Advances in Alzheimer Therapy (AAT) March 9-12, 2016

Masitinib for the treatment of Alzheimer's disease: Clinical and preclinical data

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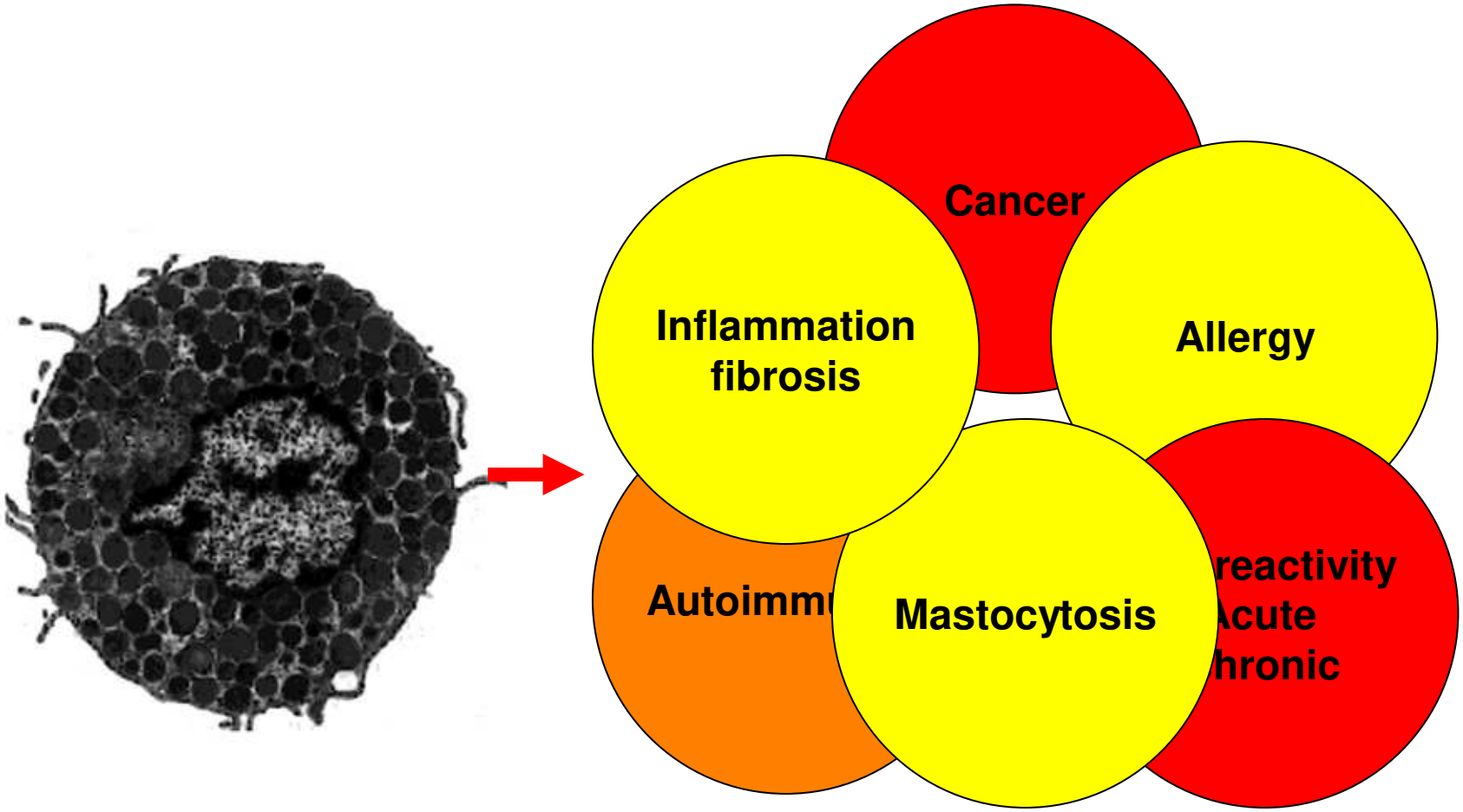
Disclosure

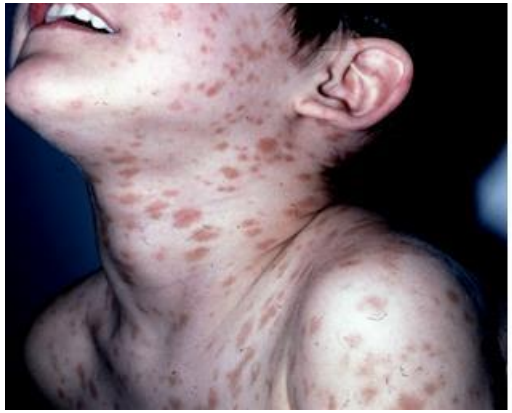
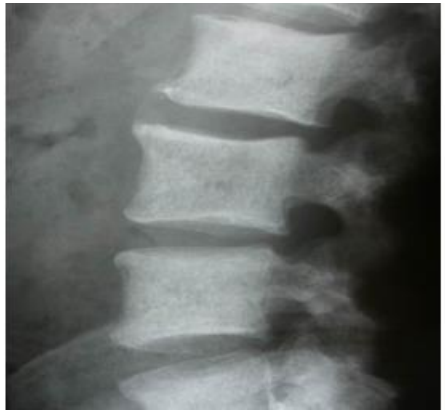
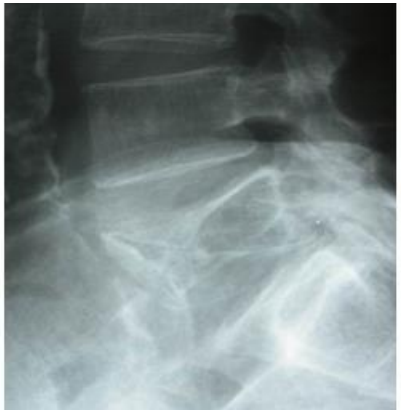
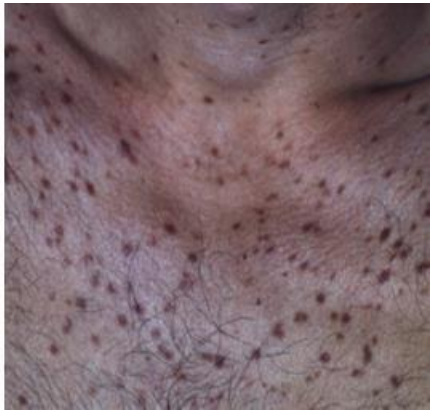
Co-founder of AB science
Scientific consultant
Research grants

MAST CELLS AND DISEASES



MASTOCYTOSIS DEFINITION

- Mast cell accumulation in various organs (Skin, GI tract, Liver, Bone and Bone Marrow, etc)
- Myeloproliferative disorder; Aggressive vs indolent disease
- Association with hematological disorders
- Clinical heterogeneity (Infiltration vs Mediators release)

Photos Pr Bodemer et Dr Barete

IDENTIFICATION OF ALL SYSTEMIC MANIFESTATIONS IN PATIENTS SUFFERING FROM MASTOCYTOSIS

- From 2004, 363 mastocytosis patients and 90 controls in France were asked to rate their overall disability (OPA score) and the severity of 38 individual symptoms.

- A specific questionnaire (AFIRMM V1), encompassing these 38 symptoms, has been created and validated.

PLoS ONE. 2008 May 28;3(5):e2266

OPEN ACCESS Freely available online

PLoS one

Case-Control Cohort Study of Patients' Perceptions of Disability in Mastocytosis

Olivier Hermine[1,2,3*], Olivier Lortholary[3,4], Phillip S. Leventhal[3], Adeline Catteau[3], Frédérique Soppelsa[3], Cedric Baude[3], Annick Cohen-Akenine[3], Fabienne Palmérini[3,4,6], Katia Hanssens[3,4,6], Ying Yang[4], Hagay Sobol[6], Sylvie Fraytag[5], David Ghez[1,2], Felipe Suarez[2], Stéphane Barete[1,7], Philippe Casassus[3,8], Beatrice Sans[9], Michel Arock[10], Jean Pierre Kinet[3], Patrice Dubreuil[3,4,6], Alain Moussy[3]

IDENTIFICATION OF ALL SYSTEMIC MANIFESTATIONS IN PATIENTS SUFFERING FROM MASTOCYTOSIS

Symptom	Patients					*P*-value[b]	
	Any disability[c]	Severe or intolerable disability[d]	*n*	Any disability[c]	Severe or intolerable disability[d]	Any disability[c]	Severe or intolerable disability[d]
Psychological impact	9 (10%)	1 (1%)	363	261 (72%)	120 (33%)	*<0.0001*	*<0.0001*
Asthenia	34 (38%)	3 (3%)	362	296 (82%)	102 (28%)	*<0.0001*	*<0.0001*
Pruritus	25 (28%)	3 (3%)	363	299 (82%)	82 (23%)	*<0.0001*	*<0.0001*
Food allergy/intolerance	9 (10%)	0 (0%)	363	222 (61%)	97 (27%)	*<0.0001*	*<0.0001*
Erythemateous crisis	17 (19%)	1 (1%)	363	293 (81%)	69 (19%)	*<0.0001*	*<0.0001*
Muscle and joint pain, cramps	36 (40%)	3 (3%)	363	276 (76%)	71 (20%)	*<0.0001*	*0.0002*
Pollakiuria	58 (64%)	6 (7%)	362	263 (73%)	64 (18%)	0.12	*0.0098*
Drug allergy	16 (18%)	0 (0%)	363	205 (56%)	70 (19%)	*<0.0001*	*<0.0001*
Aerophagia/eructation	43 (48%)	1 (1%)	363	229 (63%)	62 (17%)	*0.0080*	*<0.0001*
Dyspnea/bronchoreactivity	15 (17%)	3 (3%)	362	154 (43%)	94 (26%)	*<0.0001*	*<0.0001*
Headache	34 (38%)	4 (4%)	362	250 (69%)	48 (13%)	*<0.0001*	*0.0190*
Bone pain	16 (18%)	0 (0%)	363	196 (54%)	65 (18%)	*<0.0001*	*<0.0001*
Reduced sexual relations	11 (12%)	4 (4%)	362	132 (36%)	65 (18%)	*<0.0001*	*0.0014*
Epigastric pain	35 (39%)	2 (2%)	362	249 (69%)	40 (11%)	*<0.0001*	*0.0100*
Ocular discomfort	43 (48%)	1 (1%)	363	219 (60%)	55 (15%)	*0.0309*	*0.0003*
Memory loss	32 (36%)	0 (0%)	362	240 (66%)	34 (9%)	*<0.0001*	*0.0025*
Tinnitus	29 (32%)	1 (1%)	363	166 (46%)	47 (13%)	*0.0205*	*0.0011*

PLoS ONE. 2008 May 28;3(5):e2266

IDENTIFICATION OF PSYCHOPATHOLOGICAL MANIFESTATIONS IN PATIENTS SUFFERING FROM MASTOCYTOSIS

- Determine the prevalence and to describe features of depression in a large cohort of mastocytosis patients (n = 288)
- Use of 17 items Hamilton Depression Scale (Ham-D17)

PLoS ONE. 2011 October:6(10): e26375

OPEN ACCESS Freely available online

PLoS one

Depression in Patients with Mastocytosis: Prevalence, Features and Effects of Masitinib Therapy

Daniela Silva Moura[1,2], Serge Sultan[2,3], Sophie Georgin-Lavialle[1,4], Nathalie Pillet[5], François Montestruc[5], Paul Gineste[5], Stéphane Barete[6], Gandhi Damaj[7], Alain Moussy[5,8], Olivier Lortholary[9], Olivier Hermine[1,4,5,8]*

IDENTIFICATION OF PSYCHOPATHOLOGICAL MANIFESTATIONS IN PATIENTS SUFFERING FROM MASTOCYTOSIS

- 64% of Patients are depressed (Hamilton Score)
  - Moderate 56 %
  - Severe 10 %
- Characterisitics of the depression
  - Anxiety and depression
    - Depressed mood
    - Psychiatric and somatic anxiety
    - Impairement and weakness for social and professional interactions
  - Sleep disturbances
- <u>NO CORRELATION WITH COGNITIVE FUNCTIONS</u>

PLoS ONE. 2011 October:6(10): e26375

EVALUATION OF COGNITIVE IMPAIRMENT IN PATIENTS SUFFERING FROM MASTOCYTOSIS

- **Describe the prevalence and features of cognitive impairment in a large cohort of patients with this rare disease (n = 57)**
- **Explore the relations between memory impairment and depression**
- **Memory impairment evaluated using the 3(rd) edition of the Clinical Memory scale of Wechsler. Depression symptoms evaluated using the Hamilton Depression Rating Scale**

PLoS One. 2012;7(6):e39468.

OPEN ACCESS Freely available online

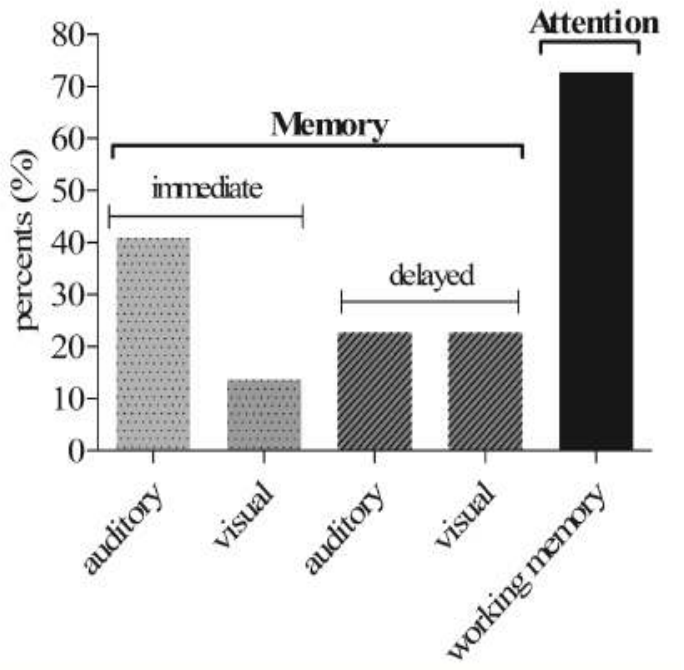
PLoS one

Evidence for Cognitive Impairment in Mastocytosis: Prevalence, Features and Correlations to Depression

Daniela Silva Moura[1,2*], Serge Sultan[7,8], Sophie Georgin-Lavialle[1,3,4], Stéphane Barete[1,3,5], Olivier Lortholary[1,6], Raphael Gaillard[9,10], Olivier Hermine[1,3,11,12*]

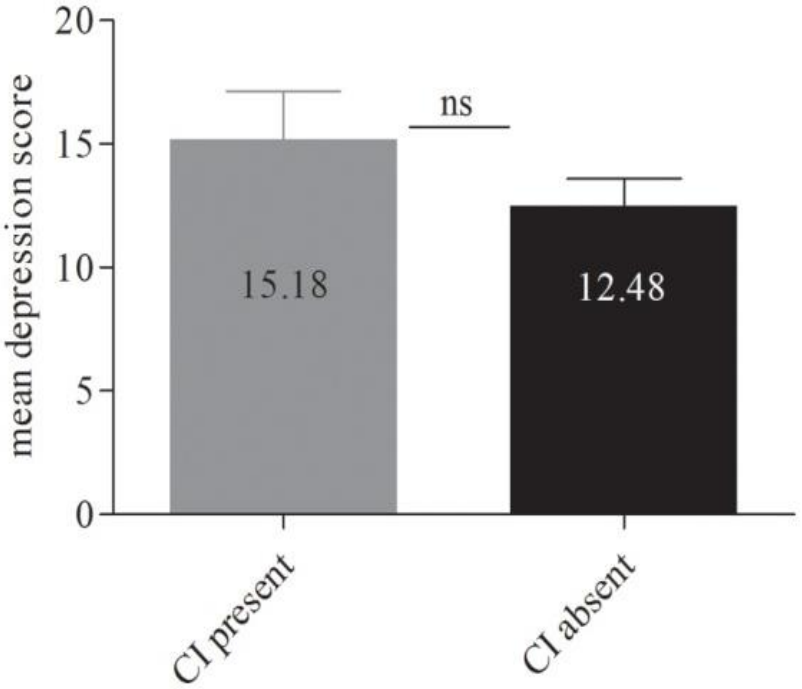
EVALUATION OF COGNITIVE IMPAIRMENT IN PATIENTS SUFFERING FROM MASTOCYTOSIS

Cognitive dysfunctions in mastocytosis



Memory impairment is a symptom associated with Mastocytosis

unpaired t-test to compare depression scores of patients with and without cognitive impairment

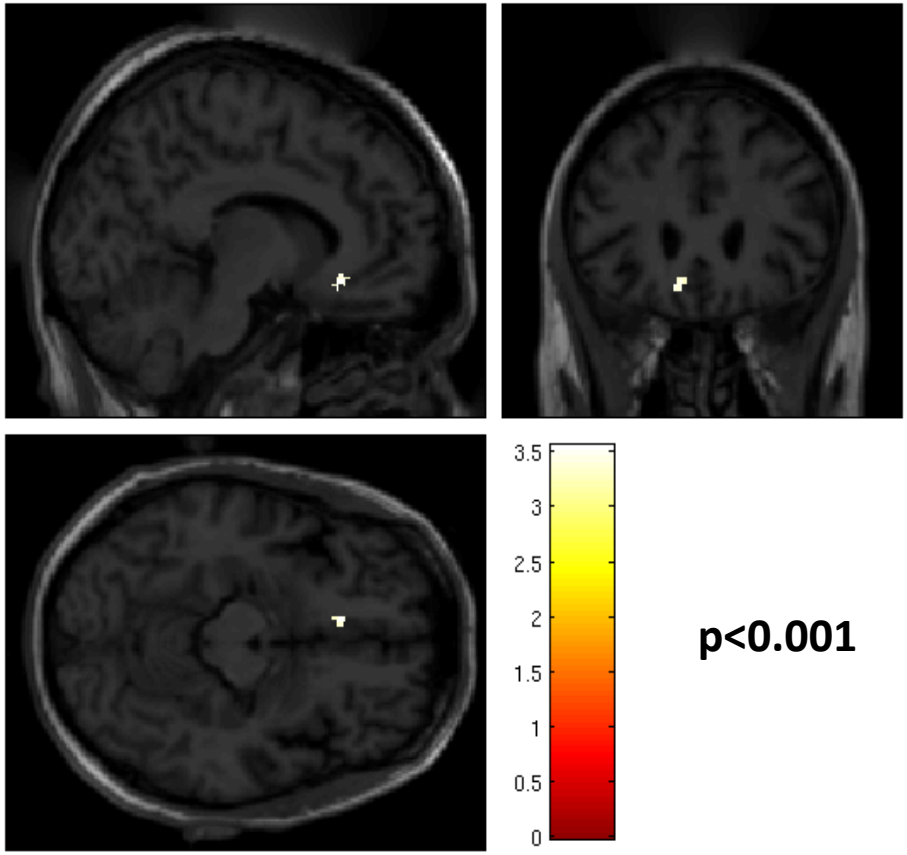


Cognitive impaired patients are no more depressed than patients without cognitive impairment.

PLoS One. 2012;7(6):e39468.

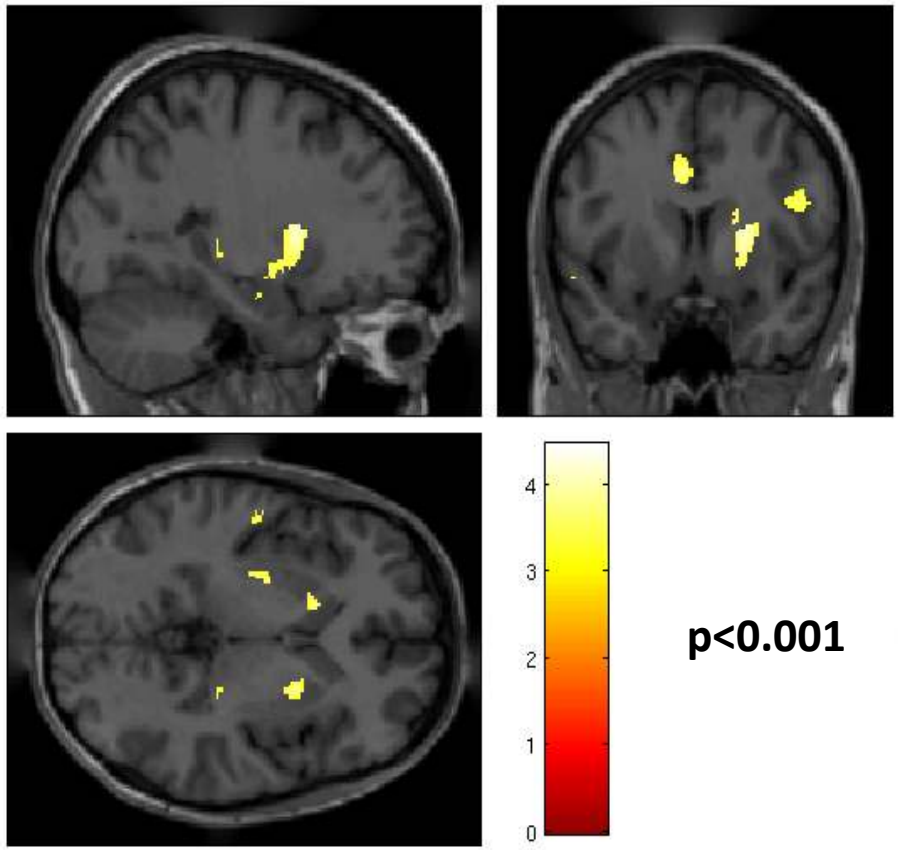
MASTOCYTOSIS: BRAIN BLOOD PERFUSION

Hypoperfusion of the anterior Cingulum antérieur in 10 patients with depression and mastocytosis Vs. 18 patients with Mastocytosis but not depressed



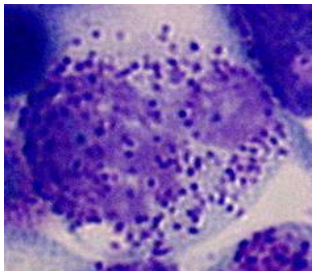
p<0.001

Hyperperfusion of central grey nuclei : 11 patients with cognitive imapirement vs 33 controls

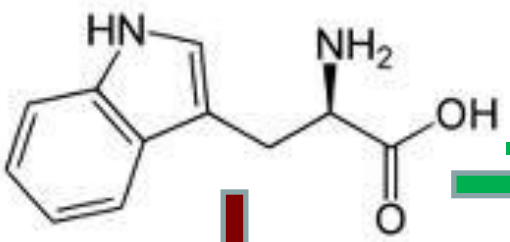


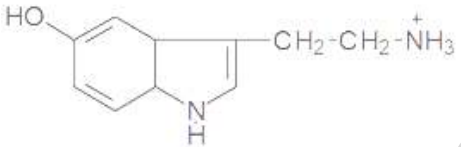
p<0.001

HYPOTHESIS

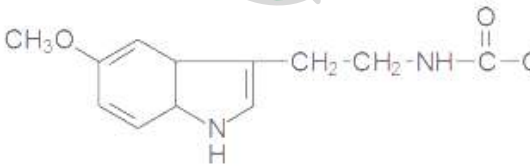


Tryptophane





Serotonin
(5-hydroxytryptamine)



Melatonin

Histamine
Others

ASL
abnormalities

TNFα

IDO

Kynurenine

Acid
xanthurenic

Acid
quinolenic

serotonin

Low serotonin

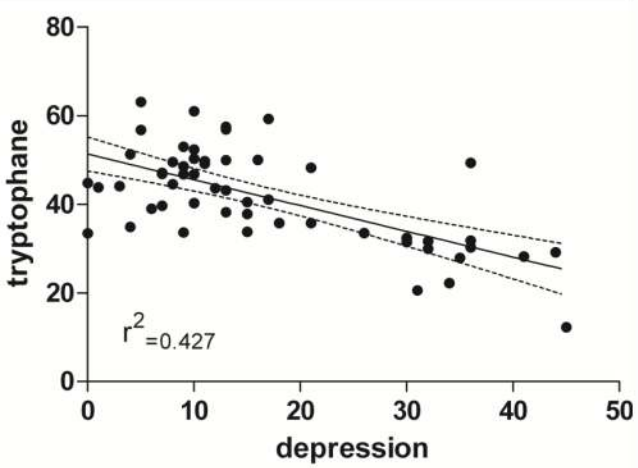
Depression ?

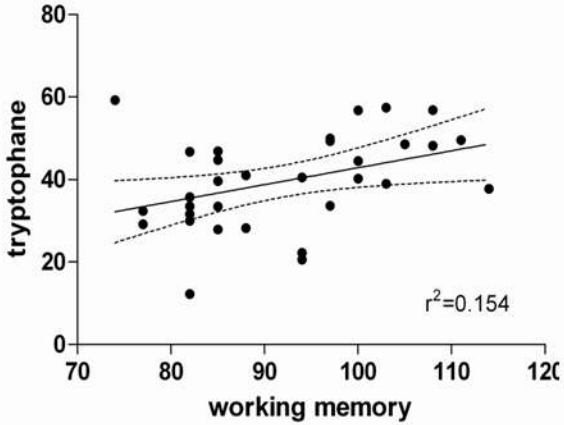
Proteases

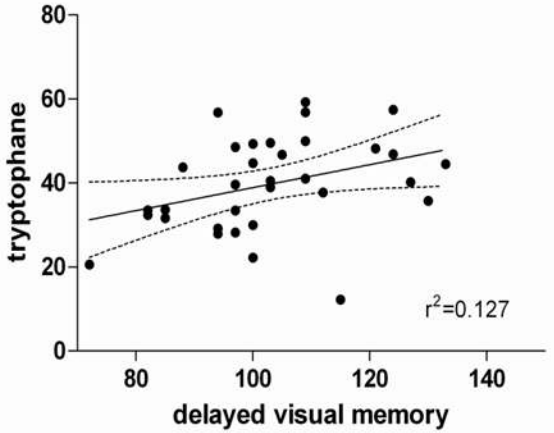
Neurotoxicity
Oxidative stress
apoptosis

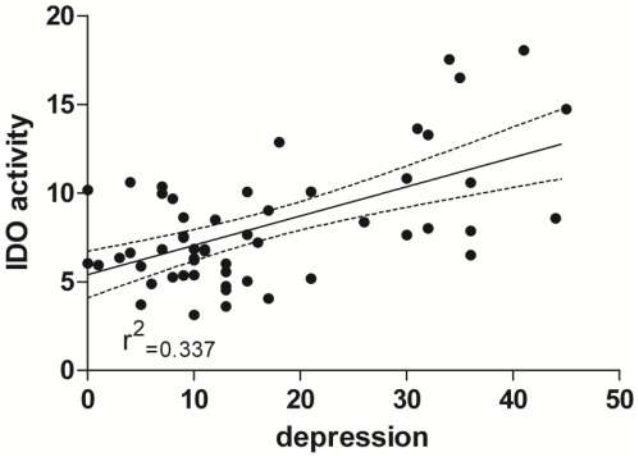
Cognition (?)

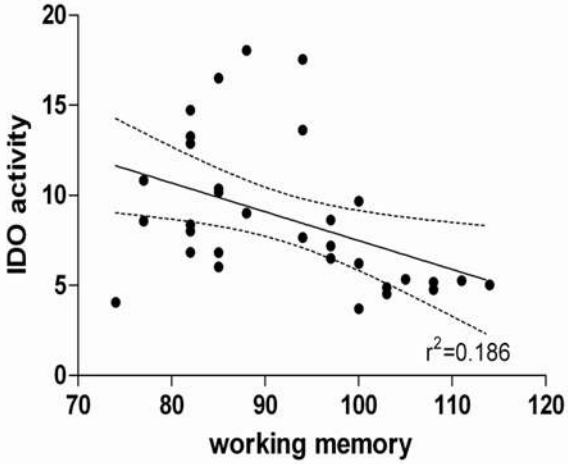
TRYPTOPHAN METABOLISM IS ALTERED IN MASTOCYTOSIS AND CORRELATES WITH PERCEIVED STRESS AND DEPRESSION, DEMONSTRATING MAST CELLS' INVOLVEMENT IN INFLAMMATION PATHWAYS LINKED TO DEPRESSION.











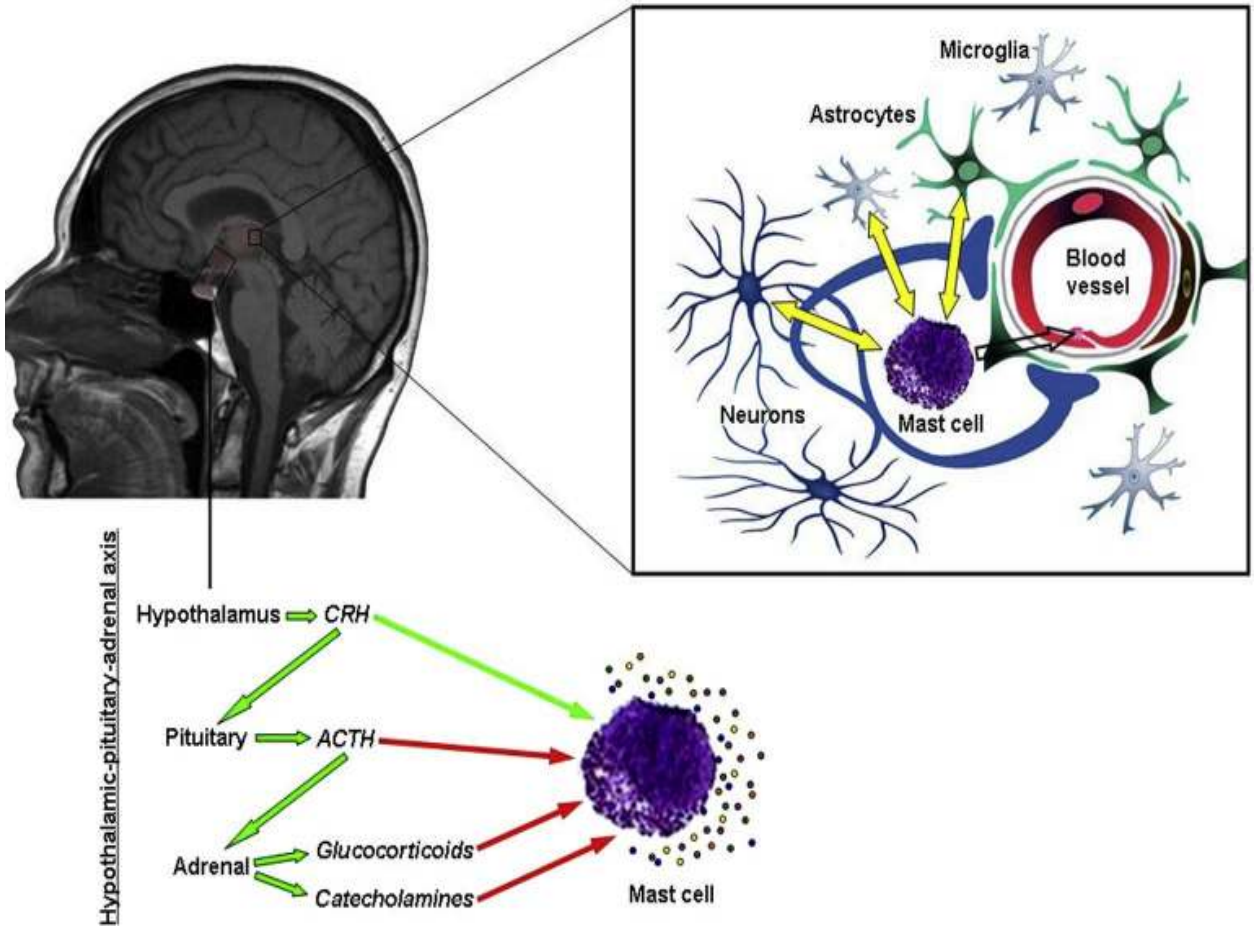
n=54pts/54 controls

Georgin Laviale, Moura D et al Mol Psychiatry, 2016

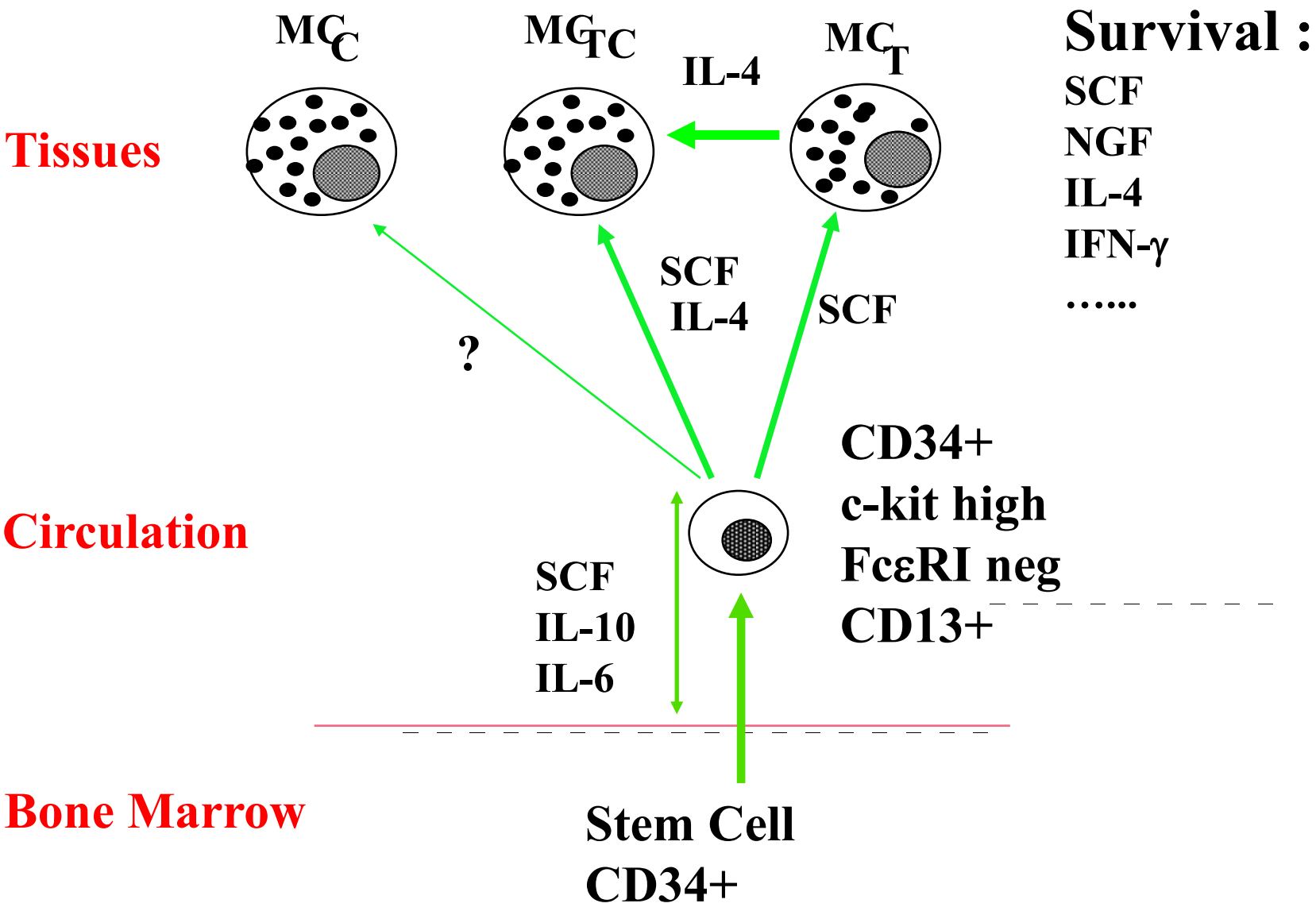
MAST CELL ACTIVATION DISEASE

Mast cell activation disease: An underappreciated cause of neurologic and psychiatric symptoms and diseases

Lawrence B. Afrin [a], Dieter Pöhlau [b], Martin Raithel [c], Britta Haenisch [d,e], Franz L. Dumoulin [f], Juergen Homann [f], Uwe M. Mauer [g], Sabrina Harzer [h], Gerhard J. Molderings [h,*]



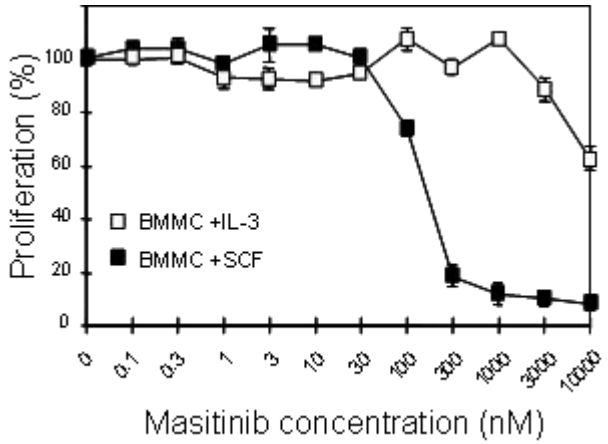
SIMPLIFIED PATHWAYS OF HUMAN MC DIFFERENTIATION

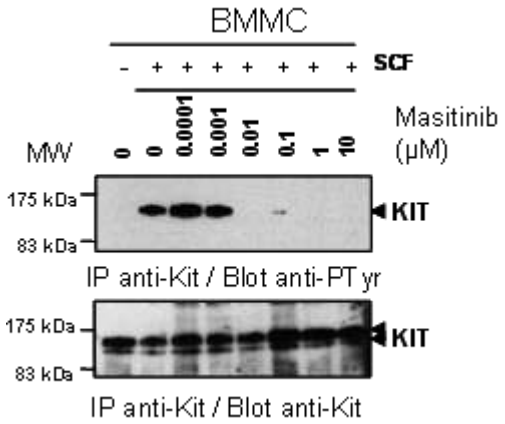


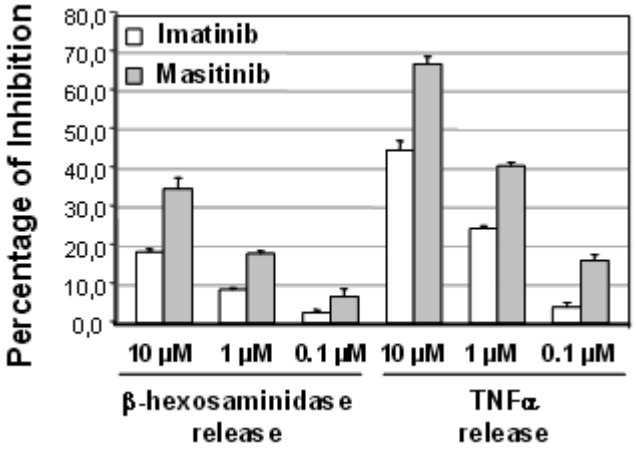
MASITINIB: SELECTIVE TYROSINE KINASE INHIBITOR, INHIBITING MAST CELL SURVIVAL, DEGRANULATION AND MIGRATION VIA C-KIT INHIBITION

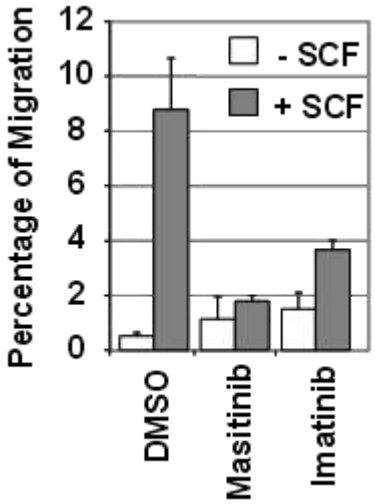
SUMMARY OF INHIBITORY EFFECTS OF MASITINIB

Target	IC_{50} [nM]	Kd [µM]
KIT wild-type	200	0.008
FYN	240	0.14
LYN	225	0.061
PDGFR-alpha	50	0.025
PDGFR-beta	110	0.008
CSF1R	90	0.008









Dubreuil 2009, PLoSONE.4(9):e7258 ; AB Science

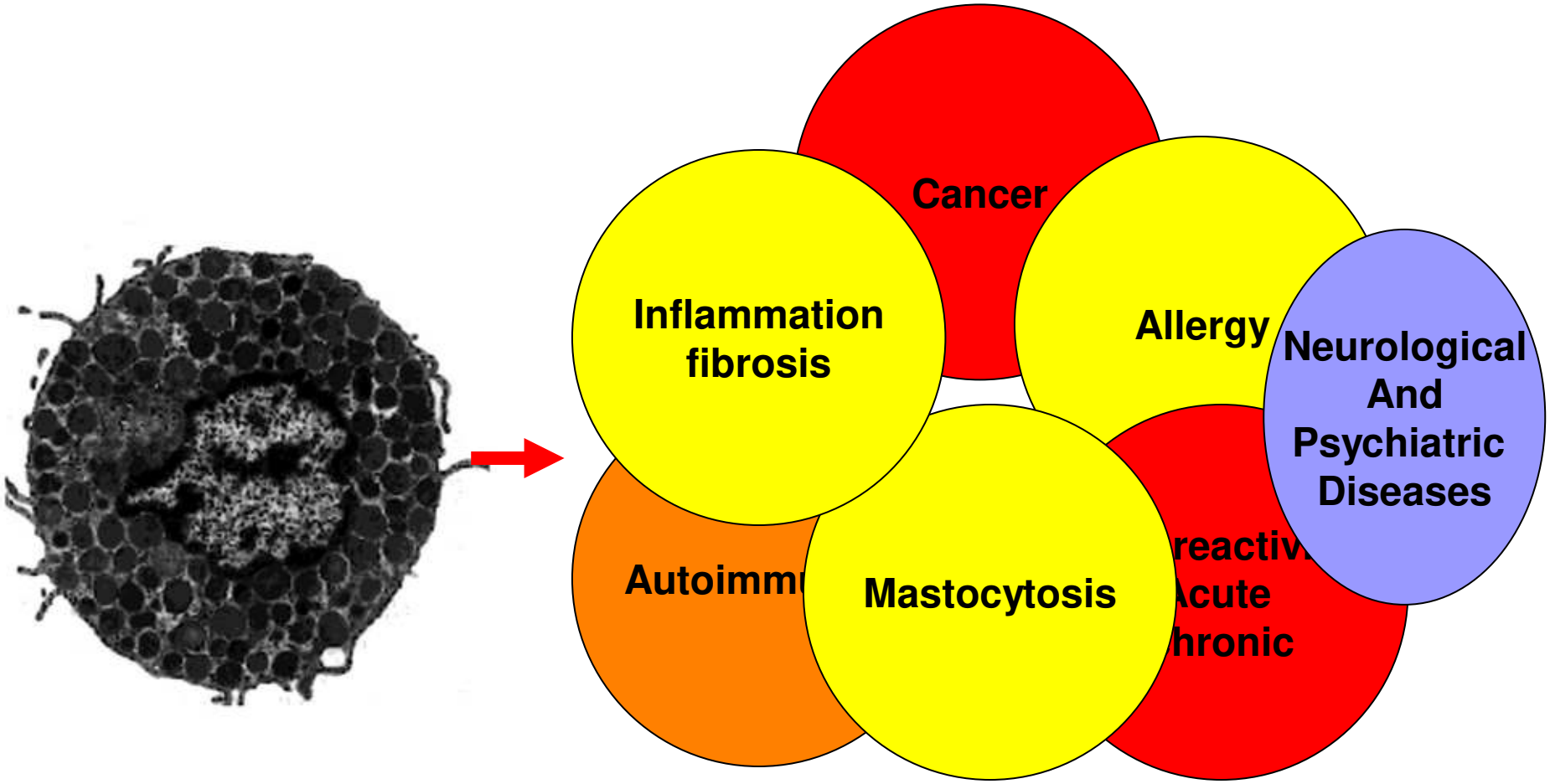
MASITINIB DEMONSTRATED EFFICACY IN IMPROVING HANDICAPS ASSOCIATED WITH MASTOCYTOSIS

Phase 3 AB06006 – efficacy analysis - W8-W24 period

			Masitinib	Placebo	p-value	Odd ratio (CI95)
Primary Analysis	4H75% Cumulative 75% response rate on the handicaps of pruritus or flushes or depression or fatigue	**mITT/MDF**	**18.7%**	**7.4%**	**0.0076***	**3.63**
Secondary Analyses	3H75% Cumulative 75% response rate on the handicaps of pruritus or flushes or depression	mITT/MDF	24.7%	9.8%	0.0071	3.06
	2H75% Cumulative 75% response rate on the handicaps of pruritus or flushes	mITT/MDF	27.2%	10.7%	0.038	2.63
	Pruritus 75% Cumulative 75% response rate on the handicaps of pruritus	mITT/MDF	22.0%	7.3%	0.0322	3.13
Other supportive analyses	Flush 75% Cumulative 75% response rate on the handicaps of flush	mITT/MDF	39.9%	19.0%	NS	3.03
	Depression (Hamilton 75%) Cumulative 75% response rate on the handicaps of depression	mITT/MDF	18.6%	7.6%	NS	2.71
	Fatigue (FIS 75%) Cumulative 75% response rate on the handicaps of fatigue	mITT/MDF	7.7%	3.2%	<5%	4.84

* With 10,000 rerandomization

MAST CELLS AND DISEASES

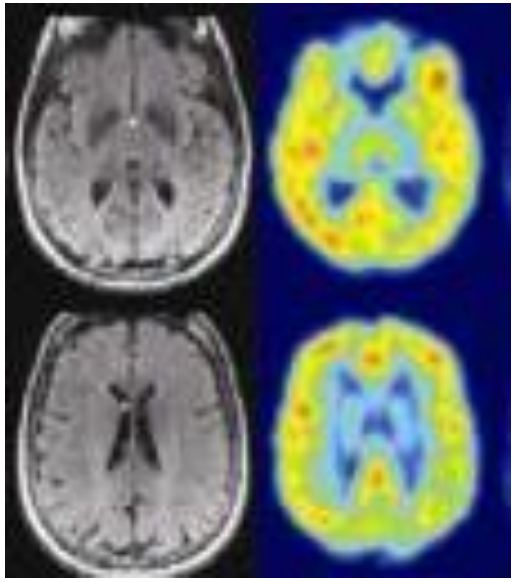


BRAIN BLOOD PERFUSION: SIMILARITY MASTOCYTOSIS AND ALZHEIMER'S DISEASE

Representative images from a control patient (Fig. A&B), an AD patient (Fig. C), and a mastocytosis patient (Fig. D), illustrating the impaired cognitive functions.

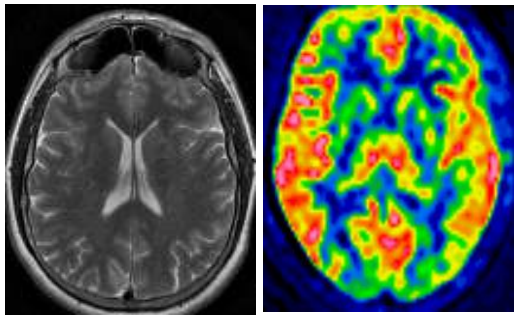
Control

A



Healthy volunteer

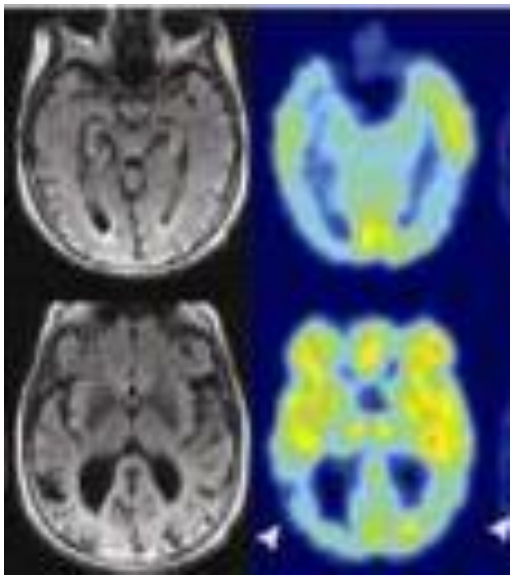
B



Healthy volunteer

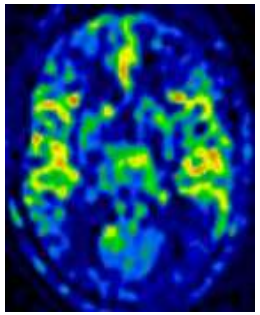
Patients

C



Alzheimer

D



Mastocytosis

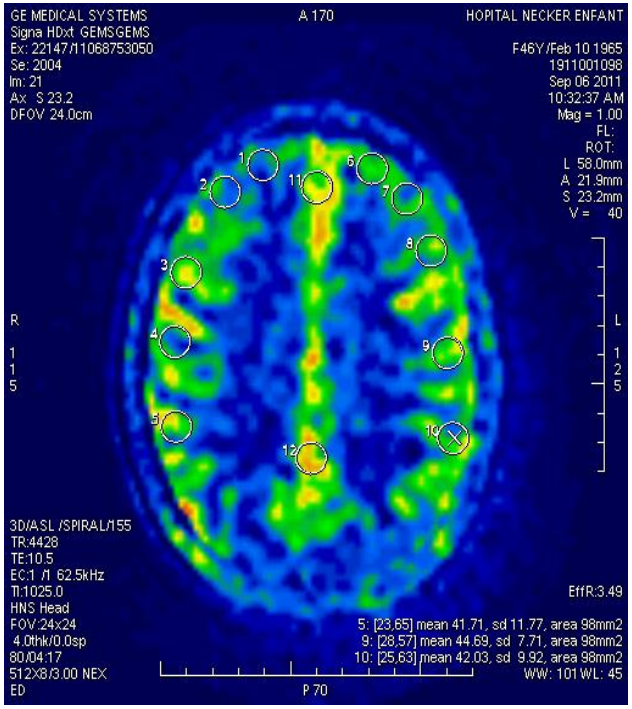
Measurement of cerebral blood flow using arterial spin labeling MRI reveals similar hypoperfusion patterns between mastocytosis patients with impaired cognitive functions (memory and/or attention) and AD patients

[Figs. A&C] Alzheimers Dement. 2012 Jan; 8(1): 51–59. [Figs. B&D] Pr Bodaert Pr O. Hermine. Hôpital Necker-Paris.

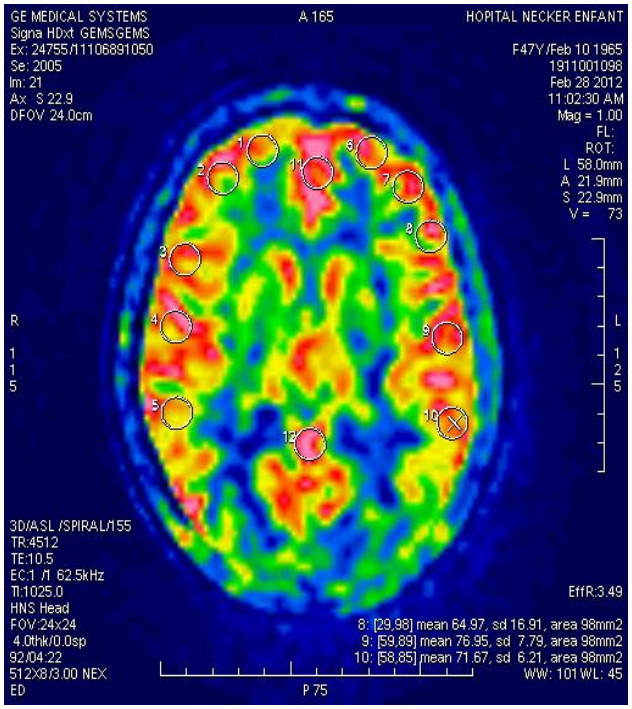
BRAIN BLOOD PERFUSION: SIMILARITY MASTOCYTOSIS AND ALZHEIMER'S DISEASE

Representative images from mastocytosis patient comparing ASL-MRI before masitinib treatment (A) and after 6 month treatment (B)

A

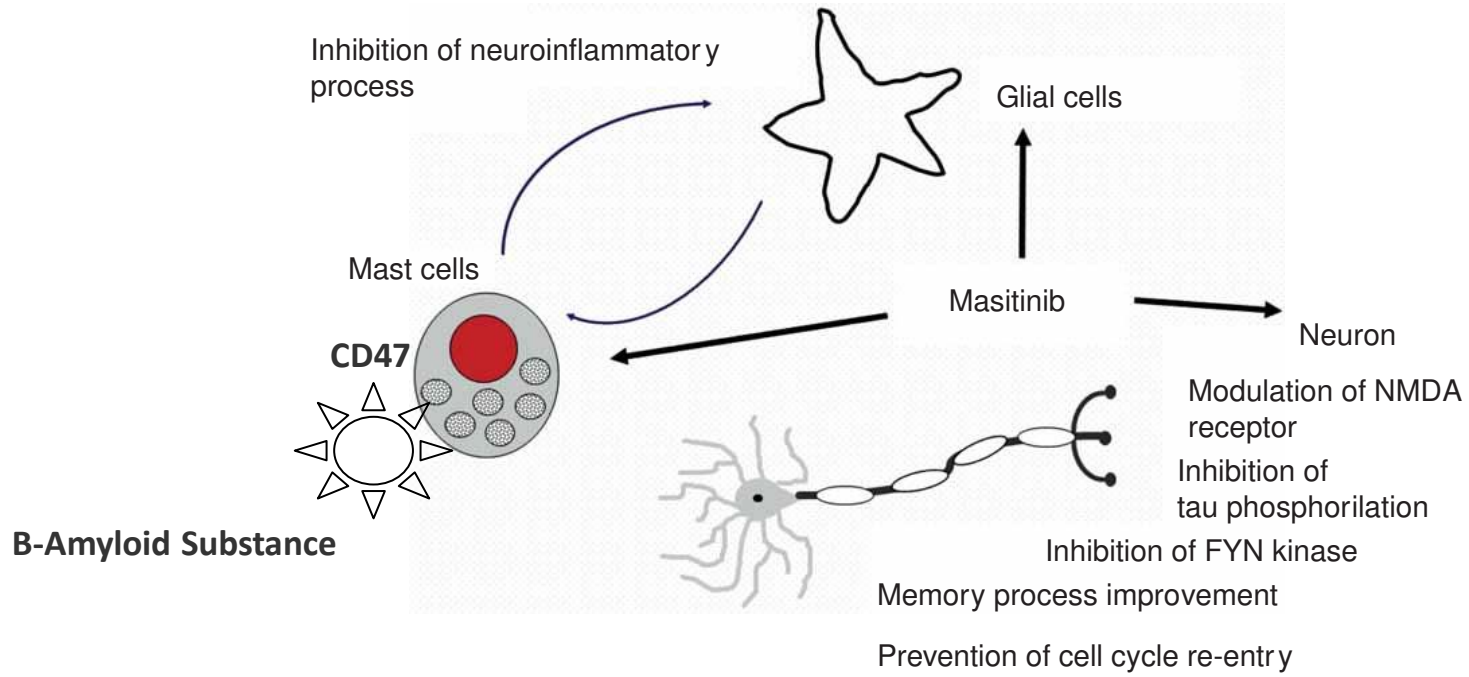


B



Preliminary evidence suggests that masitinib may be able to reverse hypoperfusion in mastocytosis patients, with a concomitant improvement in cognitive functions.

PUTATIVE MECHANISM OF ACTION OF MASITINIB IN ALZHEIMER'S DISEASE



Jaume Folch[1], Dmitry Petrov[2], Miren Ettecho[2], Ignacio Pedrós[1], Sonia Abad[2], Carlos Beas-Zarate[3,4], Alberto Lazarowski[5], Miguel Marin[6], Jordi Olloquequi[7], Carme Auladell[8] and Antoni Camins*[2,6]

EXPERT REVIEWS

Masitinib for the treatment of mild to moderate Alzheimer's disease

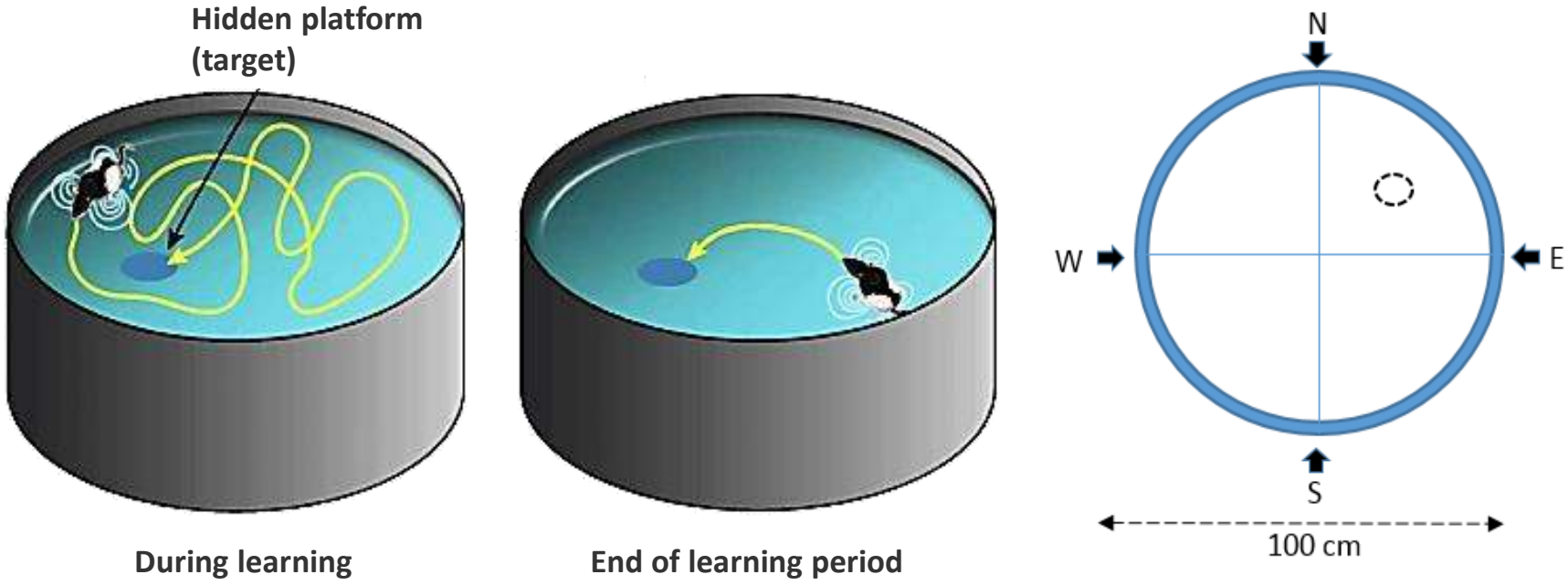
Expert Rev. Neurother. Early online, 1–10 (2015)

ANIMAL MODEL (APPXPS1DE9): COGNITIVE EVALUATION IN A CURATIVE SETTING

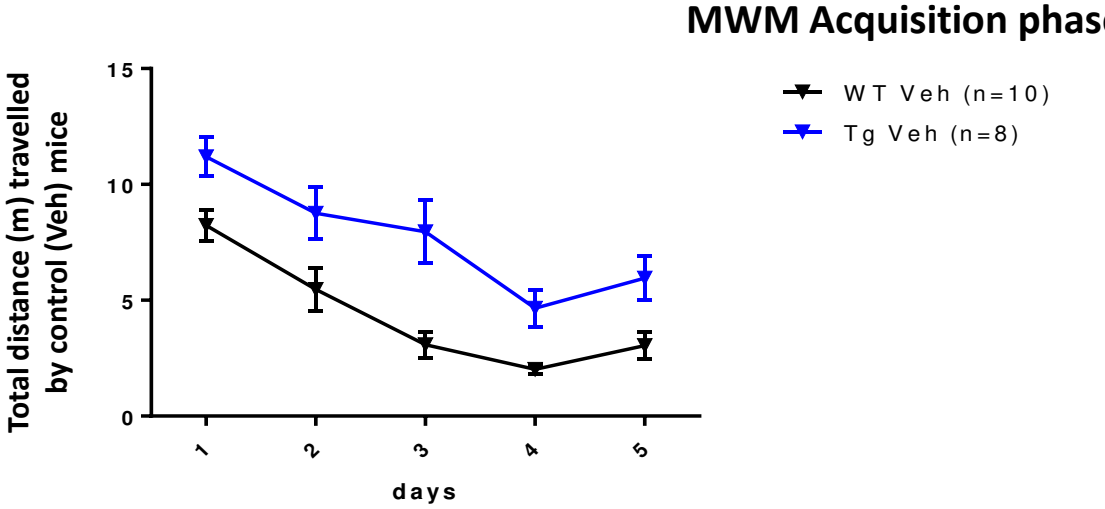
- Masitinib was evaluated for its effect on memory deficit in AD mice (Tg) versus using the Morris Water Maze (MWM) in a curative setting (mice aged 12-14 months)

- The MWM test evaluates hippocampal-dependent learning, including acquisition of spatial memory and long-term spatial memory, which is often affected in AD.

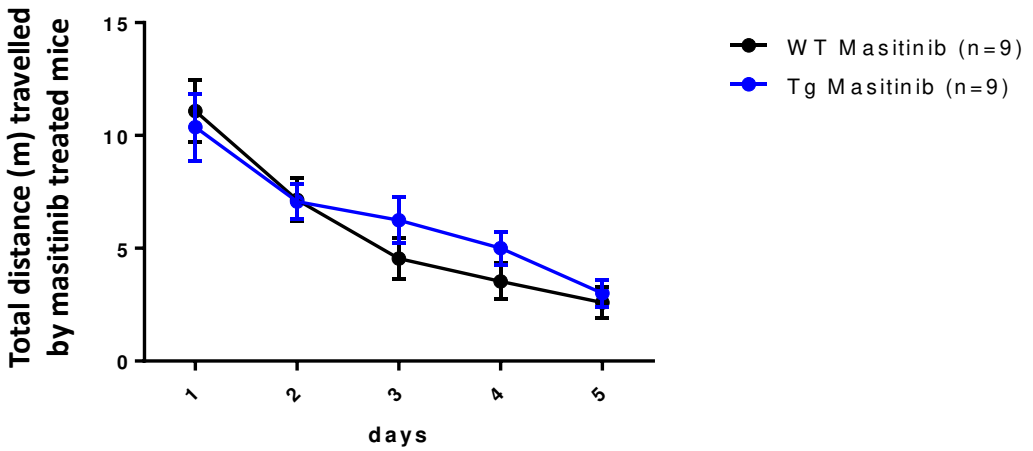
- Blinded study



IN VIVO PROOF OF CONCEPT FOR MASITINIB'S EFFECT ON COGNITIVE FUNCTION IN AD HAS BEEN ESTABLISHED VIA A MOUSE MODEL (APPXPS1DE9) INDICATING IMPROVED SPATIAL MEMORY IN A CURATIVE SETTING



- Genotype effect observed between wild-type (WT) and APPxPS1dE9 (Tg) mice treated with vehicle (Veh)



- Disappearance of genotype effect on mice treated with masitinib
- Masitinib treatment improves cognitive function, with spatial memory returning to normal levels

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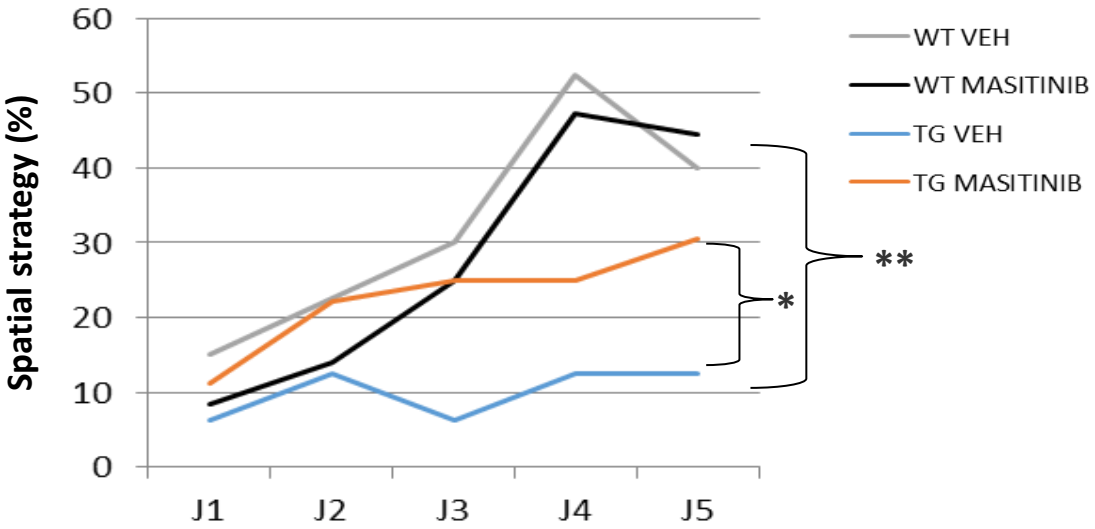
MWM Spatial Strategy



Percentage use of spatial strategy. ** p<0.001. * p<0.05. WT = wild-type mice. Tg = APPxPS1dE9 mice. M = masitinib treatment. Veh = vehicle treatment.

Group	p-value	
Tg Veh vs. Tg M	0.034	Treatment effect
Tg Veh vs. WT Veh	<0.001	Genotype effect
Tg M vs. WT M	0.038	Genotype effect
WT Veh vs. WT M	1	Negative control

- Percentage of spatial response increased through training for all mice except the Tg Veh group.
- Tg mice treated with masitinib showed significant improvement compared with controls (Veh).

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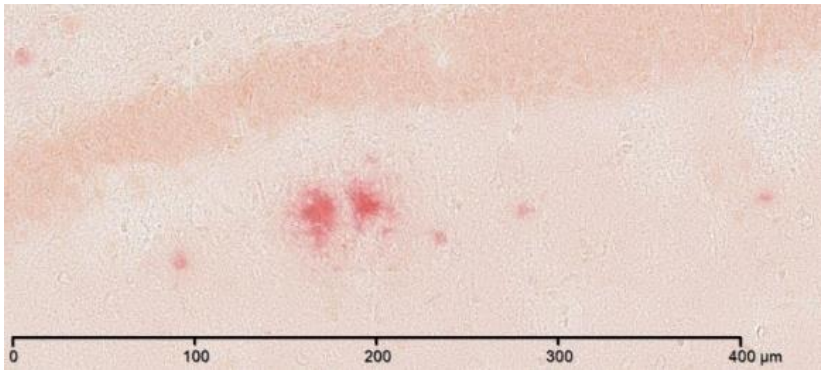
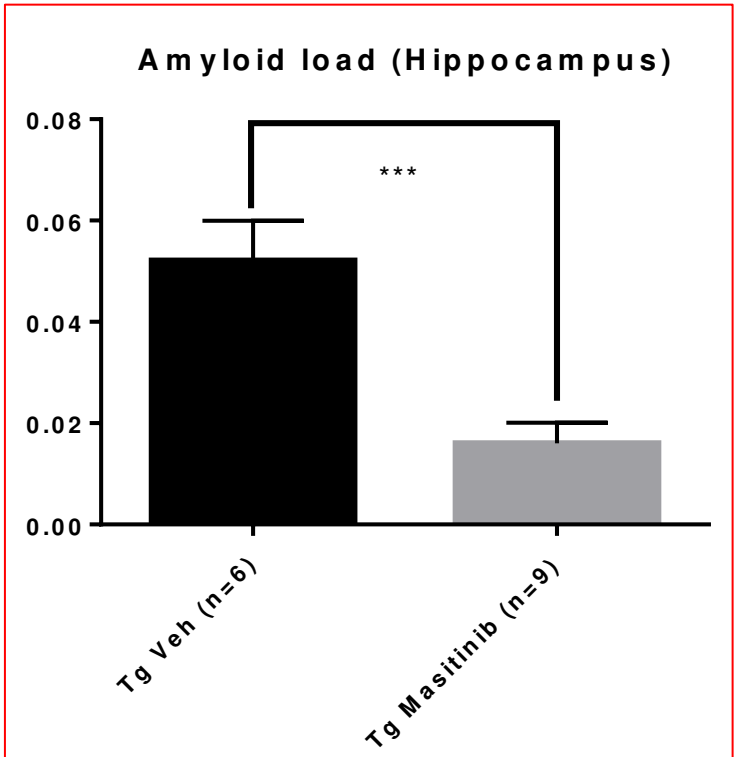
IN VIVO PROOF OF CONCEPT FOR MASITINIB'S EFFECT ON AMYLOID LOAD IN AD HAS BEEN ESTABLISHED VIA A MOUSE MODEL (APPXPS1DE9) INDICATING REDUCED HIPPOCAMPAL AMYLOID LOADS IN A PREVENTIVE SETTING (MICE AGED 4-6 MONTHS)





Masitinib treatment decrease the amyloid charges (Congo red +) in the hippocampus of young APP/PS1dE9 mice

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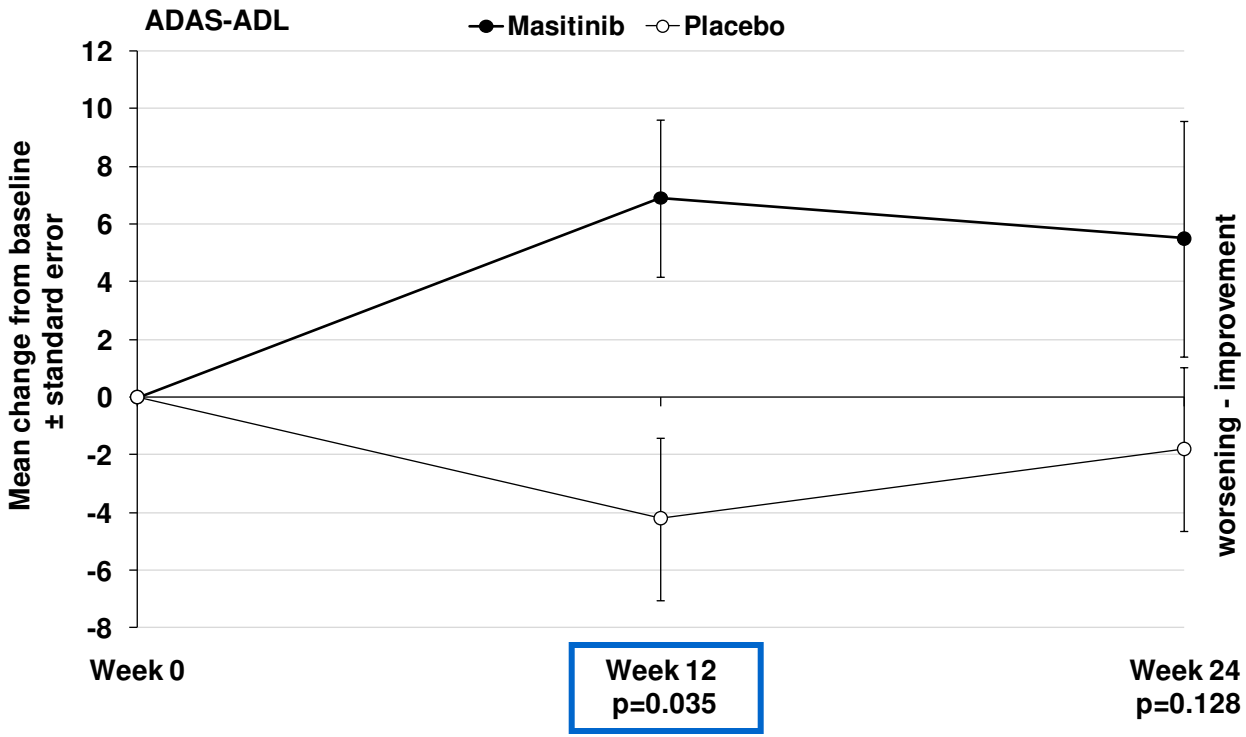
PROOF OF CONCEPT CLINCAL STUDY

Efficacy results in mild-to-moderate Alzheimer's disease
(Phase 2 ; n=34 patients)

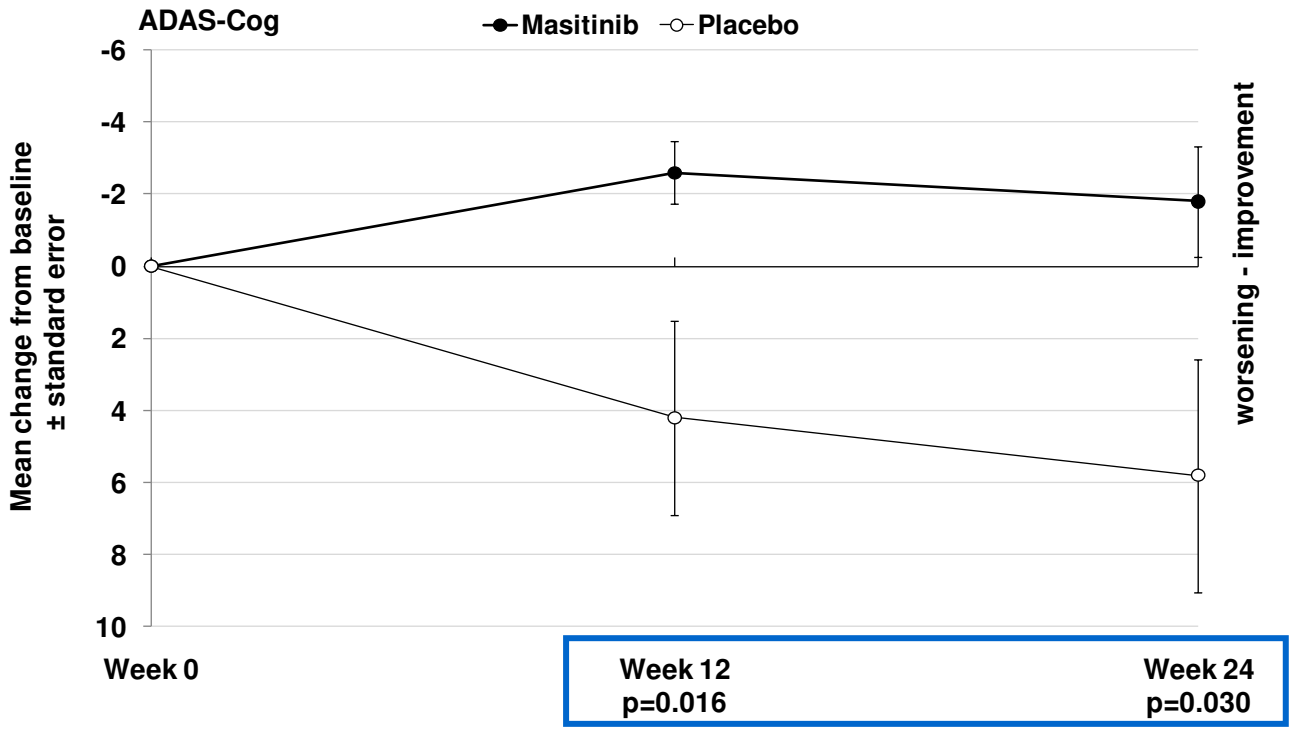


Masitinib generated efficacy in phase 2 on ADCS-ADL.

Alzheimers Res Ther. 2011 Apr 19;3(2):16. doi: 10.1186/alzrt75.

PROOF OF CONCEPT CLINCAL STUDY

***Efficacy results in** mild-to-moderate Alzheimer's disease*
(Phase 2 ; n=34 patients)

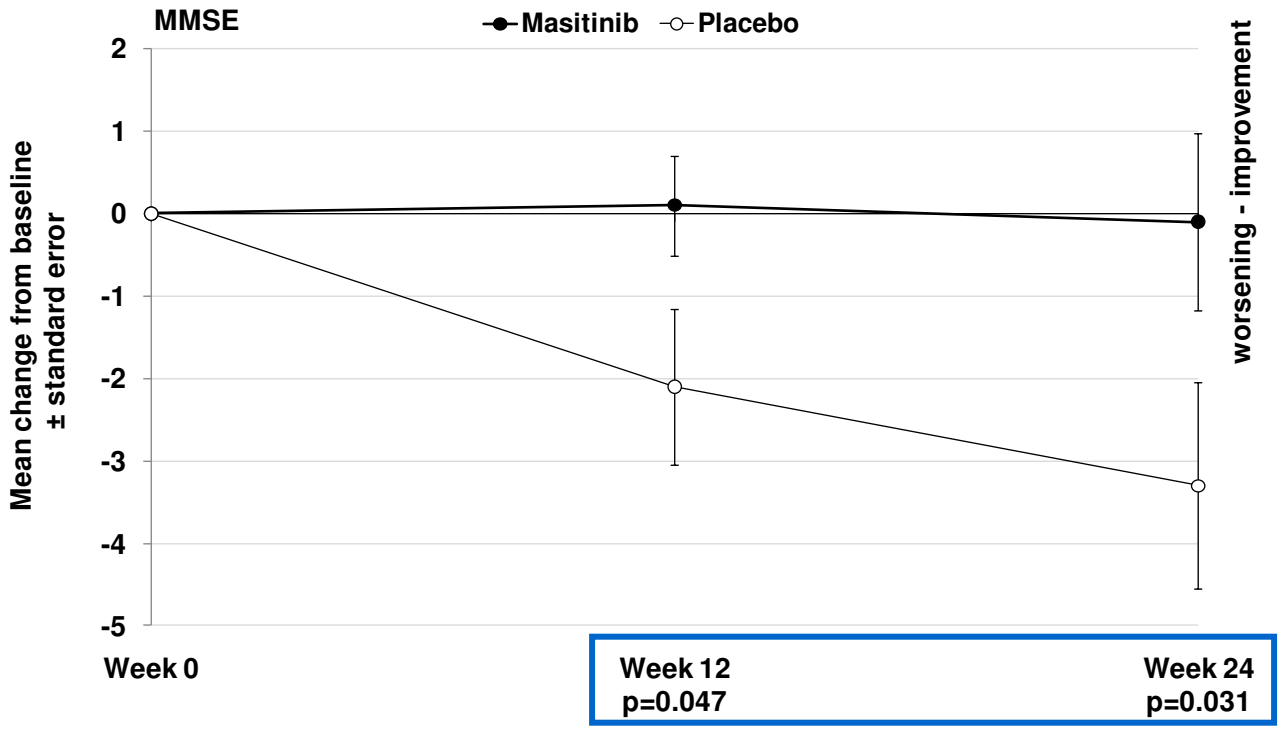


Masitinib generated efficacy in phase 2 on ADAS-Cog.

Alzheimers Res Ther. 2011 Apr 19;3(2):16. doi: 10.1186/alzrt75.

PROOF OF CONCEPT CLINCAL STUDY

Efficacy results in mild-to-moderate Alzheimer's disease
(Phase 2 ; n=34 patients)



Masitinib generated efficacy in phase 2 on MMSE.

Alzheimers Res Ther. 2011 Apr 19;3(2):16. doi: 10.1186/alzrt75.

ON GOING PHASE 3 DESIGN

Study design	▪ Patients with mild to moderate Alzheimer's disease ▪ Blinded, placebo controlled ▪ 24 week treatment period ▪ 675 patients
Selection of patients	Patient with ▪ dementia of Alzheimer's type, according to DSM-IV criteria ▪ probable Alzheimer' disease according to NINCDS-ADRDA criteria ▪ MMSE ≥ 12 and ≤ 25 at baseline ▪ minimum 6 month treatment at baseline with a stable dose of cholinesterase inhibitors and/or a stable dose of memantine
Clinical Endpoints	▪ Effect on ADCS-ADL from Week 8 to Week 24. ▪ Effect on ADAS-Cog from Week 8 to Week 24
Dosing	3 doses ▪ 3 mg/kg/day masitinib ▪ 4.5 mg/kg/day masitinib ▪ 4.5 mg/kg/day with a switch to 6 mg/kg/day masitinib

ON GOING PHASE 3 PASSED FUTILITY TEST

- **Efficacy : DSMB performed a futility analysis with efficacy data**
  - Definition of futility test : test the inability of a clinical trial to achieve its efficacy objective
  - Test performed on ADCS-ADL and ADAS-Cog
  - Test performed after about one third of the patients were enrolled into the study and had reached the 24 week treatment duration period
  - IDMC statement : Study Not Futile
- **Safety : Independent Data and Safety Monitoring Board (DSMB) reviews every 6 months the safety data**
  - On this basis, and before the futility analysis, the IDMC always recommended the continuation of the study

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MASITINIB FOR THE TREATMENT OF ALZHEIMER'S DISEASE: CLINICAL AND PRECLINICAL DATA

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Cognitive dysfunction is a hallmark symptom of Alzheimer's disease (AD). Mastocytosis (MCO), a mast cell (MC) related disease, is also associated with

cognitive impairment. Around 40% of MCO patients (pts) present with impaired cognitive functions (memory and/or attention). We performed morphological and functional MRI in pts with MCO. Arterial spin labeling (ASL) MRI revealed an abnormal pattern of hypoperfusion in the brain when compared with healthy subjects, which correlated also with loss of cognitive functions. This pattern was similar to that observed in AD. In an open study, a few pts with MCO showed an improved blood flow in the brain that correlated with an increase in cognitive abilities following treatment with masitinib. Masitinib is an inhibitor of tyrosine kinases including c-Kit and Lyn, two kinases that may participate in the abnormal accumulation and activation of MCs in MCO. Hence, masitinib may also be efficient in AD. Proof of concept for masitinib in AD has been established via in vivo preclinical studies, with preliminary results from a APPxPS1dE9 mouse model of AD indicating improved spatial memory in a curative setting and reduced hippocampal amyloid loads in a preventive setting. In a phase 2 study, masitinib showed a consistent improvement in primary (ADAS-cog) and secondary (ADCS-ADL,MMSE) endpoints. Although the mechanism of masitinib in AD is expected to be multi-faceted (e.g. through its dual actions as an inhibitor of the MC–glia axis and of Fyn kinase activity in the context of AD pathology) it is hypothesized that one plausible mechanism of action is its ability to maintain or reinforce the integrity of the blood brain barrier (BBB) via inhibition of MC function; reducing the accumulation of blood-borne Aβ peptides in the brain and pool of circulating pro-inflammatory mediators. These ALS-MRI data in MCO pts with cognitive impairment corroborate this hypothesis, demonstrating its pharmacological activity as a modulator of BBB permeability. Clinical development of masitinib in AD will be presented including details of the ongoing phase 3 trial, study futility analyses, additional preclinical data and mechanistic considerations.

Keywords. Alzheimer therapy, Blood brain barrier (BBB), Masitinib, Mast cells, Mastocytosis, Tyrosine kinase inhibitor