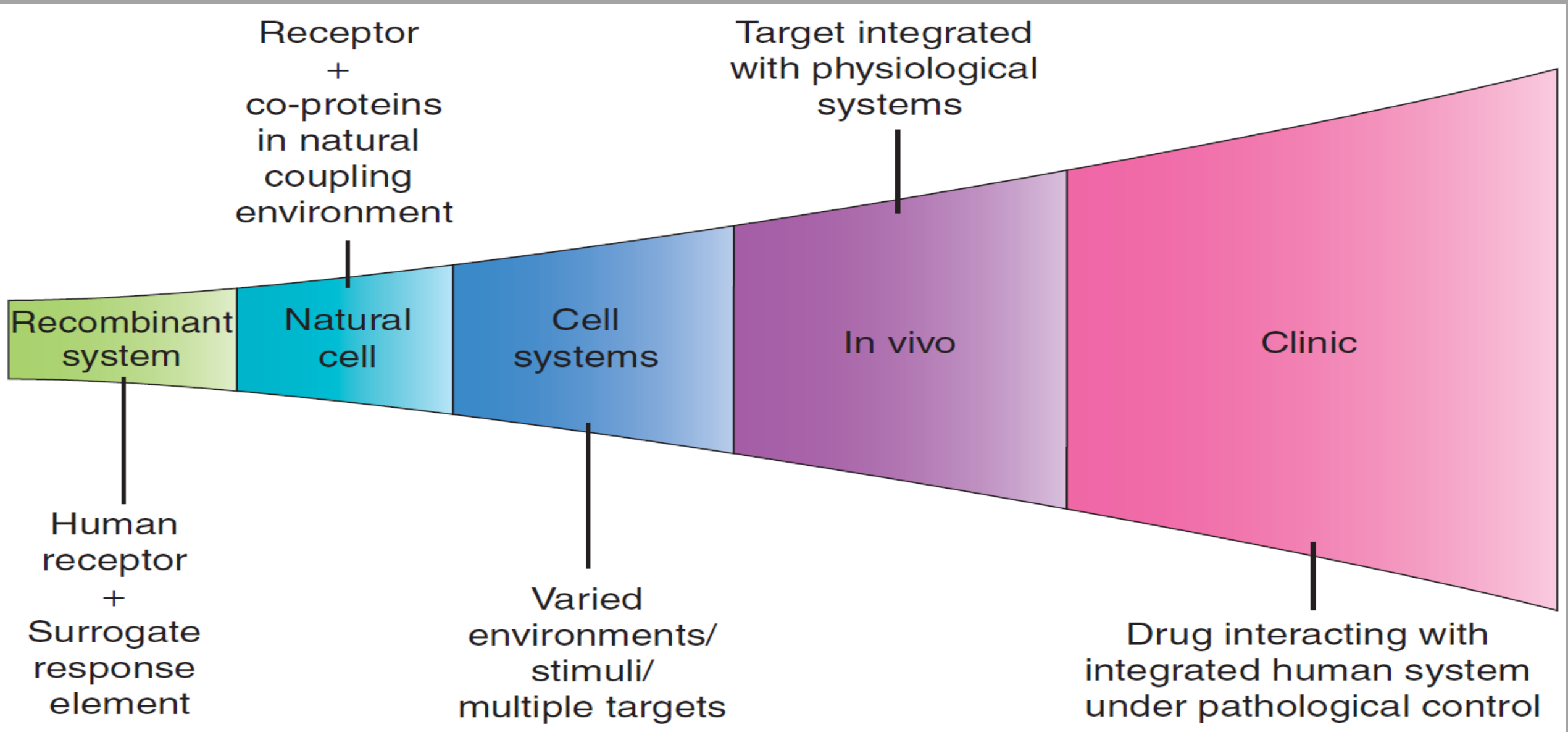
Competidor agonista inverso



GTP-shift = -1,6

Adaptado de: *Eur. J. Med. Chem. 66: 122-134, 2013*

ENSAIOS FARMACOLÓGICOS: NÍVEIS DE COMPLEXIDADE



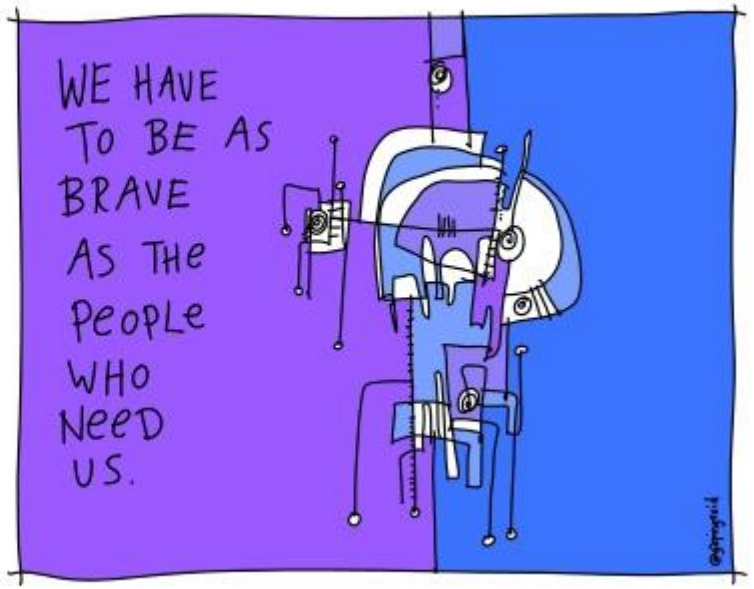
Kenakin, 2009

7. Disruptive innovation is driven by ideas that will make you unpopular.

Great ideas may not be understood at first.

That doesn't make them NOT great ideas, it just makes them not quite ready for prime time.

Don't let your biases get the better of you.



gapingvoid

"Discouraging data on the antidepressant."

Doubt is your enemy.

Waiting for permission is a weakness.

Seeking validation is a stall tactic.

The problem with failure is the culture that once defined it as, you know, failing. But in reality, failing is synonymous with trying something new and different. And for those keeping score, venturing into new territories is also synonymous with innovation.

Fail.

Fail often.

Fail fast.

the only way to guarantee

no failure

is to not do anything.

#sxsw2015

gapingvoid

PHARMACOLOGY

Historical developments in Pharmacology

- PEN PSAO (2700 BC) It was the great herbal materia medica written in china.
- Kahun Papyrus (2000 BC) is an oldest Egyptian document containing information about veterinary medicines and uterine diseases of women.
- Ebers papyrus (1550 BC) also an Egyptian document containing information about number of diseases and 829 prescription where castor oil, opium like drug are being used.
- Hippocrates (460-375 BC) A greek physician consider **"father of Medicine"**. He was the first person who recognize disease as abnormal reaction of body. He introduce use of metallic salts for the treatment of disease.

16th Century

- Paracelsus- "Father of Pharmacology"

» Swiss scientist that first advocated the use of a single drug rather than mixtures and potions

» (advantage: the dosage of a single dose can be regulated more precisely than that of complex mixtures

» Improved pharmacy and therapeutics, introducing new remedies and compounds and reducing overdosing

- **Rudolf Buchheim** (1820 – 1879)
  - **First pharmacology laboratory** in the world (1860, University of Dorpat in Estonia)
  - Introduced bioassay .

OSWALD SCHMIEDEBERG

THE FATHER OF MODERN PHARMACOLOGY

Historical developments in Pharmacology

- Theophrastus (380-287 BC) a great philosopher called father of Pharmacognosy. He classified medicinal plants on the base of medicinal characteristics.
- Dioscorides (AD 57) a greek, produced one of the first materia medica of approximately 500 plants and remedies.
- Claudius Galen (AD 129-200) first attempted to consider the theoretical background of pharmacology.
- Paracelsus (1493-1541) a Swiss scholar and alchemist, often considered the "**grandfather of pharmacology**". He introduces the use of chemicals for treatment of disease.
- Valerius Cordus (1514-1544) He compiled the first pharmacopeia where he described techniques for the preparation of drugs.

MODERN PHARMACOLOGY

- Conversion of old medicines into the modern pharmacology start taking shape following the introduction of animal experimentation and isolation of active ingredients from plants.
- Francois Megendie (1783-1855) a first pharmacologist established the foundation of modern pharmacology. He developed experiment to elucidate the physiological processes and action of drugs on the body.
- Frederich Sertürner, German pharmacist's assistant, isolated morphine—the first pure drug—in 1805
- Claude Bernard (1813-1878) considered Father of experimental Medicine. He identifies the site of action of curare (arrow Poisoning).

MODERN PHARMACOLOGY

- Rudolph Buchheim (1820–1879) German pharmacologist a key figure in the development of pharmacology, a who at the University of Dorpat, created the first pharmacological institute.
- Oswald Schmiedeberg (1838–1921) **"Father of Pharmacology"** established pharmacology as an independent discipline. He start teaching Pharmacology in University of Strasbourg (France).
- John Jacob Abel (1857-1938) founded first department of pharmacology in USA in the University of Michigan in 1893. In 1897 he established pharmacology department at Johns Hopkins University. Abel also co-founded the Journal of Pharmacology and Experimental Therapeutics in 1909.