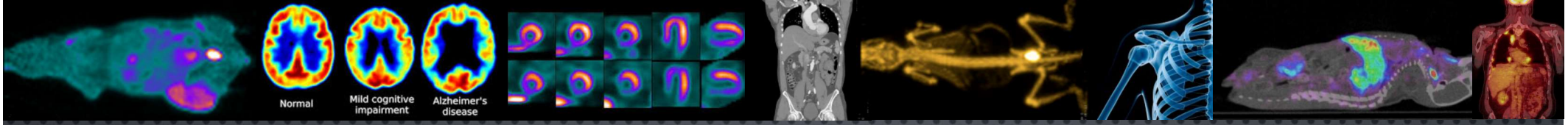
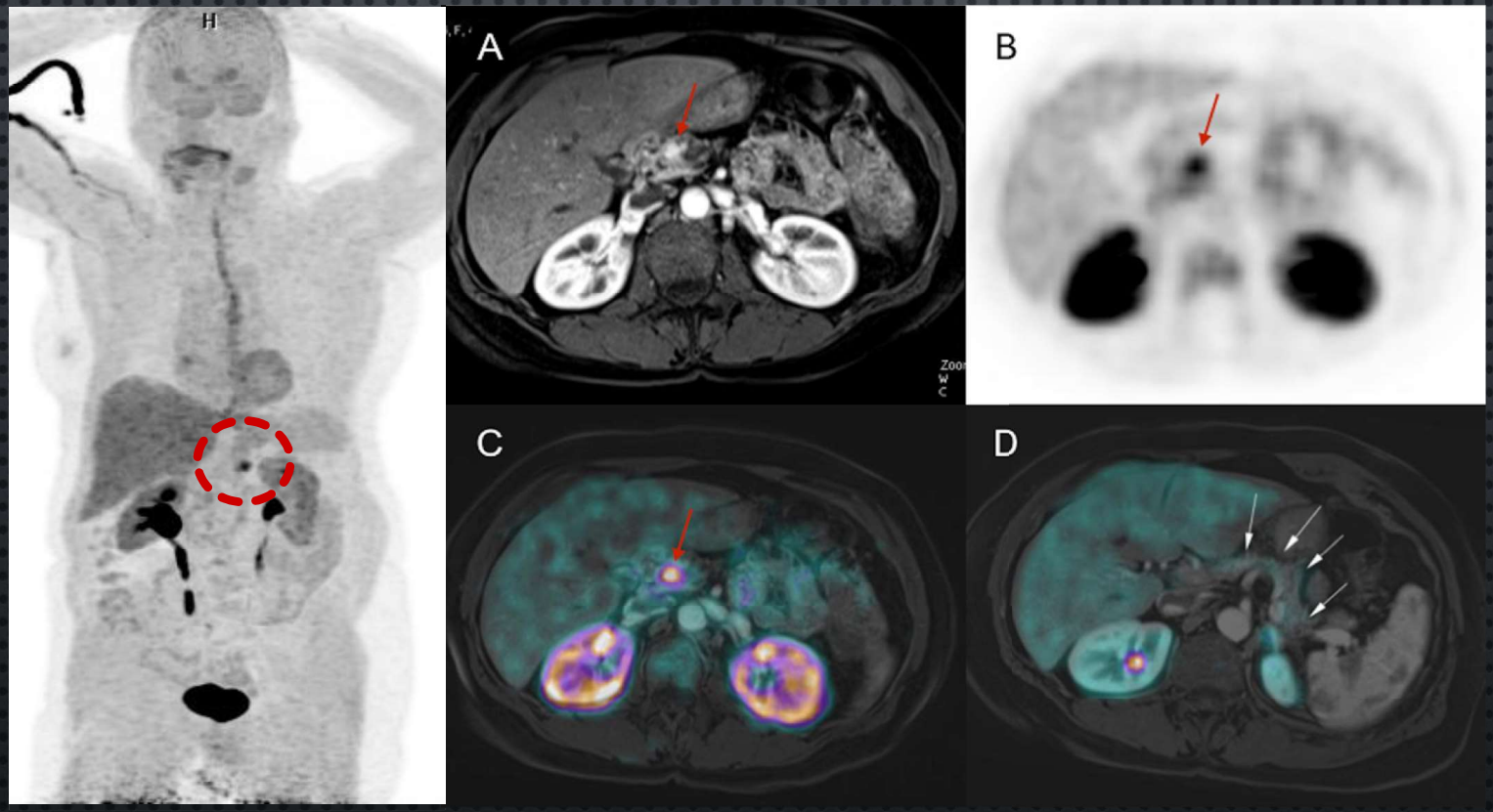
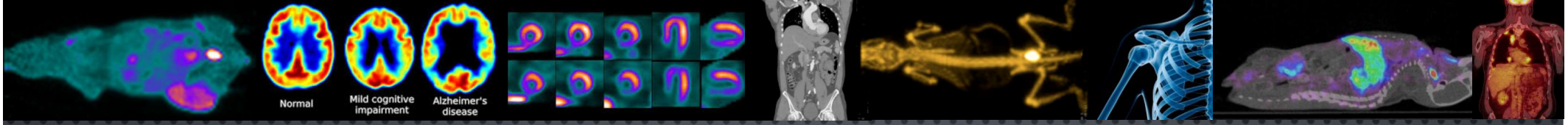



# Towards an early diagnostic of insulinoma

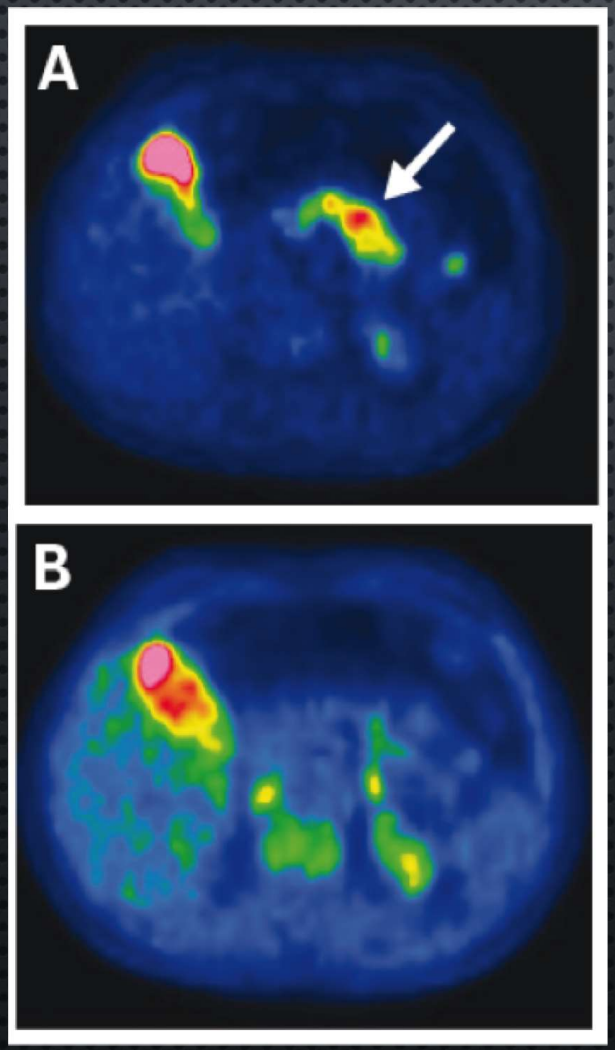
PET/CTM using Carbidopa + $^{18}$F-FDOPA




Sporadic Insulinoma, 8mm, Ki67: 1% (G1)
Imperiale et al. EJNMMI 2015




# Towards an early diagnostic of insulinoma



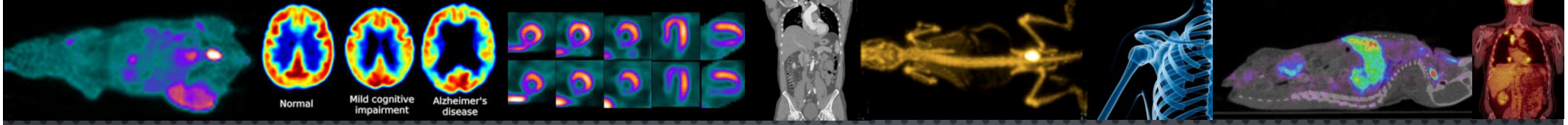

## PROBLEMATIC & OBJECTIVE

Premedication With Carbidopa Masks Positive Finding of Insulinoma and β-Cell Hyperplasia in [$^{18}$F]-Dihydroxy-Phenyl-Alanine Positron Emission Tomography

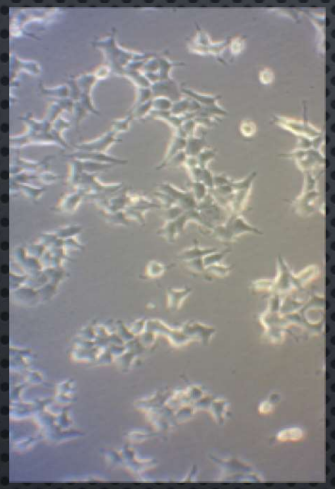
*Saila Kauhanen, Marko Seppänen, and Pirjo Nuutila*
Turku Positron Emission Tomography Centre, Turku University Hospital, Turku, Finland

J Clin Oncol. 2008 Nov 10;26(32):5307-8;

TO EVALUATE IN VITRO AND IN VIVO THE EFFECT OF CARBIDOPA ON THE UPTAKE OF 18F-DOPA

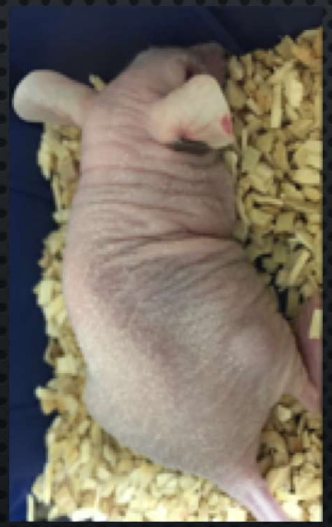



# Towards an early diagnostic of insulinoma



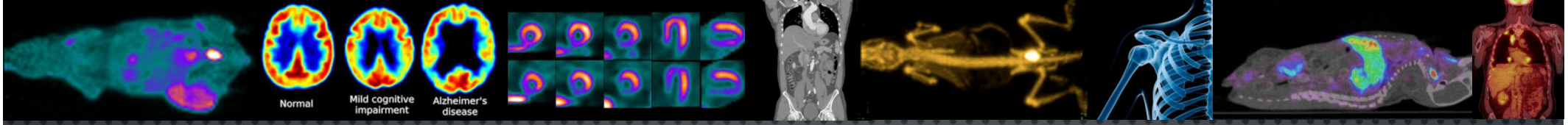
*in vitro*

- ✓ beta cells RIN-m5F
- ✓ insuline secretion +++
- ✓ AA Decarboxylation +++



*in vivo*

- ✓ Xenograft developed on athymic nude mice after subcutaneous injection of RIN-m5F cells




# Towards an early diagnostic of insulinoma

**Effect of Carbidopa on $^{18}$F-FDOPA Uptake in Insulinoma: From Cell Culture to Small-Animal PET Imaging**

Julien Detour[1,2], Alice Pierre[1,2], Fréderic Boisson[3], Guillaume Kreutter[4,5], Thomas Lavaux[6], Izzie Jacques Namer[2,5,7], Laurence Kessler[4,5,8], David Brasse[3], Patrice Marchand[3], and Alessio Imperiale[2,3,5,7]

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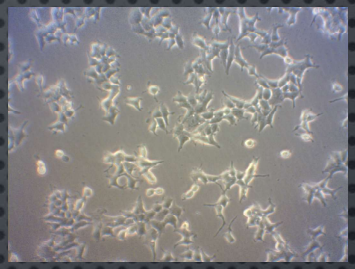
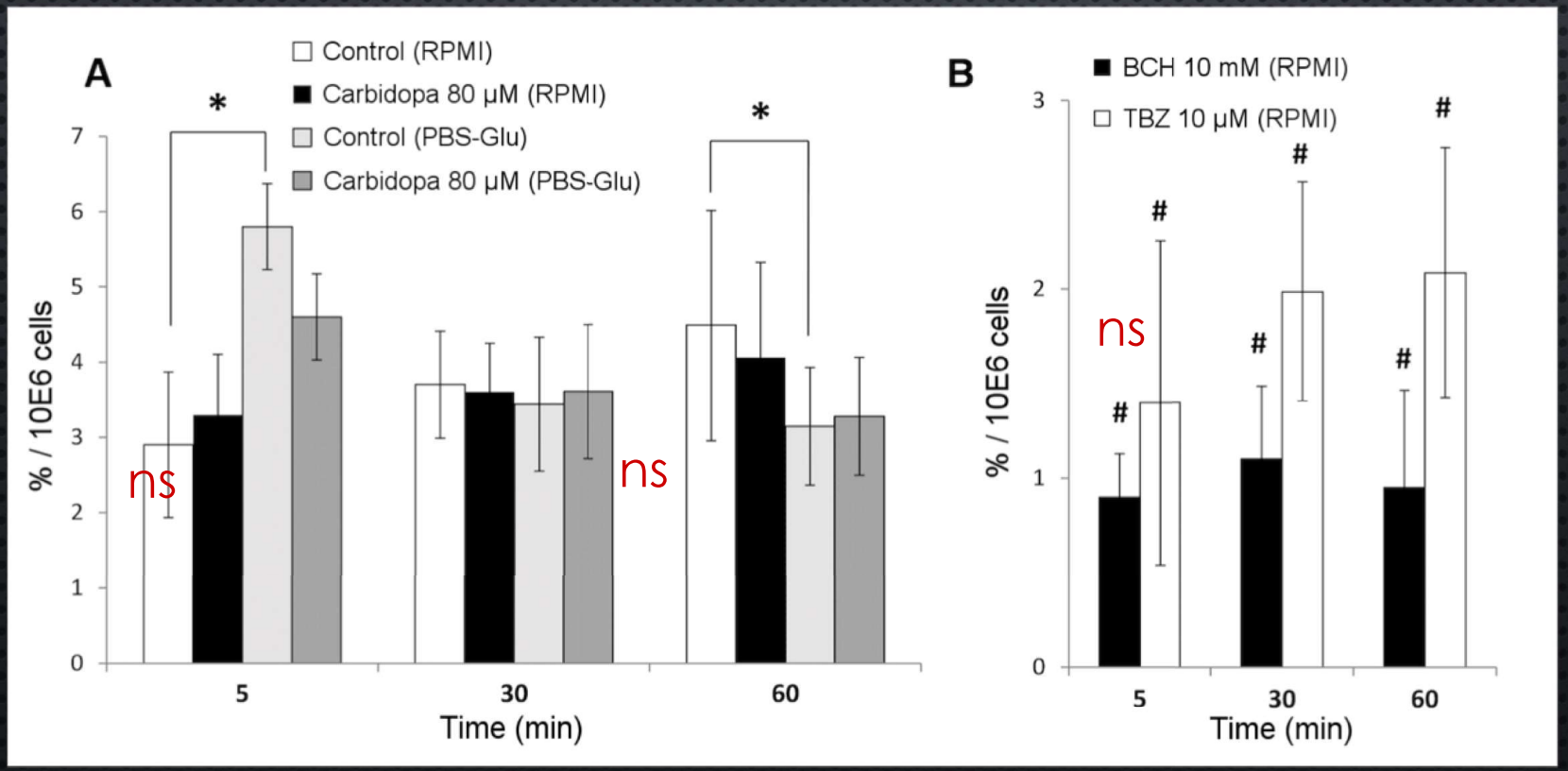
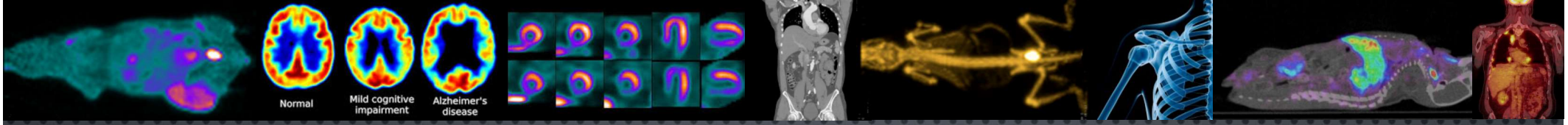
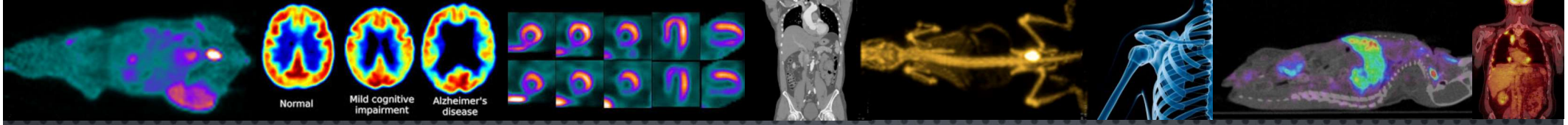







# Towards an early diagnostic of insulinoma

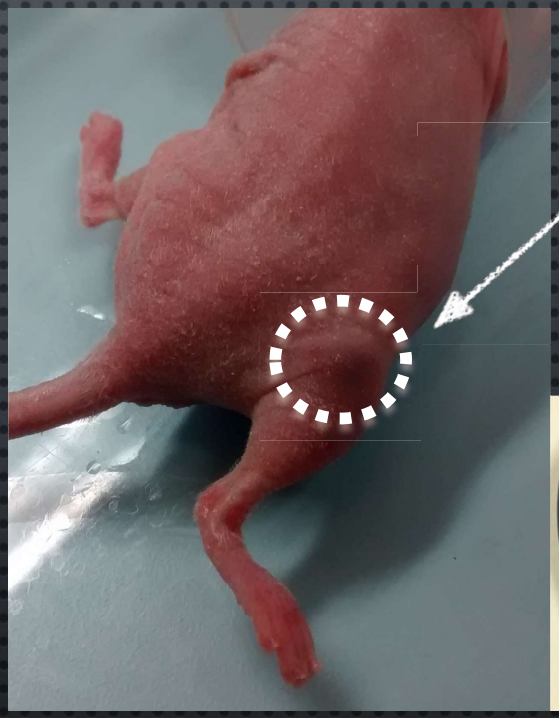
Basal capillary blood glucose




# Towards an early diagnostic of insulinoma

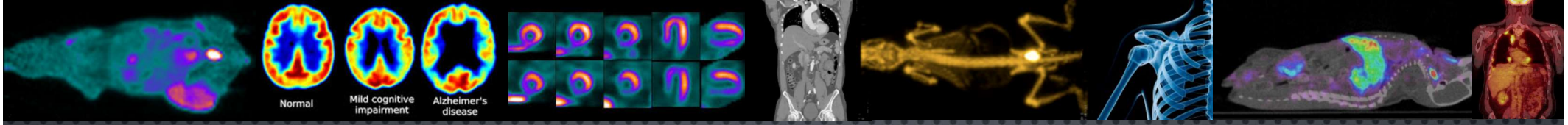
4 x 4 mm

20 days after cells injection

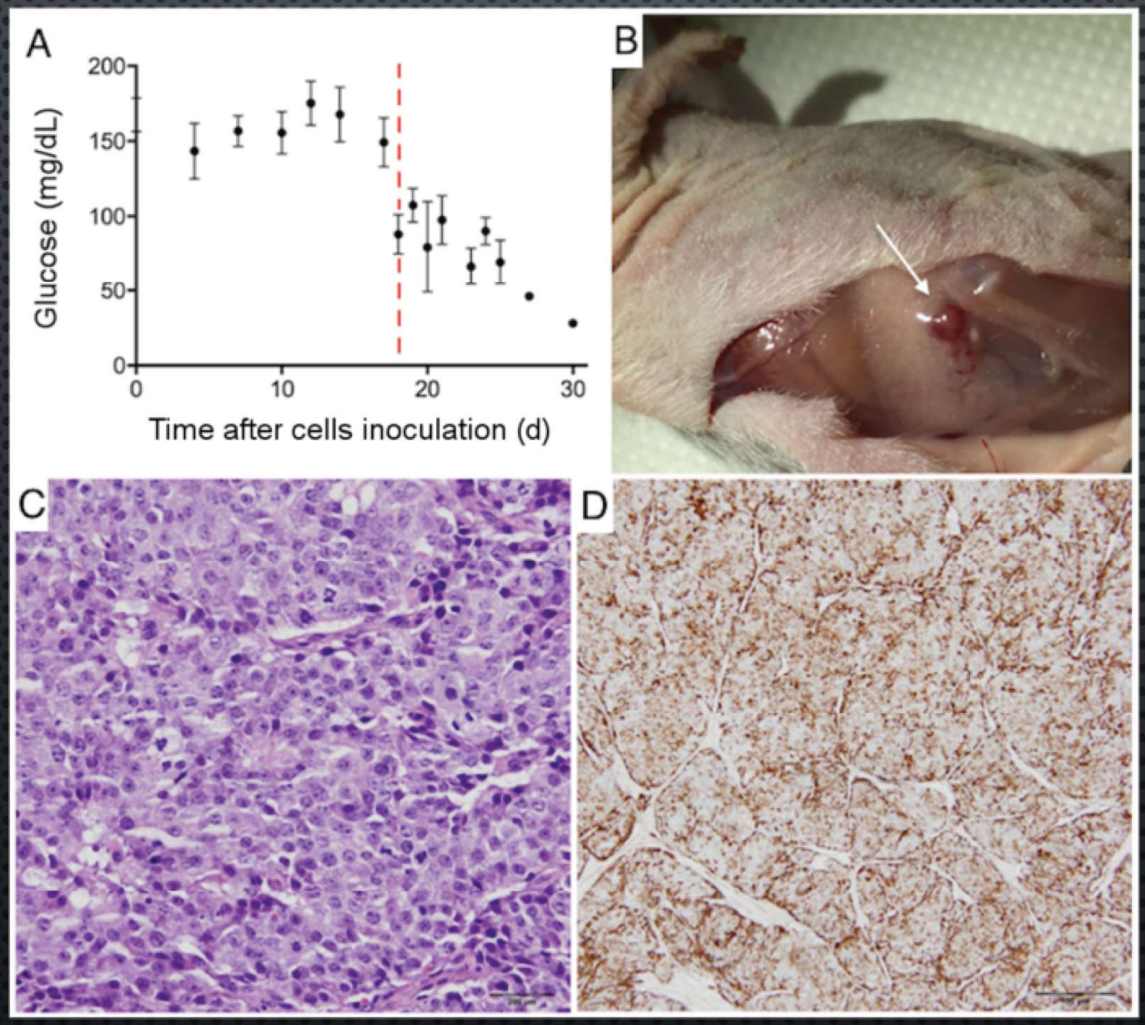


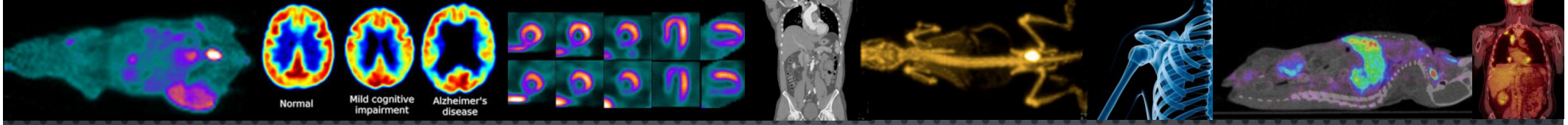
7 x 6 mm

30 days after cells injection




# Towards an early diagnostic of insulinoma

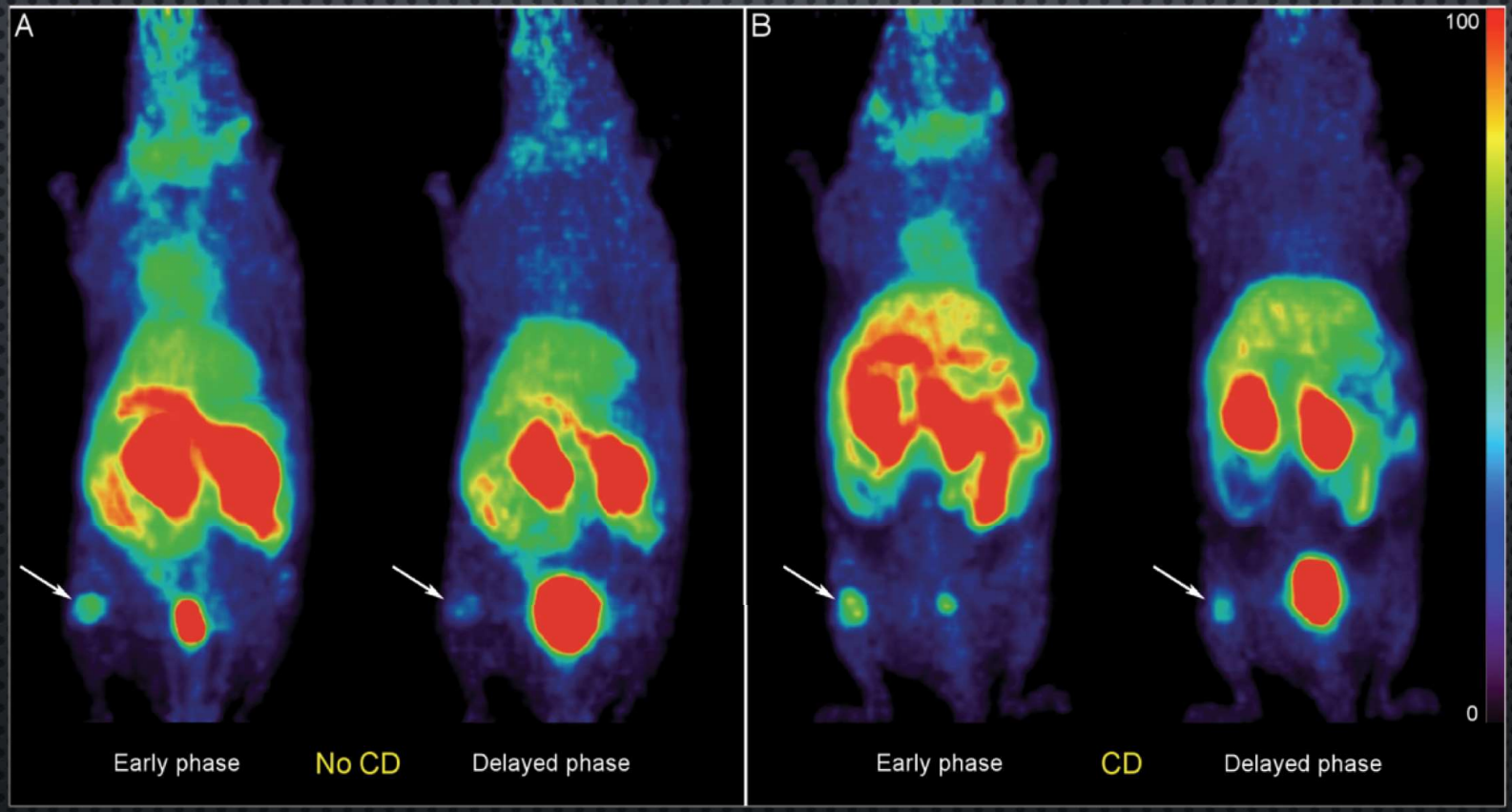





# Towards an early diagnostic of insulinoma

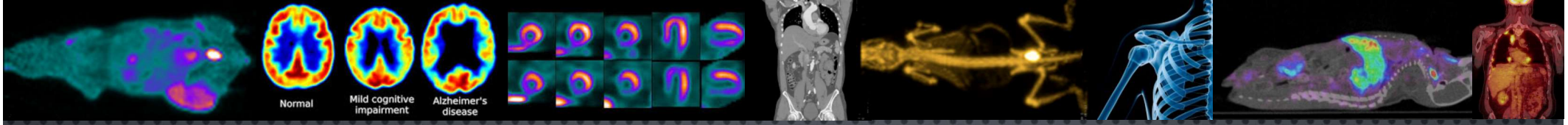
Without Carbidopa

Carbidopa




38 $mm^3$ tumor
Early phase (0-5 min) **SUV : 0.94**
Delayed phase : (15-20 min) **SUV : 0.46**

52 $mm^3$ tumor
Early phase (0-5 min) **SUV : 1.46**
Delayed phase : (15-20 min) **SUV : 1.03**




# Towards an early diagnostic of insulinoma

**Effect of Carbidopa on $^{18}$F-FDOPA Uptake in Insulinoma: From Cell Culture to Small-Animal PET Imaging**

Julien Detour[1,2], Alice Pierre[1,2], Fréderic Boisson[3], Guillaume Kreutter[4,5], Thomas Lavaux[6], Izzie Jacques Namer[2,5,7], Laurence Kessler[4,5,8], David Brasse[3], Patrice Marchand[3], and Alessio Imperiale[2,3,5,7]

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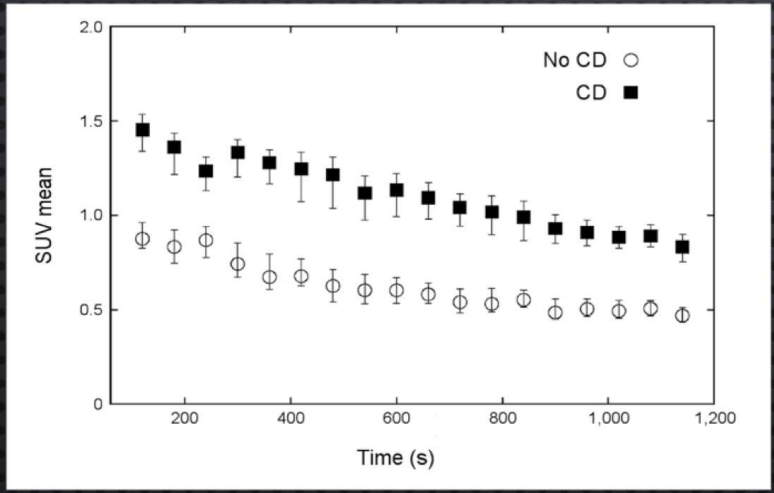
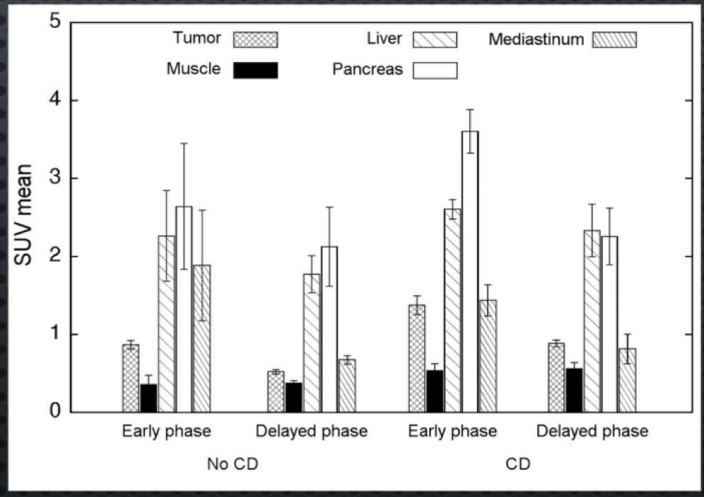
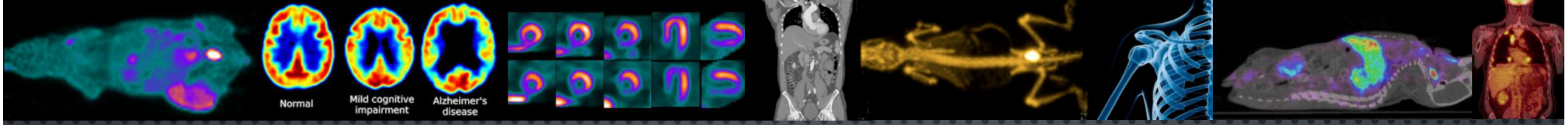


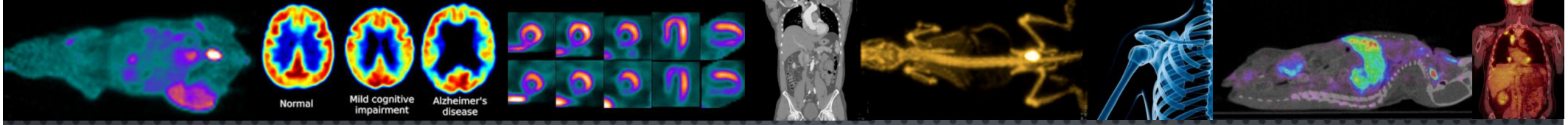




- ✓ Tumor detectable in all mice
- ✓ Similar dynamic profile uptake between treated and untreated
- ✓ Early increase and progressive decay of uptake
- ✓ SUV tumot carbidopa > SUV control ($p < 0.05$)

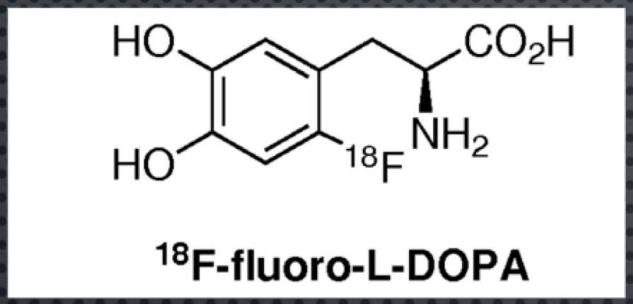



# First conclusion

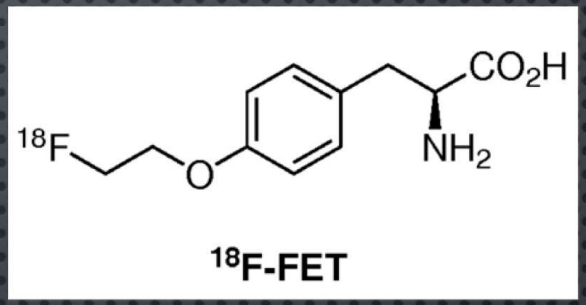
- ✓ First preclinical investigation of the effect of carbidopa on the 18F-FDOPA uptake in insulinoma
- ✓ Carbidopa does not significantly influence the *in vitro* accumulation of 18F-FDOPA in RIN-m5F cells
- ✓ Carbidopa improves the visualization of insulinoma *in vivo*
- ✓ In humans, in the absence of radiolabeled GLP-1 analogues, we recommend 18F-FDOPA PET/CT with carbidopa and early pancreatic acquisition




# Translational Approach




$^{18}$F-fluoro-L-DOPA

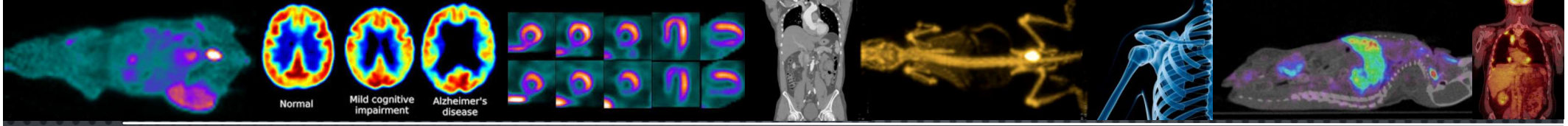



$^{18}$F-FET

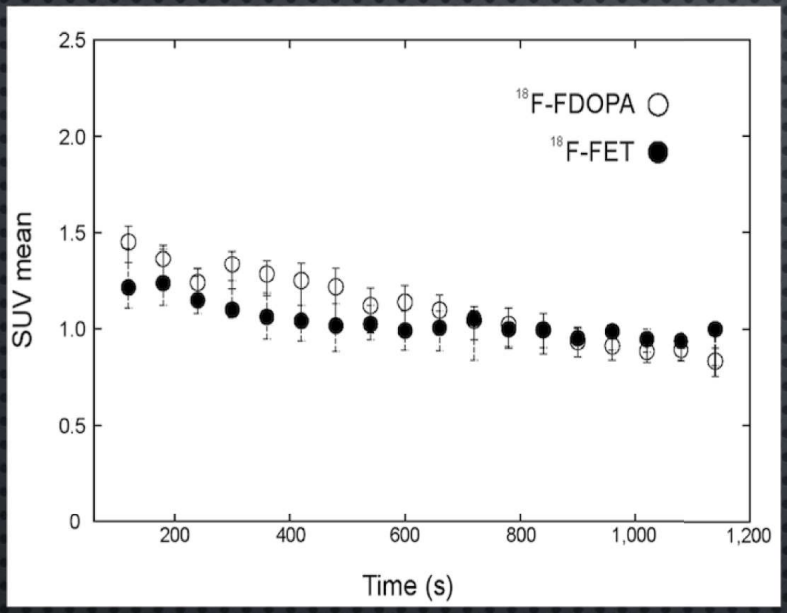
*O*-(2-[$^{18}$F]-fluoroéthyl)-L-tyrosine ($^{18}$F-FET) :

- ✓ is a tyrosine / phenylalanine analogue
- ✓ its cellular uptake depends on LATs as for $^{18}$F-DOPA
- ✓ is clinically available (lower price than $^{18}$F-DOPA)
- ✓ No pancreatic physiological uptake in humans

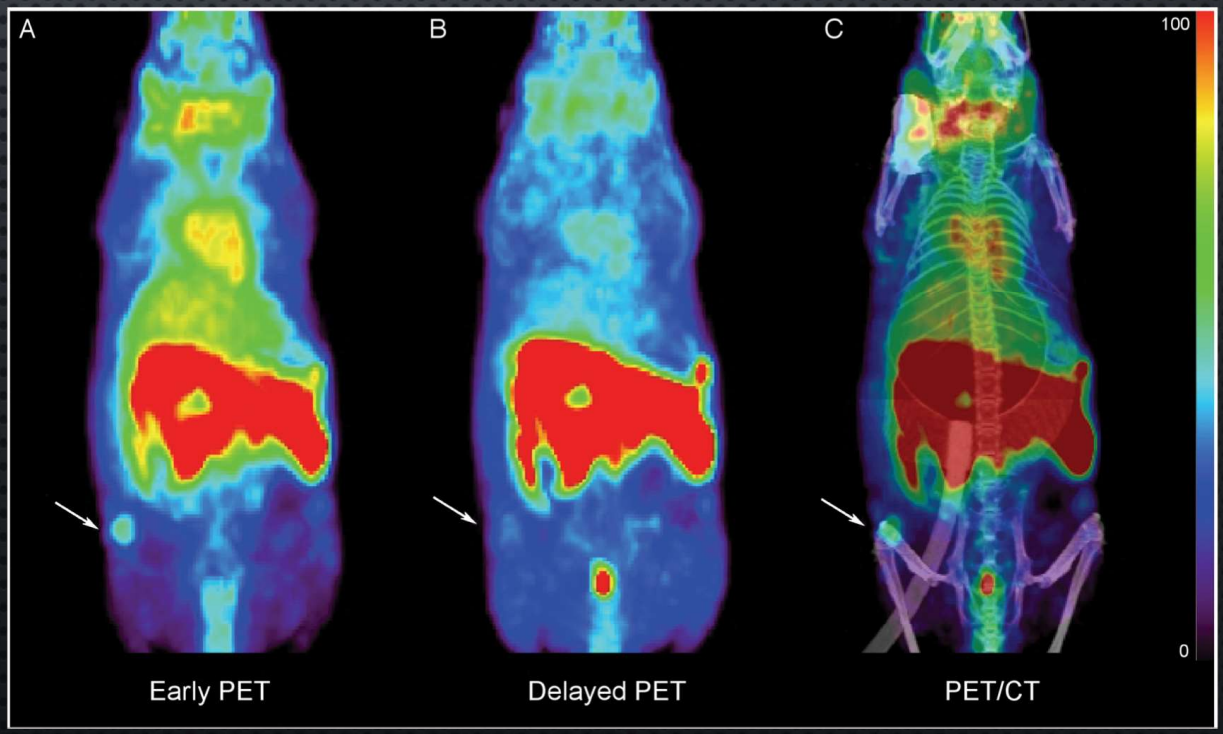
1. To evaluate the uptake of 18F-FET in comparison with 18F-DOPA in insulinoma from a murine xenograft model
2. Perform clinical proof of concept in a patient with endogenous hyperinsulinemic hypoglycemia




# Translational Approach

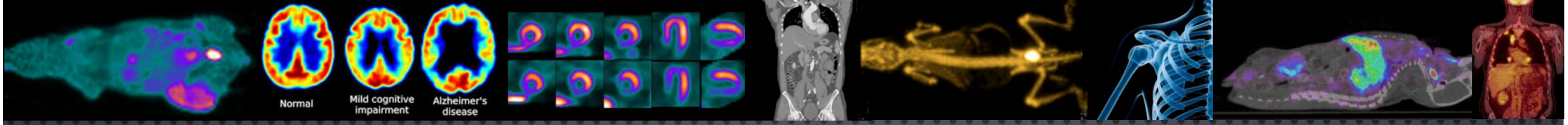



- ✓ Similar kinetic uptake in the VOI
- ✓ Early detection of the tumor

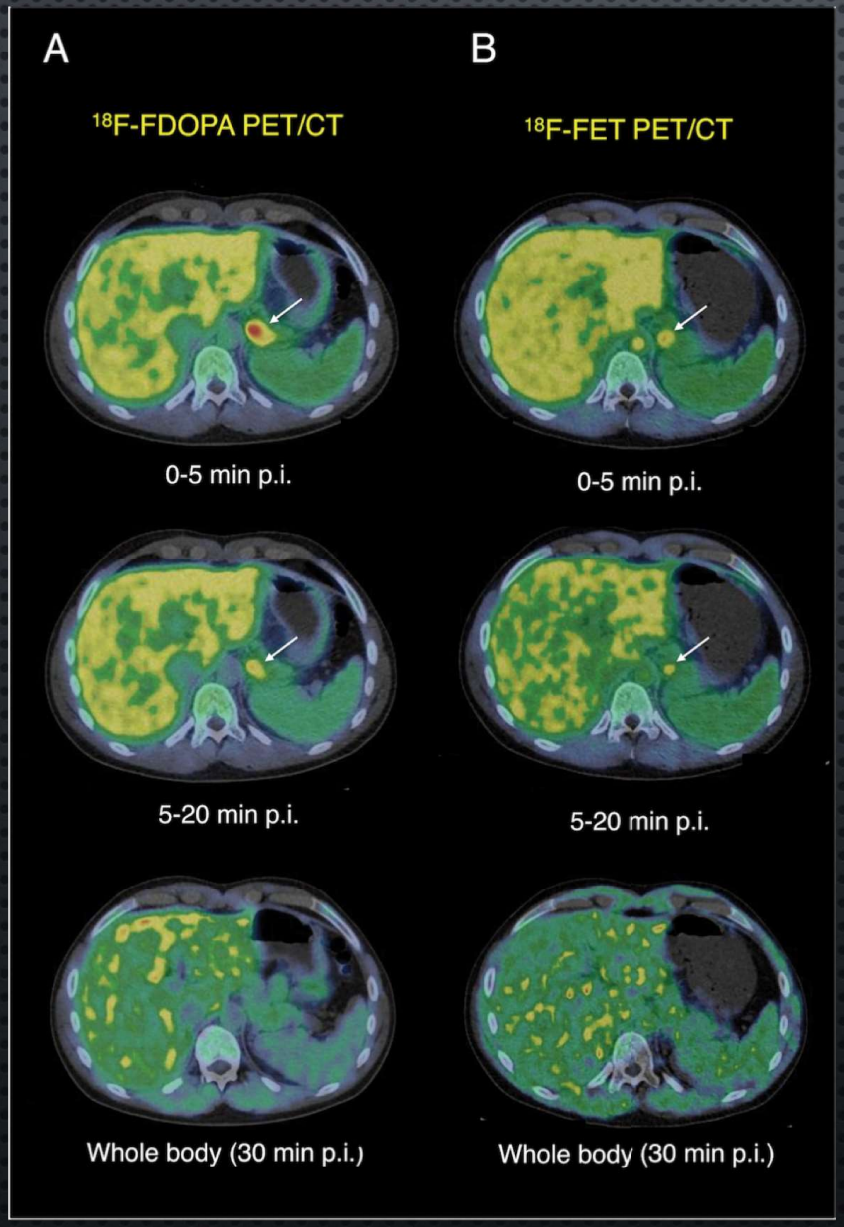



Translational approach:

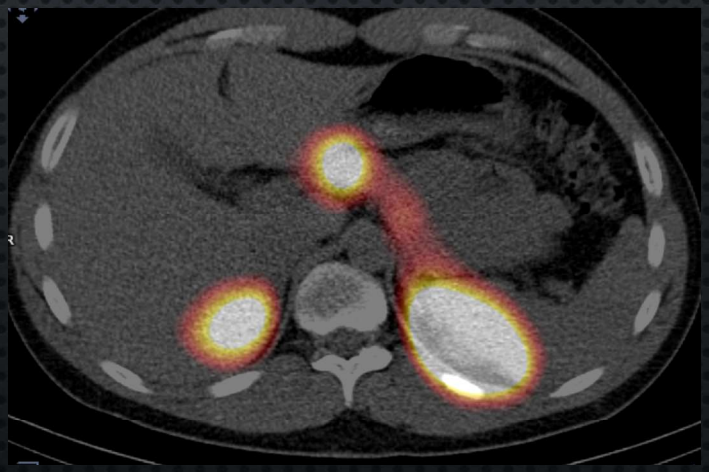
- ✓ $^{18}$F-FET : FDA in human
- ✓ No physiological pancreatic uptake

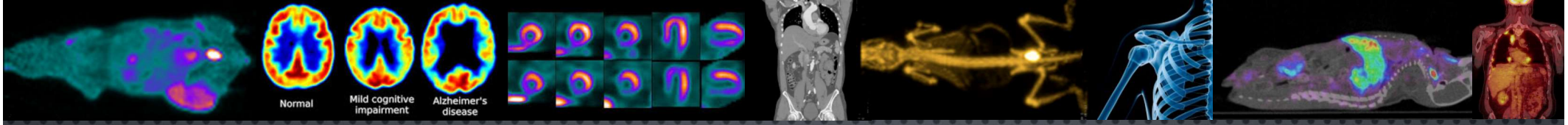



# Translational Approach




$^{111}$In-DTPA-exendin-4 (GLP-1)

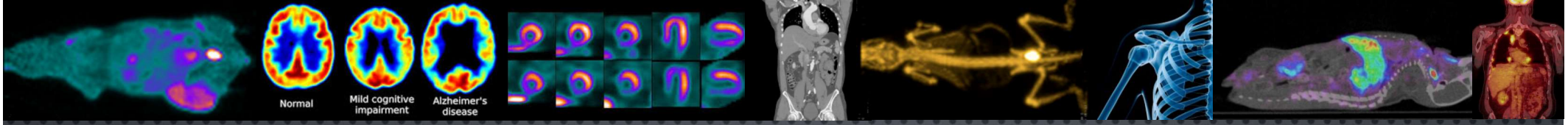





# Conclusion

- ✓ In our preclinical model of insulinoma as well as in one patient, the binding patterns of $^{18}$F-FET and $^{18}$F-FDOPA were comparable
- ✓ The role of $^{18}$F-FET in the clinical detection of insulinoma seems interesting and should be explored in the patient in prospective studies
- ✓ Radiolabeled analogues of GLP-1 will be preferred when available in clinical routine

Many preclinical developments found outcomes in clinic




# Preclinical serving Clinical

## (Radio-) pharmaceutical development

**Chemistry**
- chemical product selection
- high-throuput screening
- compound optimisation

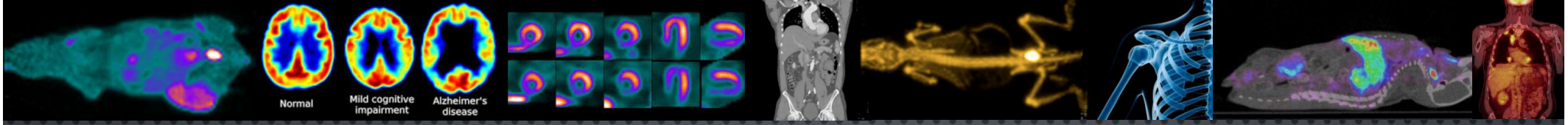
**Biology**
- target selection
- tests developments
- selective screening

**Preclinical studies**
- target specificity
- biodistribution
- pharmacokinetic
- toxicology

**Clinical studies**
- phase 0
- phase I
- phase II
- phase III

Product approbation for clinical use

- ✓ Animal models: *in vivo* studies
- ✓ Technical developments
- ✓ Imaging protocols




# Acknowledgments

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*Patrice Marchand*
*Lionel Thomas*
*Ali Ouadi*
*Patrice Laquerriere*
*Laurent Daeffler*
*Bruno Jessel*
*Jacky Schuler*
*Alessio Imperiale*
*David Brasse*

**... for your attention !!**