LE TROISIEME RECEPTEUR DE L'HISTAMINE : DE L'IDENTIFICATION A L'APPLICTION THERAPEUTIQUE

Jean-Charles SCHWARTZ

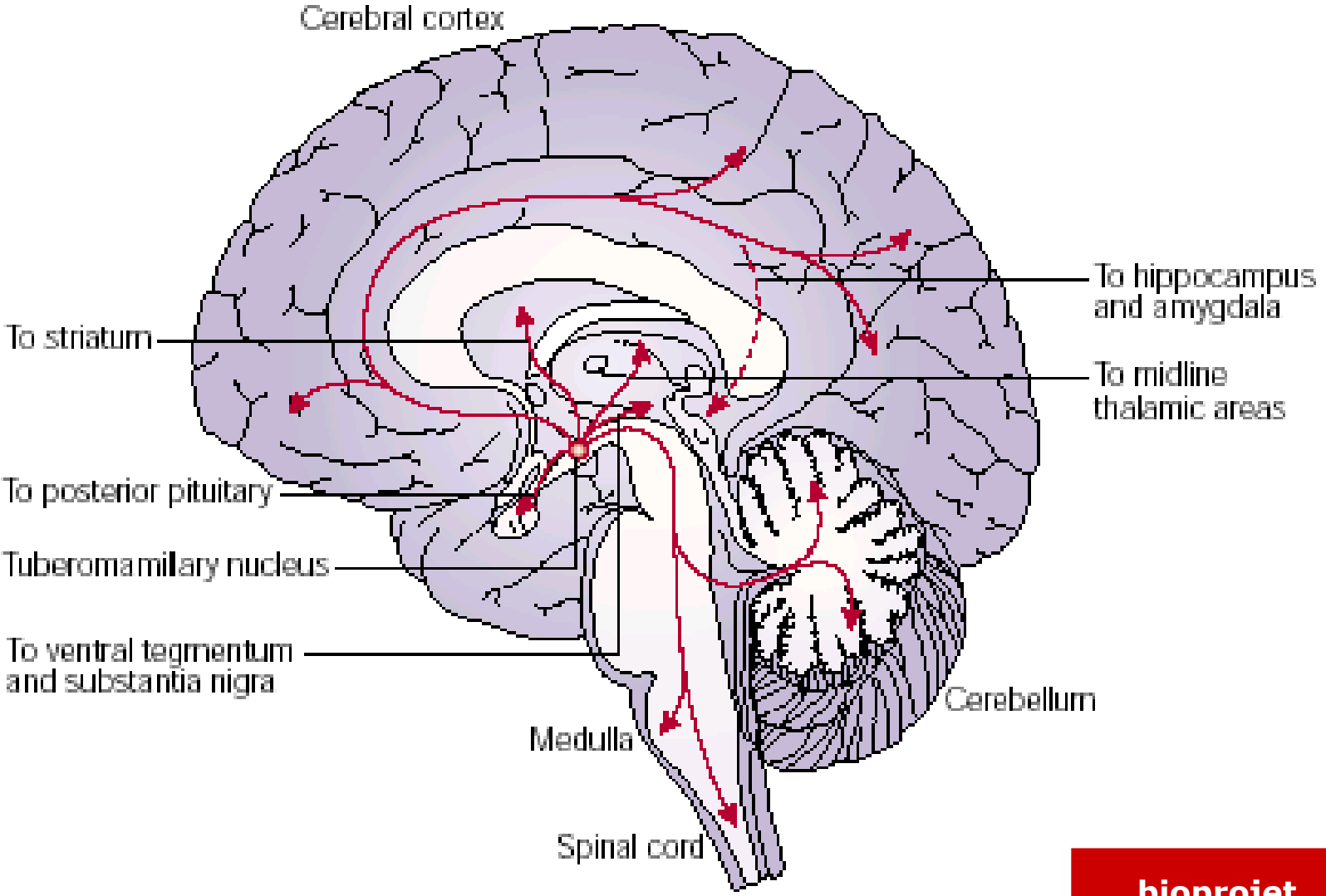
Professeur émerite Université René Descartes et IUF
Membre de l'Académie des Sciences
Co-fondateur et Directeur scientifique de Bioprojet

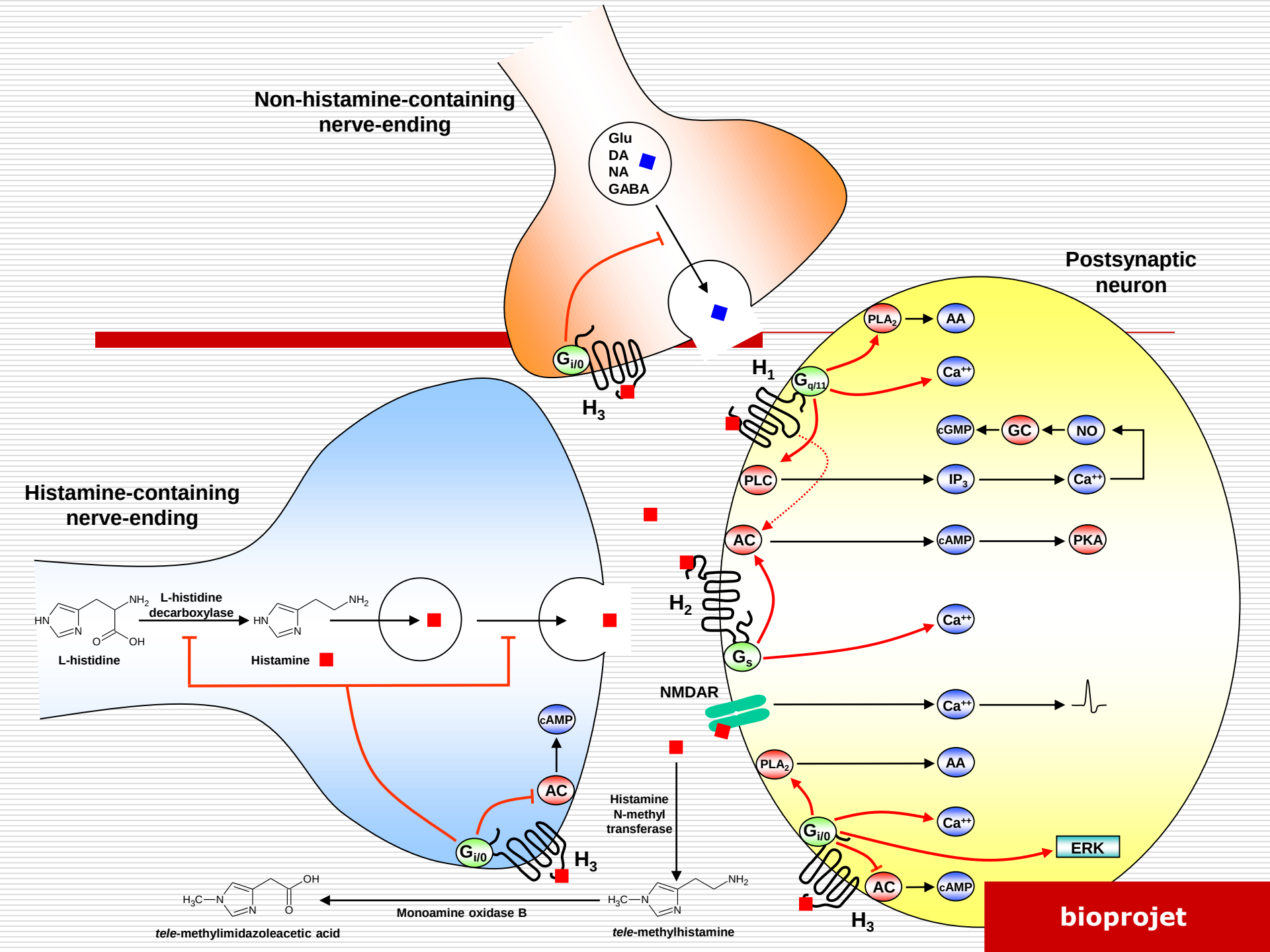
bioprojet

De l'histamine comme neurotransmetteur cérébral à l'identification du récepteur H3

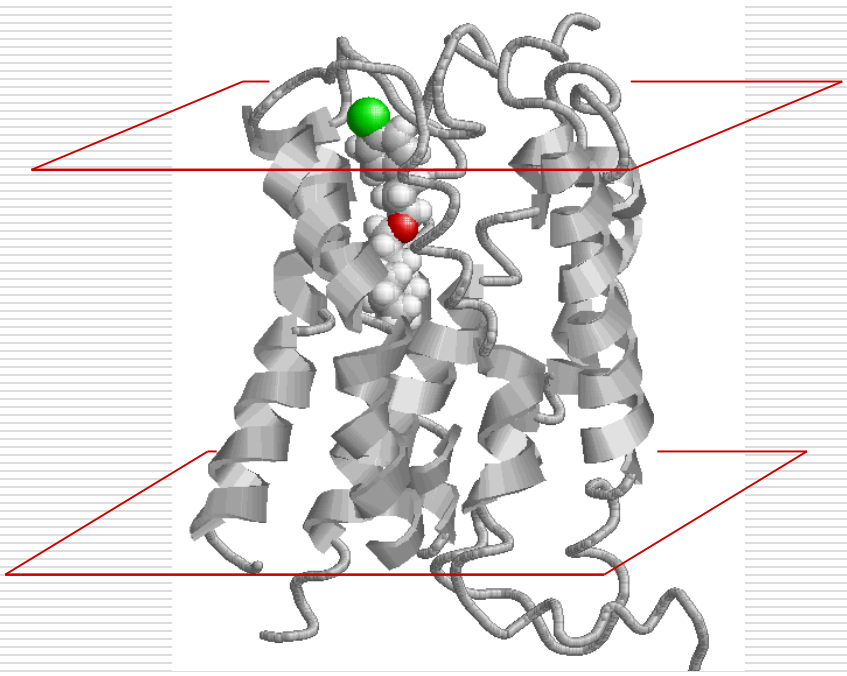
- Garbarg M, Barbin G, Feger J, Schwartz JC. A histaminergic pathway in rat brain evidenced by lesions of the medial forebrain bundle. *Science* 186: 833-35, 1974.
- Baudry M, Martres MP, Schwartz JC. H1- and H2-receptors in the histamine-induced accumulation of cyclic AMP in guineapig cortical slices. *Nature* 25: 362-63, 1975.
- : Schwartz JC. Histamine as a transmitter in brain. Life Sci. 17:503-17,1975.
- Arrang JM, Garbarg M., Schwartz JC. Auto-inhibition of brain histamine release mediated by a novel class (H3) of histamine receptor. *Nature* 302: 832-37, 1983.
- Arrang JM, Garbarg M, Lancelot JC, Lecomte JM, Pollard H, Robba M, Schunack W, Schwartz JC. Highly potent and selective ligands for histamine H3-receptors. *Nature* 327:117-23, 1987
- **High constitutive activity** of native **H3 receptors** regulates **histamine** neurons in brain.Morisset S, Rouleau A, Ligneau X, Gbahou F, Tardivel-Lacombe J, Stark H, Schunack W, Ganellin CR, Schwartz JC, Arrang JM *Nature* 408:860-4, 2000

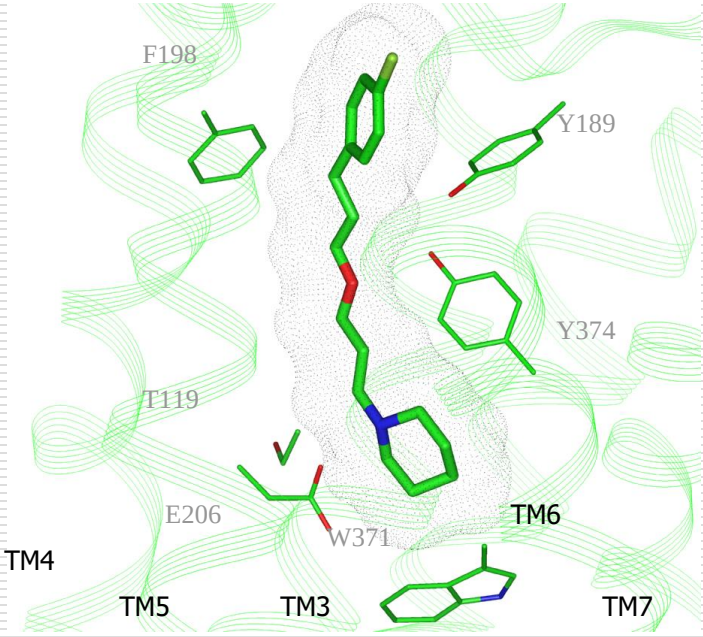
Le système neuronal histaminergique du cerveau




Non-histamine-containing nerve-ending
Glu
DA
NA
GABA
Postsynaptic neuron
Histamine-containing nerve-ending
L-histidine
L-histidine decarboxylase
Histamine
cAMP
AC
Histamine N-methyl transferase
Monoamine oxidase B
tele-methylimidazoleacetic acid
tele-methylhistamine
NMDAR
PLA2
AA
Ca++
cGMP
GC
NO
PLC
IP3
PKA
ERK
H1
H2
H3
Gi/0
Gq/11
Gs
bioprojet

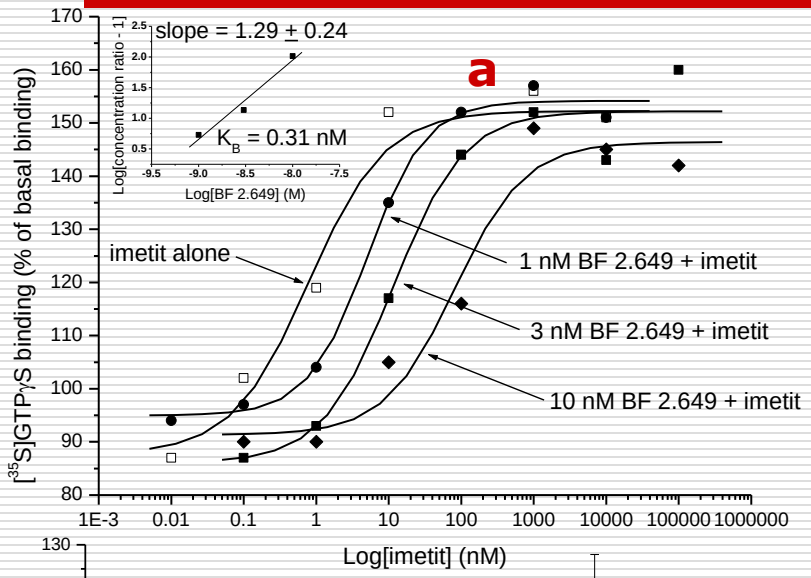
Wakix® (pitolisant, BF2.649) dans un modèle du récepteur H3 de l'histamine

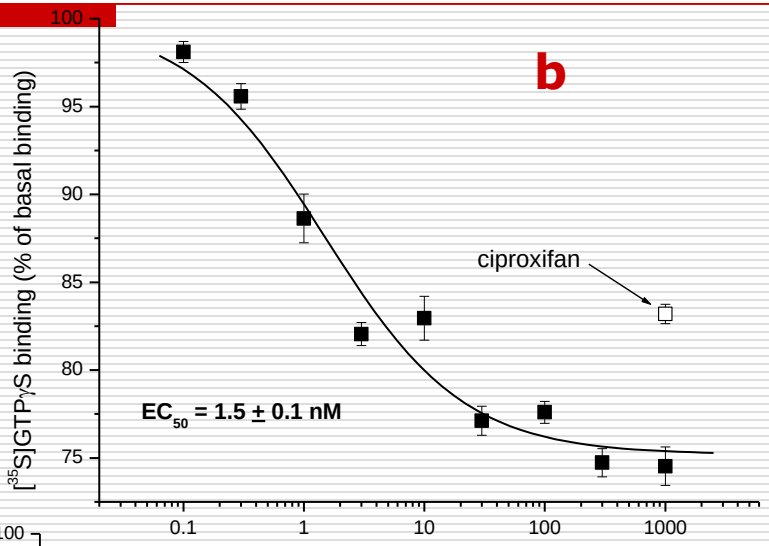


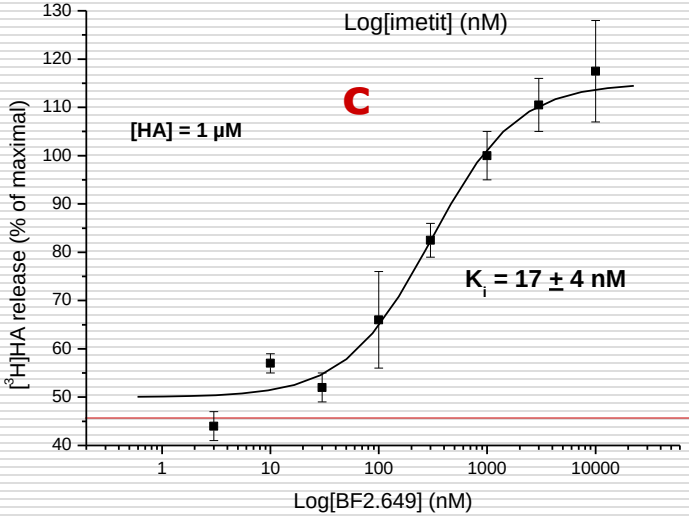


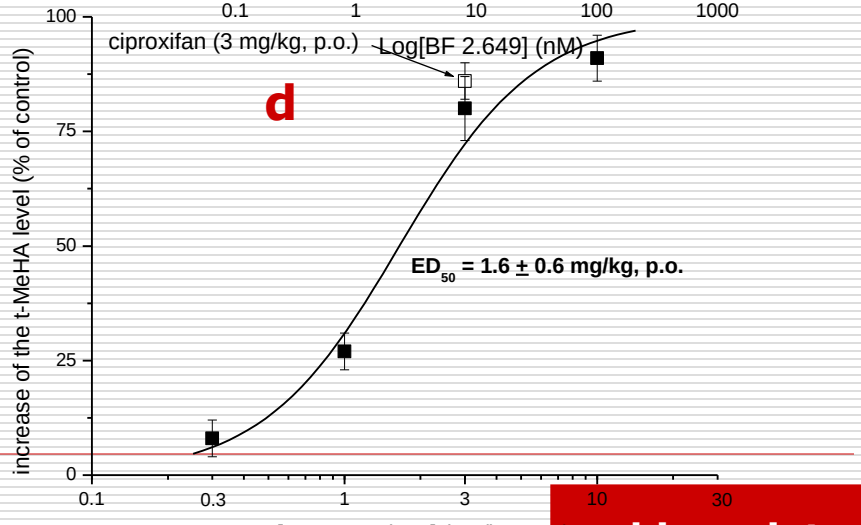
bioprojet

Wakix, un antagoniste competitif(a) et inverse agoniste(b) au hH_3R, augmente la libération d'histamine par synaptosomes(c) et dans le cerveau de souris(d)







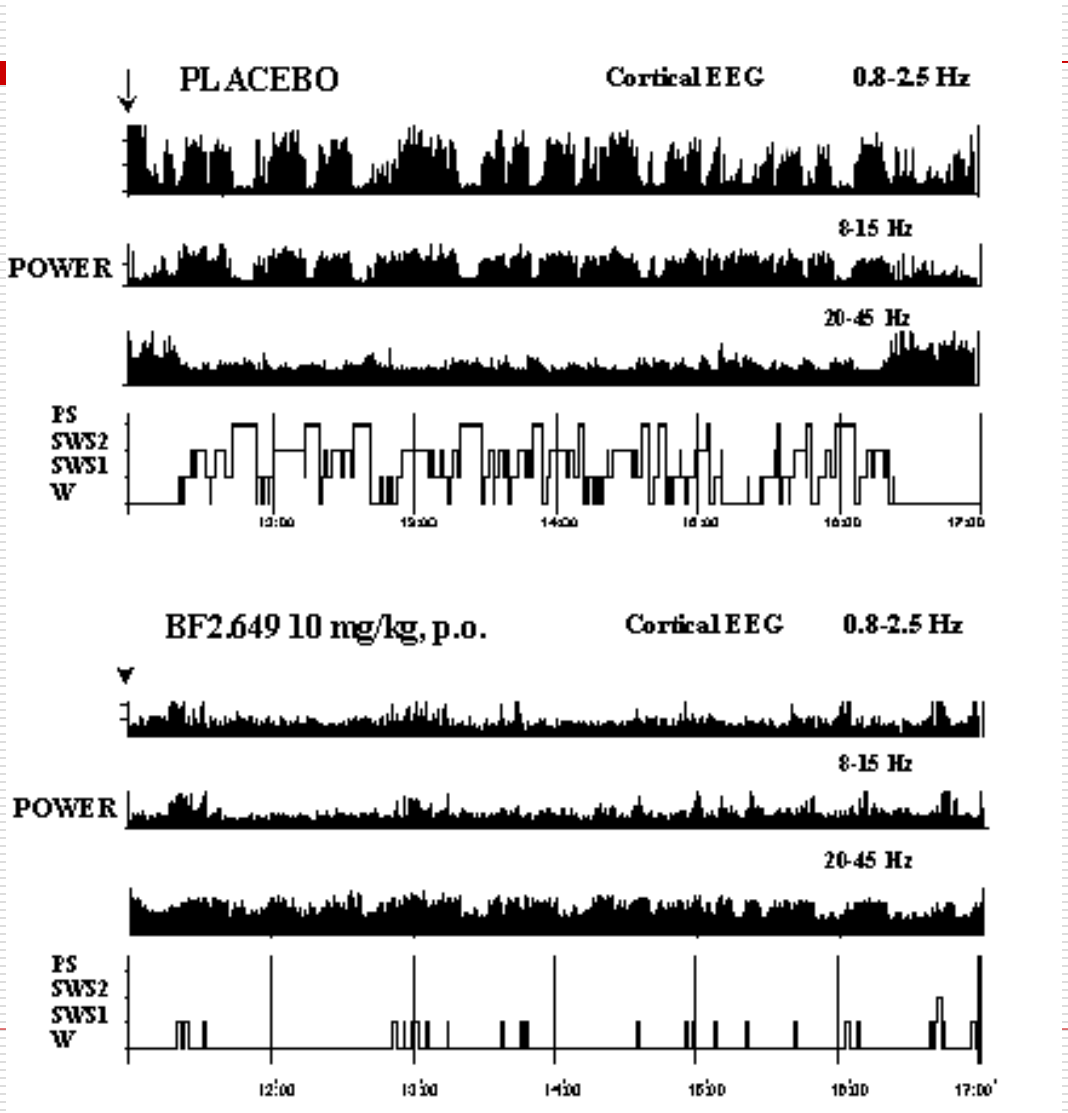


bioprojet

Resumé de la pharmacologie de Wakix®

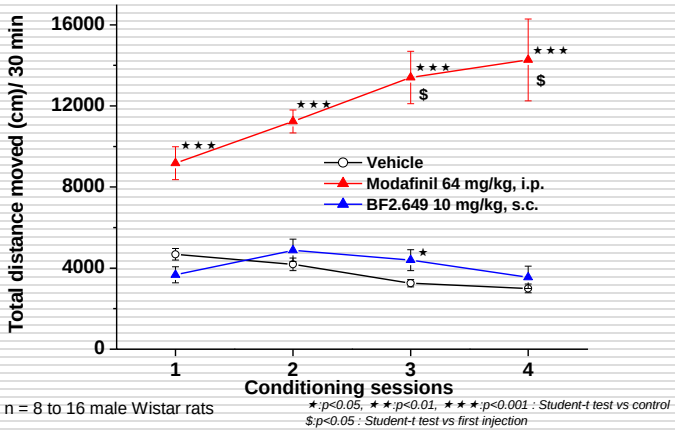
- Il augmente la libération d'histamine, noradrénaline, dopamine, acétylcholine dans le cortex préfrontal
- Il induit un éveil calme sans excitation locomotrice
- Il stimule l'attention et la mémorisation
- Chez la souris narcoleptique (orexine ko) il inhibe SOREMs et cataplexies
- Il n'induit pas de dépendance

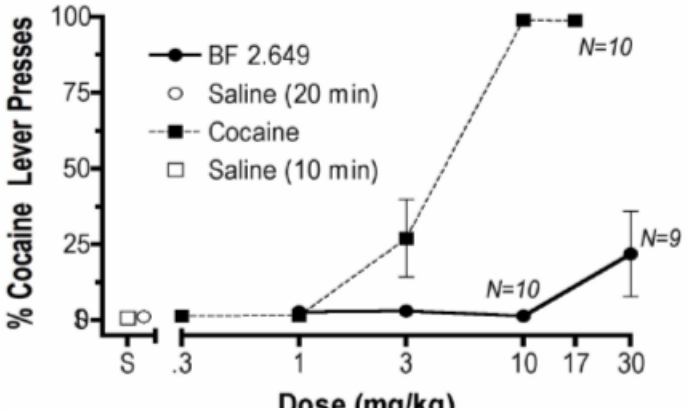
Wakix augmente l'éveil et les fréquences rapides de l'EEG chez le chat

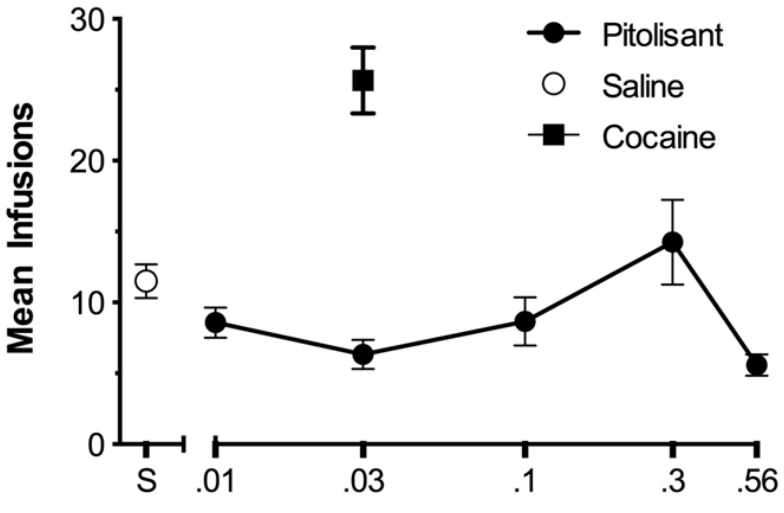


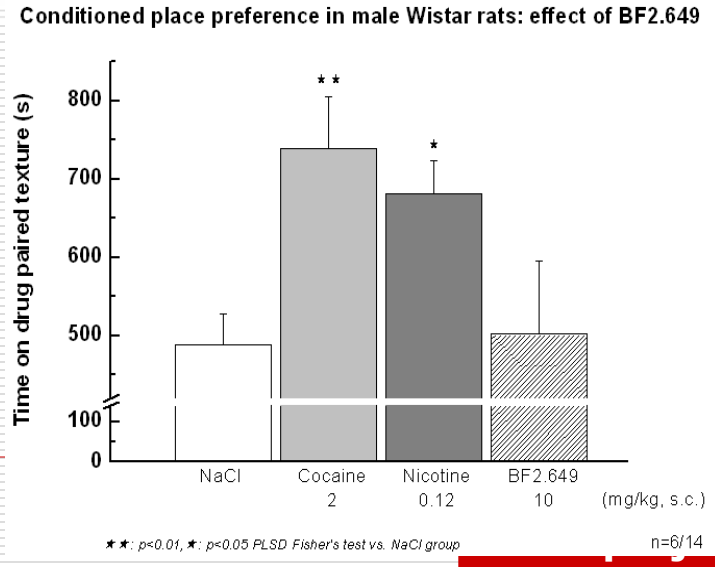
bioprojet

Wakix, contrairement aux psychostimulants amphétaminiques, ne provoque pas de signes précliniques de dépendance







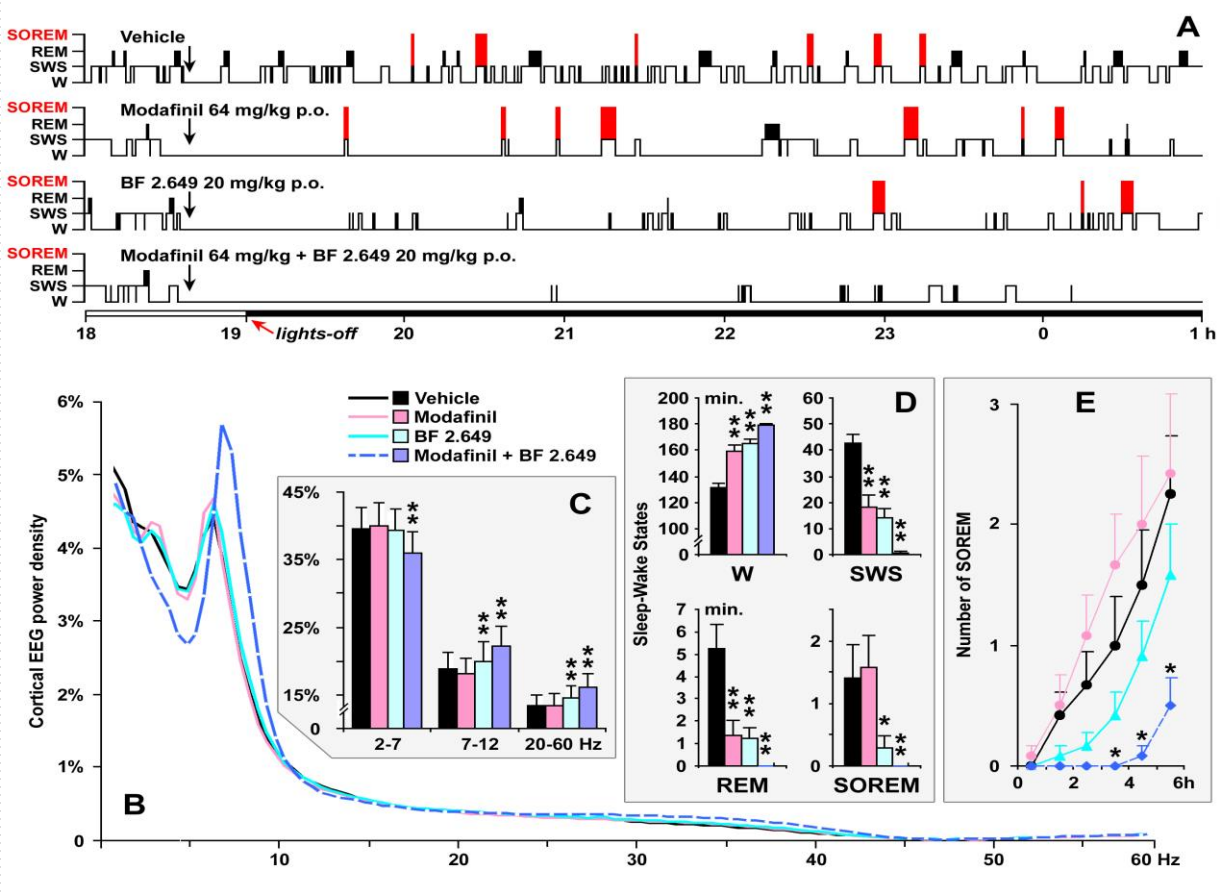


Comment Wakix augmente l'éveil

- Il active directement les neurones corticaux
- Il active les neurones thalamo-corticaux
- Il active les neurones cholinergiques, noradrenergiques et dopaminergiques projettant sur le cortex

≥ toutes actions résultant de la stimulation des H1R

Effets de Wakix et/ou modafinil sur un modèle fidèle de narcolepsie: la souris orexin$^{(-/-)}$



Wakix, like modafinil, enhances wakefulness, but unlike modafinil, suppresses SOREM and cataplexies

bioprojet

Wakix: études de toxicologie

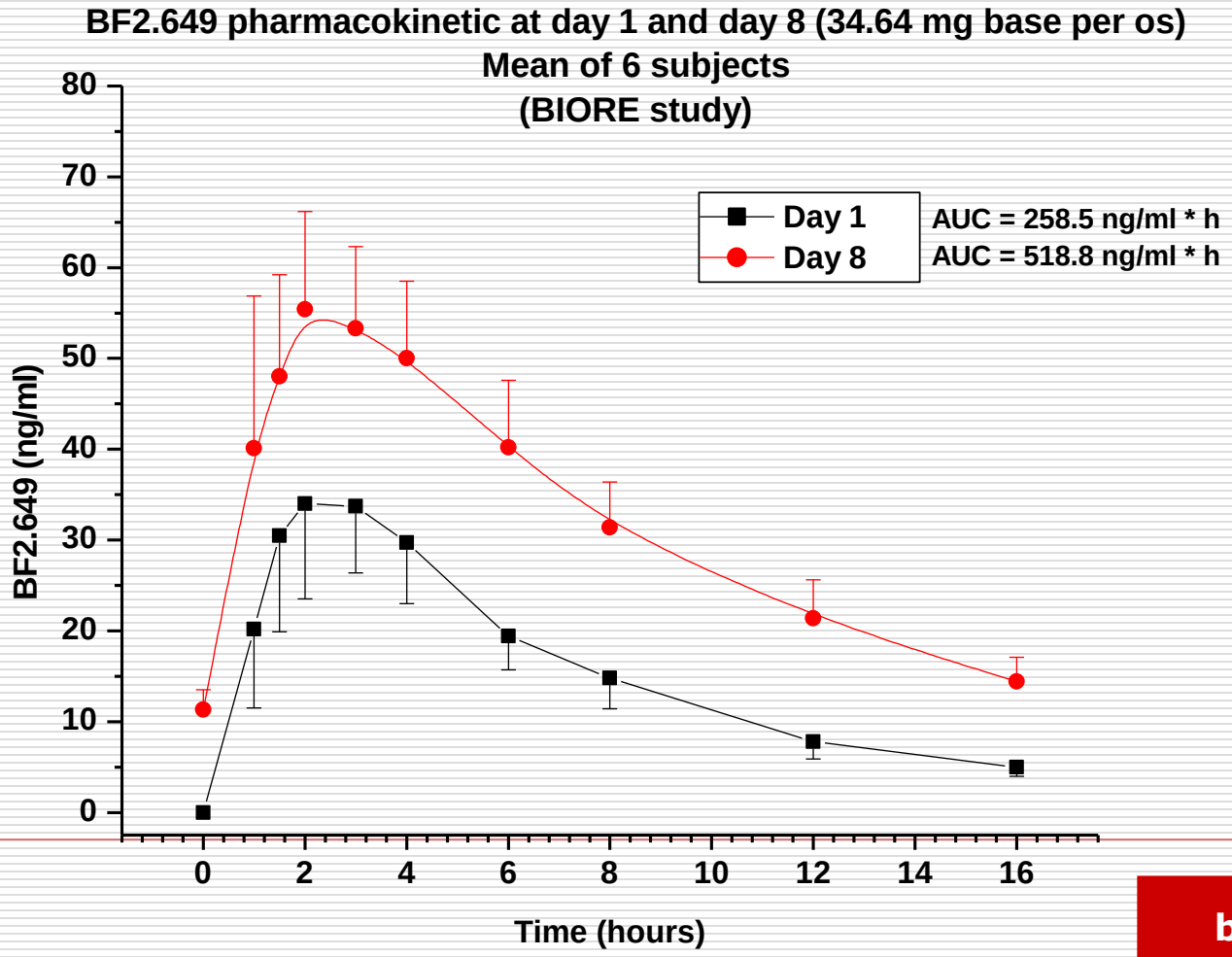
Study Type	Tested Doses (mg/kg)	Species	Nos./Sex	Study No
Single Dose				
Acute p.o.	50, 500	rat	10M/10F	T-264901
Acute p.o.	50, 500	mouse	10M/10F	T-264902
Acute i.v.	10, 12, 15, 20, 30	rat	5M/5F	T-264903
Acute i.v.	5, 10, 15, 20, 30	mouse	5M/5F	T-264904
MTD* p.o.	5, 35, 150, 250	rat	10M/10F	T-264906
MTD p.o.	30, 100, 300	mouse	3M	1009464
MTD i.p.	10, 30, 100	mouse	3M	1009464
Repeat Dose, oral				
7 day DRF**	15, 30, 60	dog	1M	CD01/7766T
7 day DRF	15, 30, 60, 80	monkey	1M	CD01/7766T
28 day DRF	40	monkey	1M/2F	CD01/7766T
13-weeks***	5, 30, 150 (100-75)	rat	10M/10F	T-264907
and 3-weeks off-dose	100-75	rat	10M/10F	T-264907
6 months^{+}	5, 30, 60-75	Rat	20M/20F	DHHL1006
And 4 weeks off-dose	60	rat		DHHL1006
13-weeks***	5, 12, 30	monkey	4M/4F	CD01/7989T
and 4-weeks off-dose	30	monkey	2M/2F	CD01/7989T
9 months^{+}	5, 12, 30	monkey	4M/4F	DHHL1005
4-weeks off-dose	30	monkey	2M/2F	DHHL1005
Genotoxicity				
Ames Test (± S9)	78.13 to 2500 µg/plate	Sal. Typh.		CD01/7754T
	39.06 to 1250 µg/plate	E. coli		
Mouse Lymphoma	2.5 to 55 µg/mL (-S9)	L5178Y		RCC-702800
	2.5 to 40 µg/mL (+S9)	L5178Y		
In vivo Micronucleus	150, p.o.	OF-1 mice	5M/5F	T-264905
Reproduction toxicity				
Fertility (segment I)	30, 52, 90	rat	24M/24F	RR04014401
embryotoxicity (segment II)$^{+}$	30, 75, 100, 140, 180	rat	6 to 10F	CD049189T
Embryotoxicity (segment II)$^{+}$	30, 67, 150	rabbit	21 to 23F	CD049172T
Pre- post-natal toxicity (segment III)	30, 52, 90	rat	21 to 23F	CD049189T

MTD** = maximum tolerated dose. ****DRF** = dose range finding. ** Toxicokinetics we performed concurrently with tested animals. + : Study on going

CNS: Central Nervous System; NR: not requested at this stage

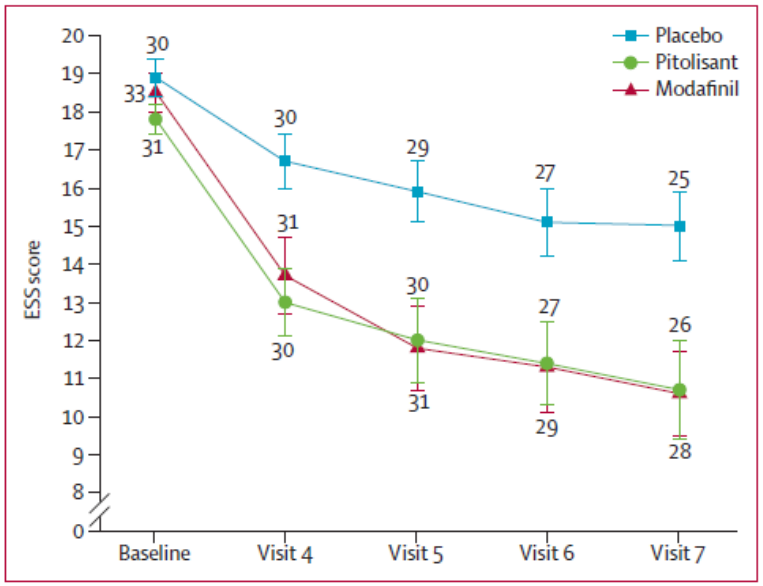
bioprojet

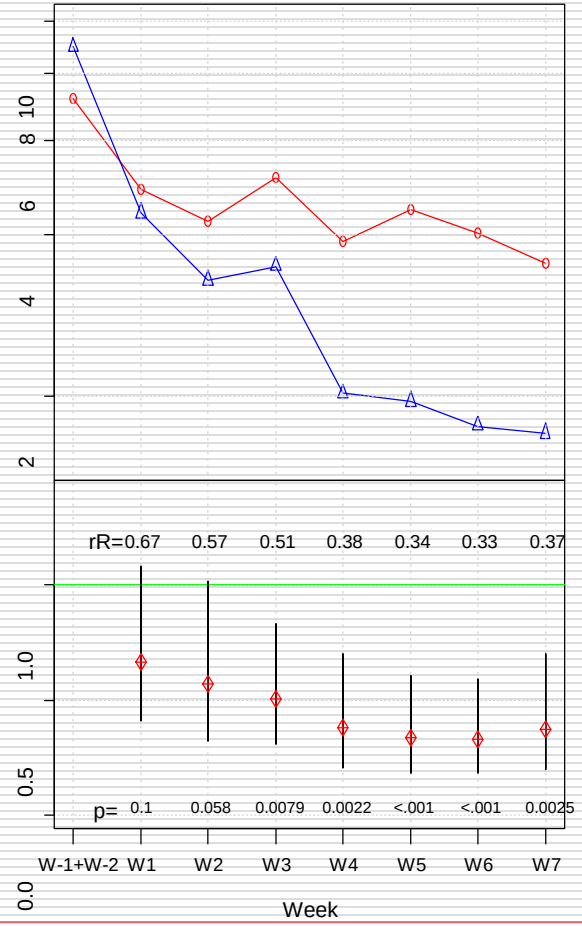
Phase I de Wakix: dose unique vs dose repétée



bioprojet

Deux études pivotales de Wakix dans la narcolepsie: scores d'Epworth et de cataplexie





bioprojet

Indications potentielles des agonistes inverses du H3R

Indications explorées

- Apnée du sommeil
- Maladie de Parkinson
- Démences
- Schizophrénie
- ADHD

Indications restant à explorer

- Dépression
- Alcoolo-dépendance
- Autisme

Principales collaborations

- *Inserm Paris*: M.Garbarg, JM.Arrang
- *Univ Berlin*: W.Schunack, H.Stark
- *UCL Londres*: CR.Ganellin
- *Bioprojet biotech Rennes*: M.Capet, X.Ligneau, I.Bertrand, P.Robert
- *Bioprojet Paris*: JM.Lecomte, JS.Julien, C.Li, E.de Paillette
- *Inserm Lyon*: JS.Lin