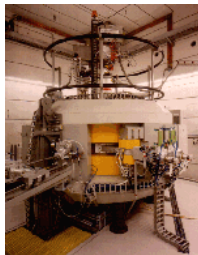


Positron Emission Tomography: a tool for diagnosis and drug development

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A particle accelerator (cyclotron) is used to produced radionuclides

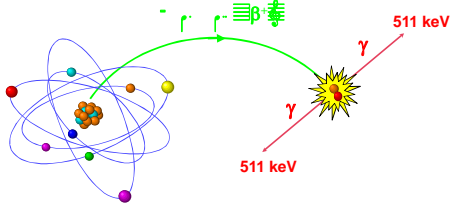
Radionuclides are incorporated by organic synthesis into molecules of biological interest:

carbohydrates, fatty acids, amino acids and even drugs

The most used positron emitters are ¹⁵O, ¹³N, ¹¹C and ¹⁸F (half life: 2, 10, 20, and 110 min, respectively)

Carbon, oxygen and nitrogen are present in most of the biological molecules and the biochemical properties will not be dramatically altered after introduction of these radionuclides in a compound.

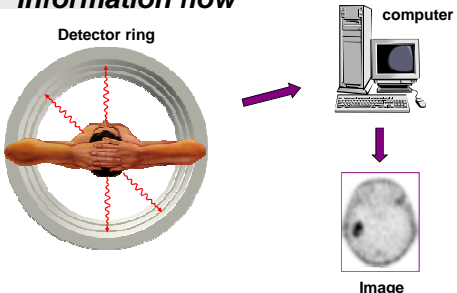
Positron emission



The radioisotope emits a positron that interact with an electron

The annihilation of the pair positron-electron generates two photons with 511 keV wandering in 180 degrees

Information flow



Detector ring

computer

Image



Discovery ST

PET is used worldwide as a diagnostic tool in oncology, cardiology and neurology

- Development of new tracers for:
 - diagnosis
 - follow-up progression of diseases
 - monitoring of treatments
- Drug development

The present cost for development of a new drug has been estimated at 800 million US dollars

DIMasi JA et al. "The price of innovation: new estimates of drug development costs", Journal of Health Economics, 2003

PET studies can be very cost effective in the drug development process

A rough estimation of the costs of the PET package including:

- chemistry development
- safety evaluation
- preclinical validation
- PET studies

...is about 300.000 US dollars

Bergström M et al., Eur J Clin Pharmacol; 2003

12 years for an experimental drug to be approved

More than 70% of candidate drugs entering clinical drug development fail

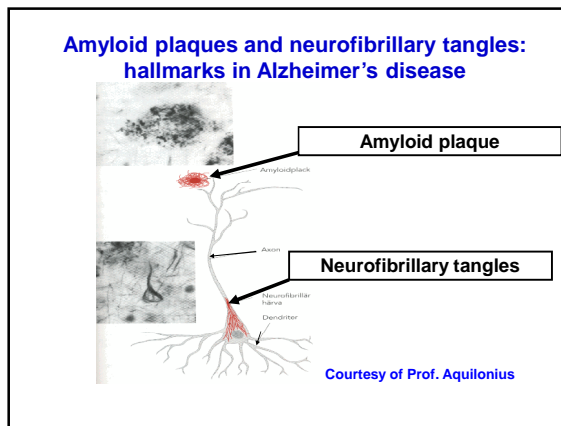
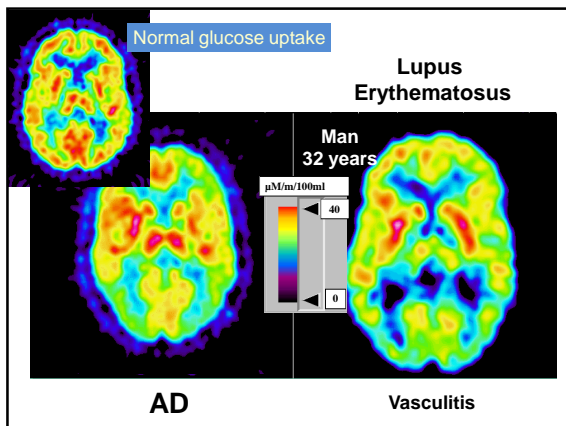
Reasons:

- Poor predictability (of properties in man) of preclinical models used for candidate selection
- Insufficient knowledge before entering human tests

Bergström M et al., Eur J Clin Pharmacol; 2003

From safety aspects, there is no major difference between the probing of a new drug and the validation of a new PET tracer

Development of a new PET tracer **PIB** to detect amyloid in Alzheimer's disease



Presently, the definitive diagnosis of AD requires histopathological demonstration of amyloid plaques and neurofibrillary tangles at autopsy

An in vivo amyloid-imaging technology could fill the need for an accurate diagnostic tool in early and perhaps pre-symptomatic stages of AD

- Early initiation of drug therapy
- Use of the substance as a surrogate marker of efficiency for new anti-amyloid drug candidates

"Imaging Brain Amyloid in Alzheimer's Disease with Pittsburgh Compound-B"

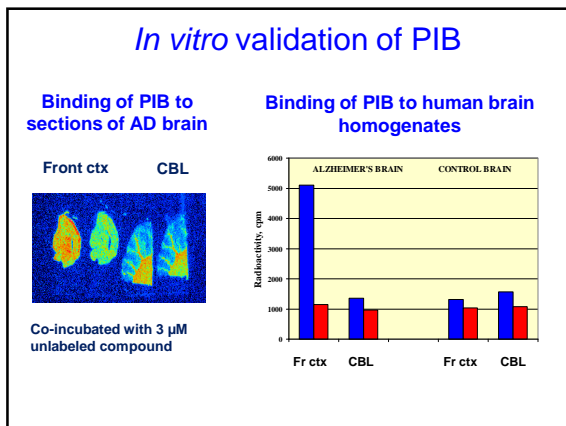
First human study with the tracers:

PIB
to detect amyloid plaques

and

FDG
to determine regional cerebral glucose rate

Klunk, Engler, Nordberg et al; Annals of Neurology, 2004



PET-microdosing

The human use of PIB was associated with a toxicity assessment using the Uppsala University PET-microdosing concept

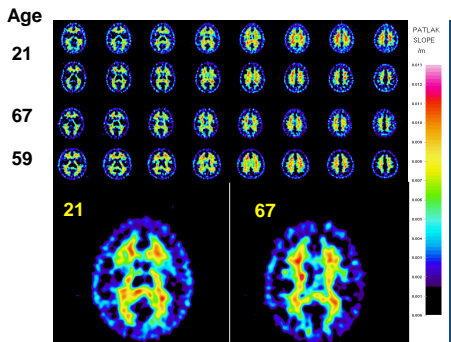
A PET tracer given in doses of a few micrograms, don't need to undergo the same extensive toxicity assessment as drugs in clinical trial, which are administrated in mg

The microdosing concept

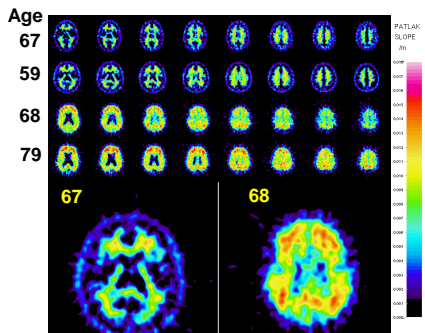
- Acute pharmacology and toxicity effects on heart rate and blood pressure in 6 rats, at doses p.b.w 100 times higher than those expected in the PET study with humans
- 3 rats are sacrificed after 2 days and 3 after 2 weeks. Histological investigation is performed in different organs
- Genotoxicity determined in bacteria and mamalian cells. The maximal concentration is 50.000 times the estimated average body concentration in a human PET-study.
- Plasma protein binding studies and organ distribution studies are performed in rats and monkeys

- 16 patients with AD
- 9 healthy controls

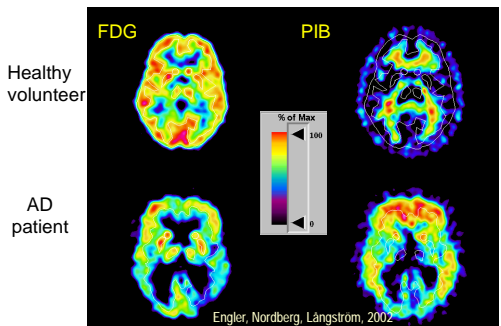
PIB uptake in healthy volunteers



PIB: Healthy volunteers and Alzheimer patients

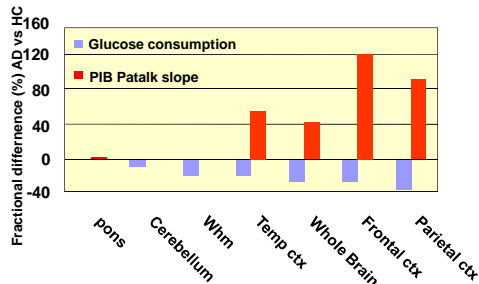


FDG-PIB: healthy volunteer and AD patient



"Long-Awaited Technique Spots Alzheimer's Toxin", August 2002; SCIENCE

Difference between AD and HC (%) measured with PIB or FDG



“Two-year follow-up of amyloid deposition in patients with Alzheimer’s disease”

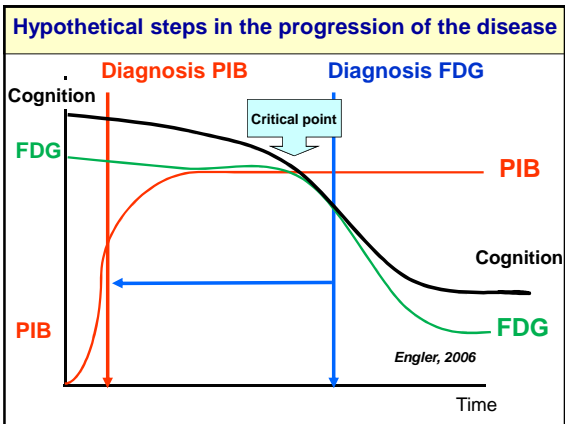
A follow up study of the 16 patients after 2 years

Engler, Forsberg, Almkvist et al.; Brain 2006

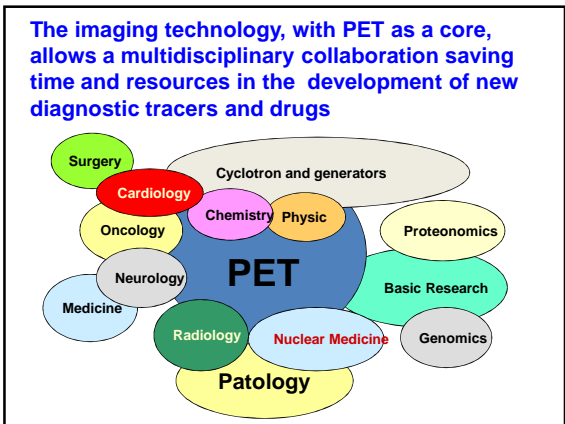
There was **not** observed an increased PIB retention over time

...but a deterioration in glucose uptake and cognitive function in some of the patients

This relative stability in the PIB retention might represent a dynamic process in amyloid deposition that reaches an equilibrium



- We have performed studies with PIB in 21 patients with Mild Cognitive Impairment (MCI): approx. 50% of them have amyloid depositions
- We have also examined patients with frontotemporal dementia and Parkinson’s disease using PET and PIB
- PIB is currently used in studies where AD patients are treated with new anti-amyloid drugs or with anti-amyloid vaccination



Uruguay: 2007

A law creating the Uruguayan Center of Molecular Imaging (UCMI) to develop the PET technology is approved by the parliament

We hope to examine the first patient in 2009

The Center will be dependent of the Ministry of Health

Acknowledgments

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