L'imagerie pharmacocinétique : un nouvel outil pour le développement des candidats médicaments

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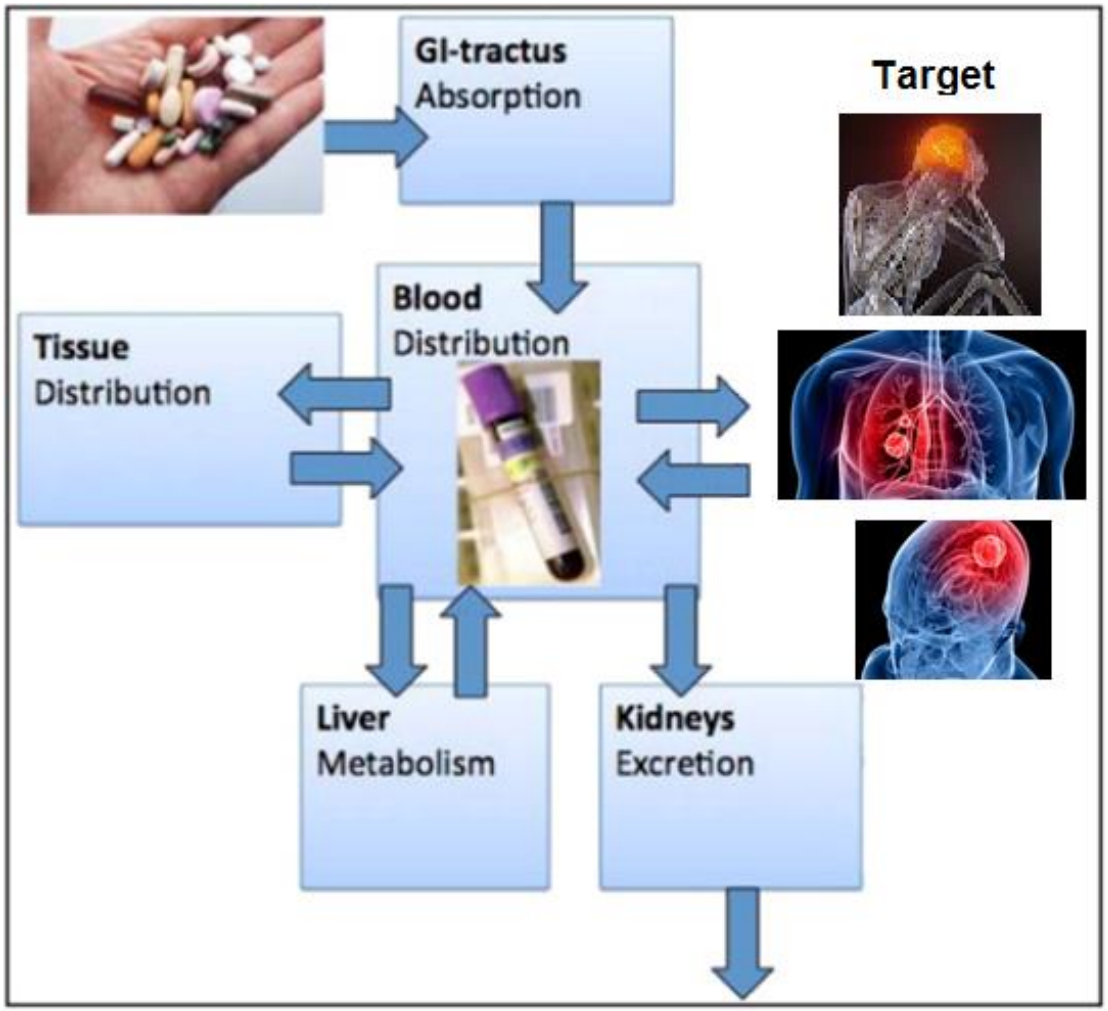
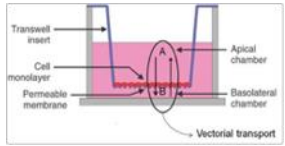
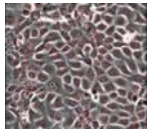
Mardi 8 novembre 2022 – 13ème reunion annuelle de l'ITMO Technologies pour la Santé

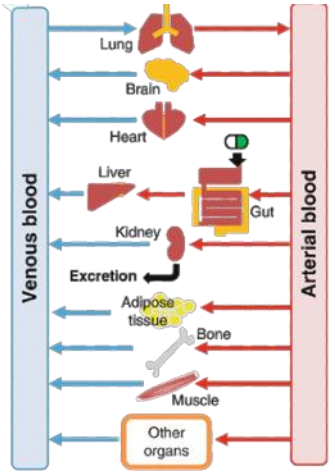
Clinical pharmacokinetic (PK) at the tissue level



Target tissue exposure ?



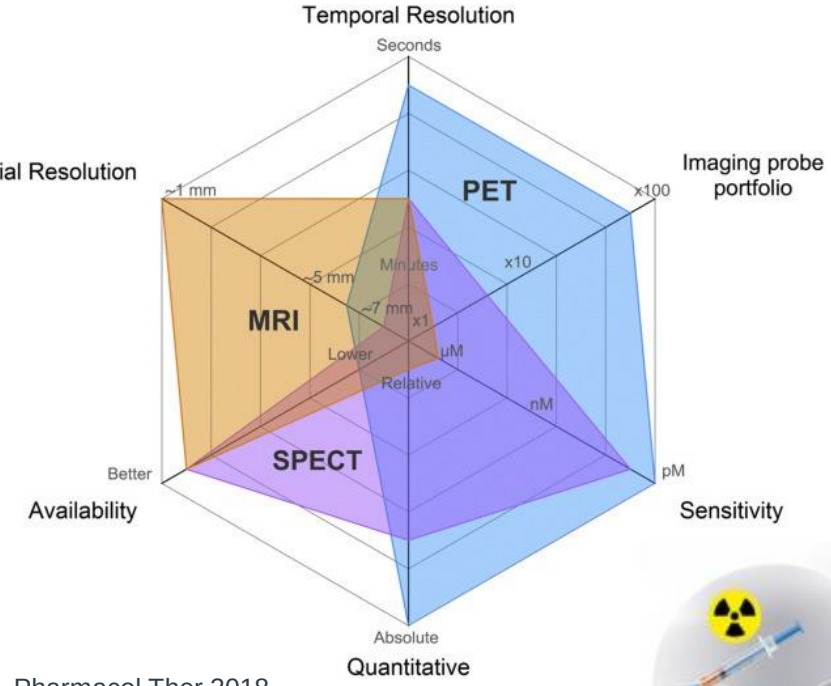




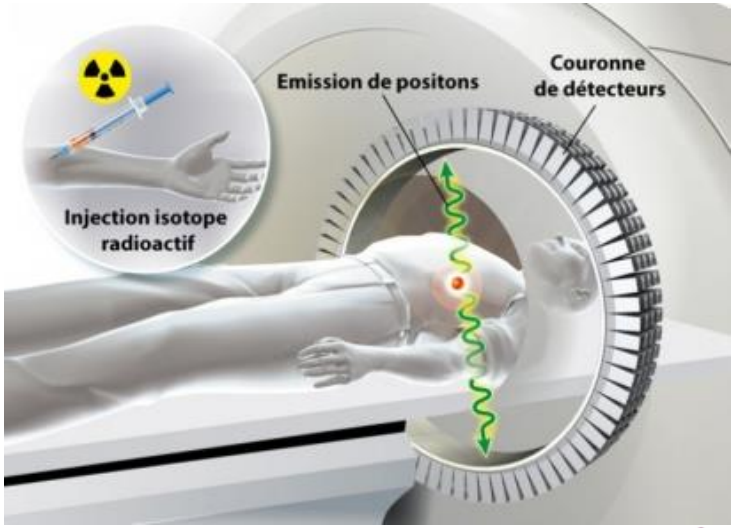
PBPK models

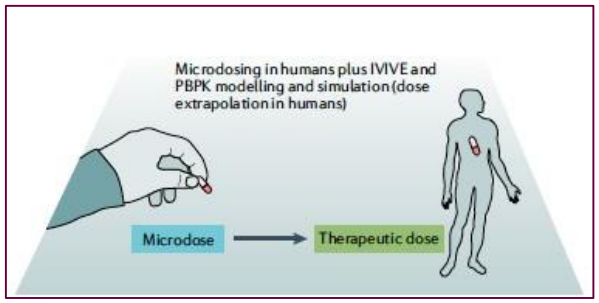
The best model for humans is human

PK molecular imaging modalities



Tournier et al., Pharmacol Ther 2018

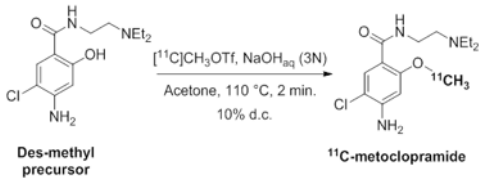




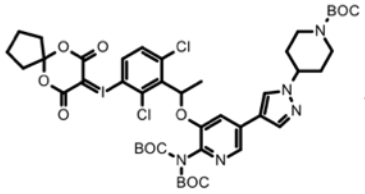
Phase 0 Phase 1

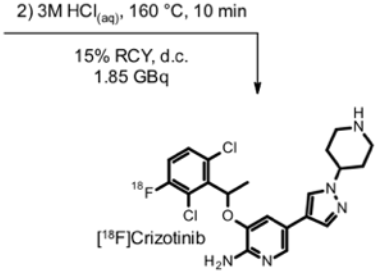
Burt et al., Nat Rev Drug, Discov 2020

Radiochemistry : the gateway to PK imaging

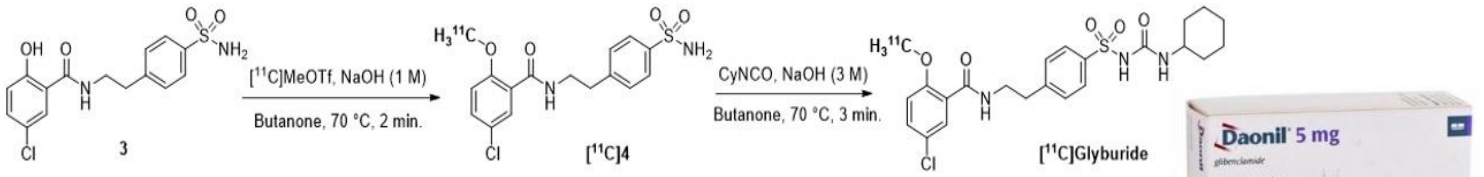


Caillé et al., 2018



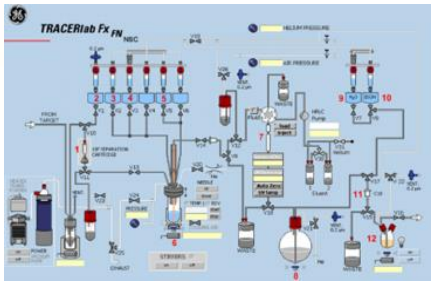


Caillé et al., 2020



Caillé et al., 2020

- Carbon-11 ($T_{1/2}$ = 20 min)
- Fluorine-18 ($T_{1/2}$ = 110 min)



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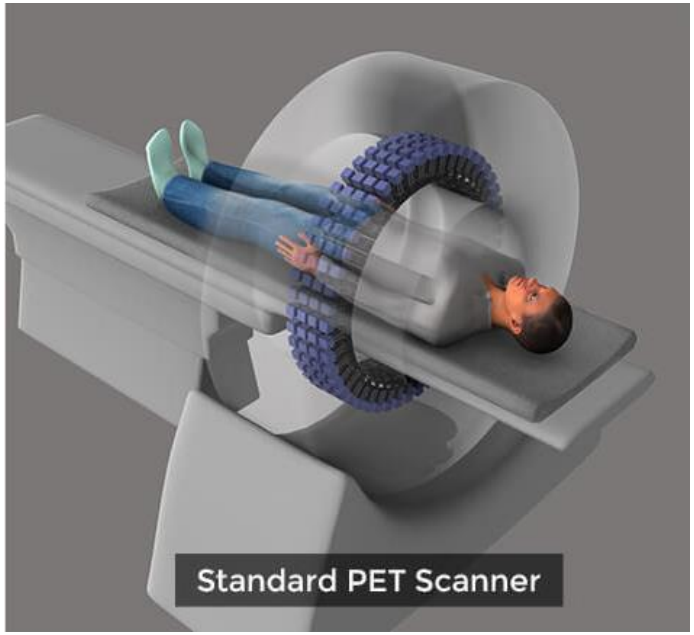
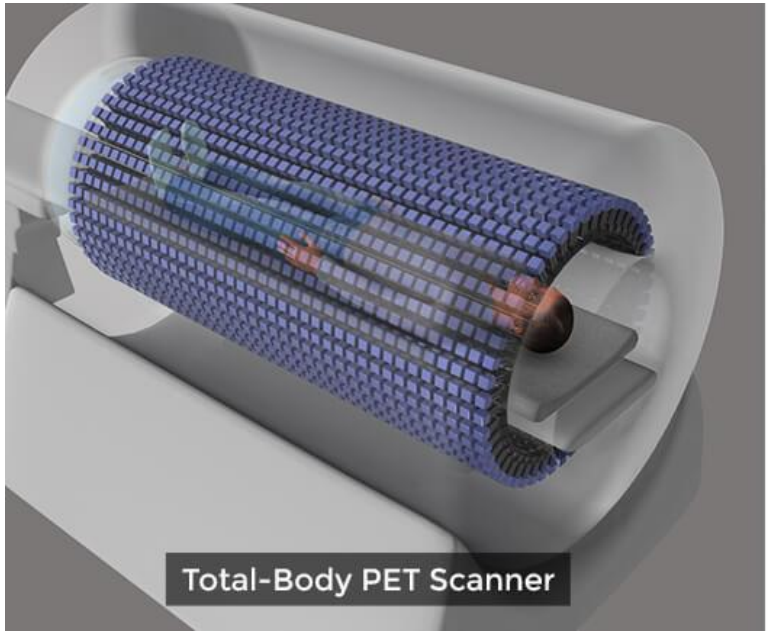
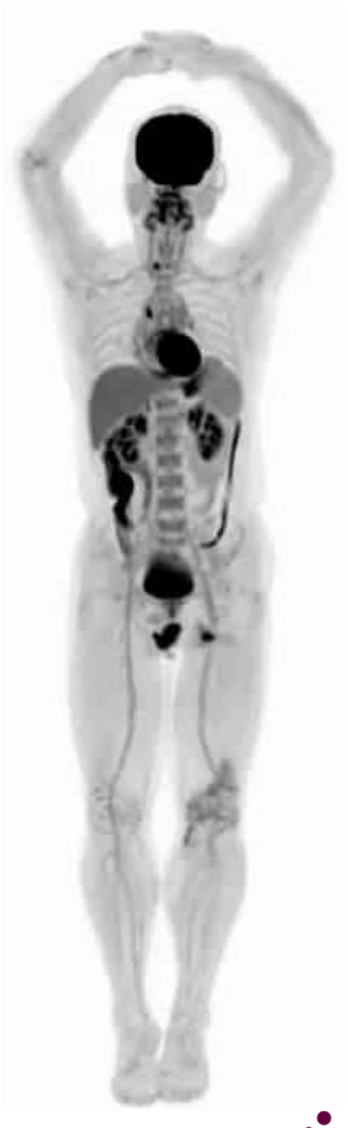
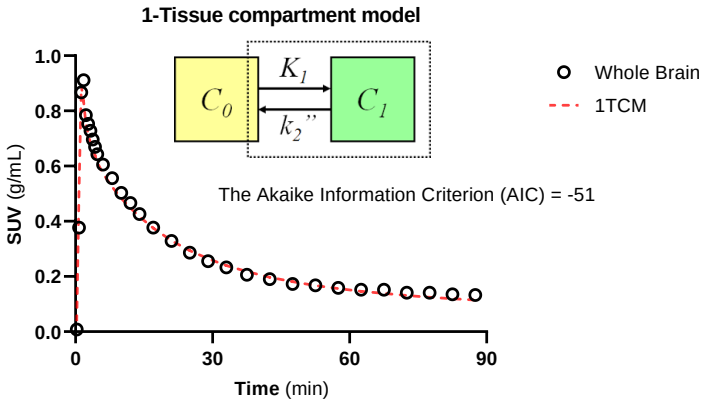
Whole-body dynamic imaging







Credit:
Simon R. Cherry,
University of California,
Davis



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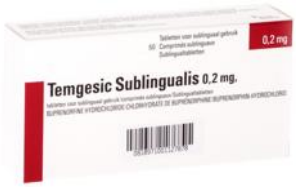
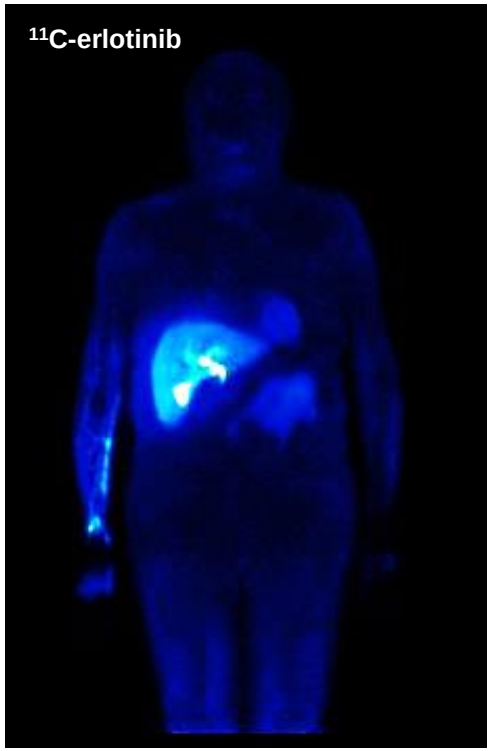
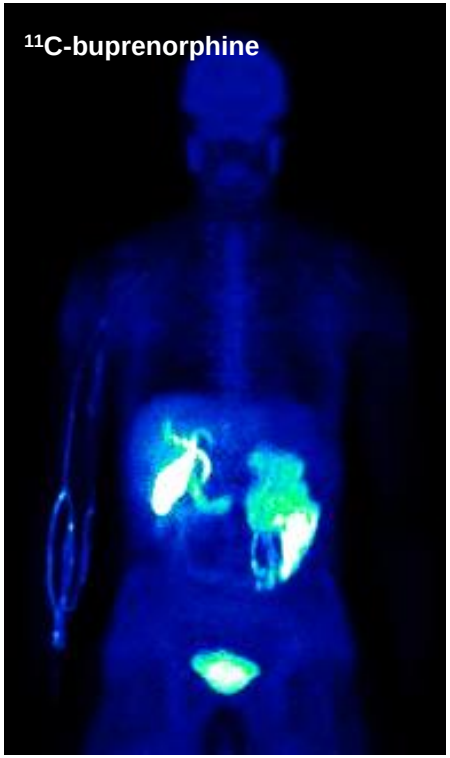
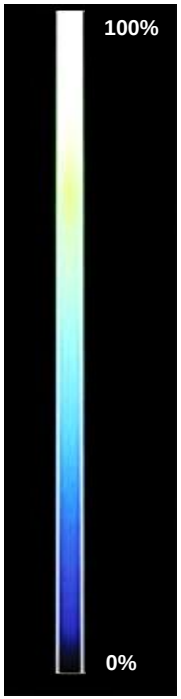
Pharmacokinetic (PK) imaging









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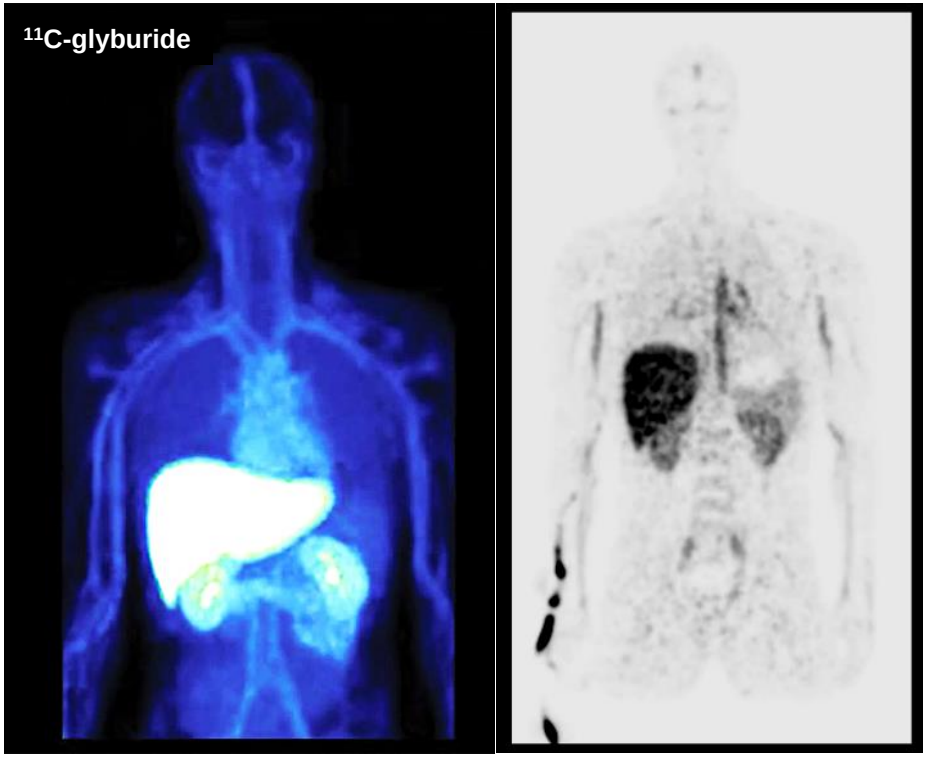
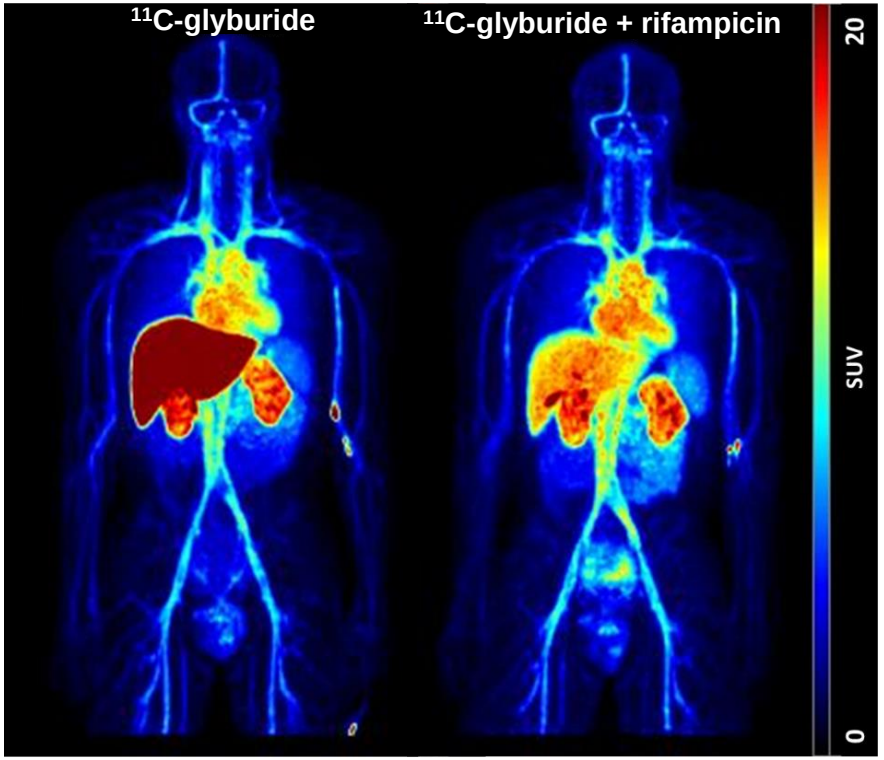
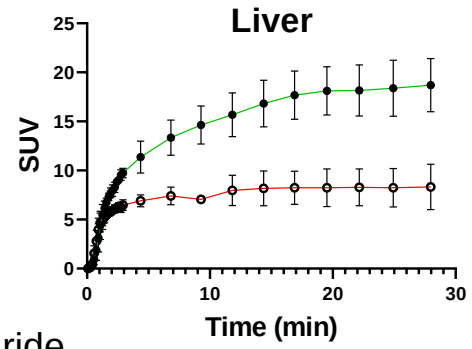
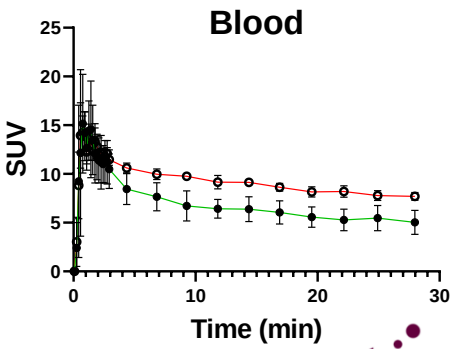
Liver distribution and elimination process

Drug-drug interaction









^{11}C-glyburide

^{11}C-glyburide + rifampicin

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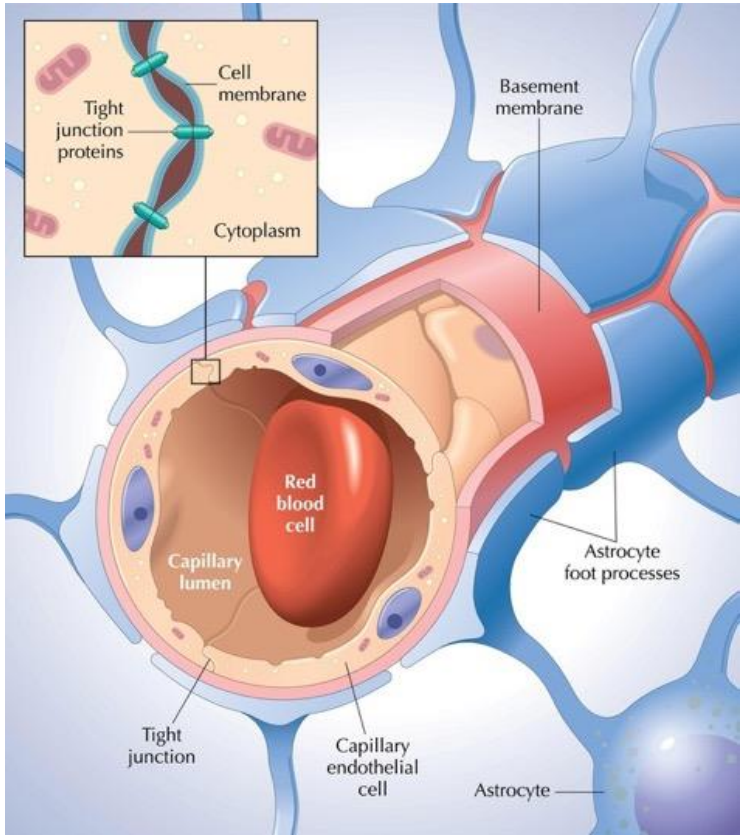
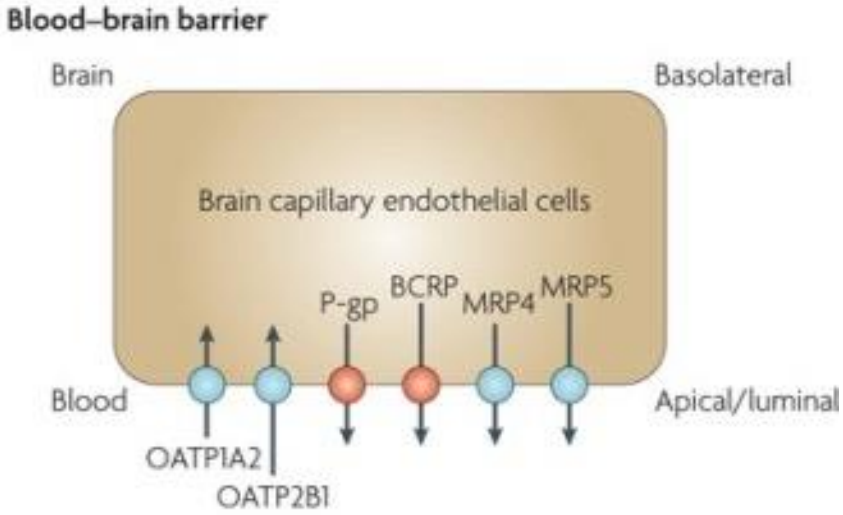
Brain distribution process



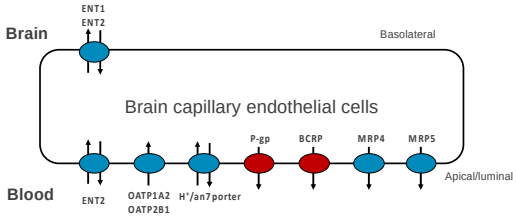
Blood brain barrier (BBB) :

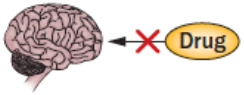
Physical and functional barrier



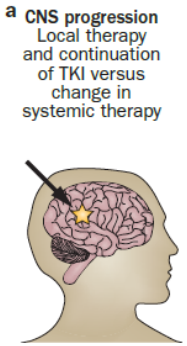
Nature Reviews | Drug Discovery

Brain distribution process

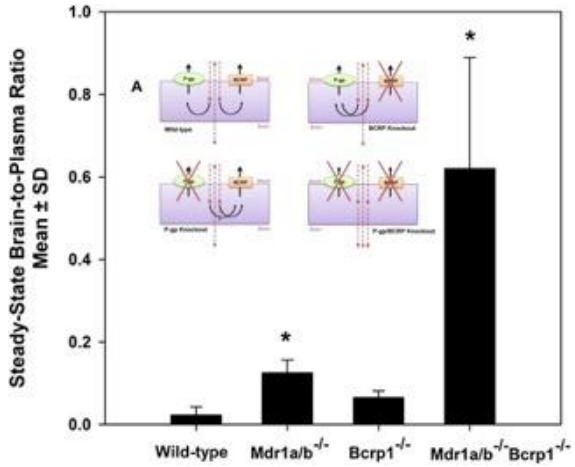




Inadequate CNS penetration

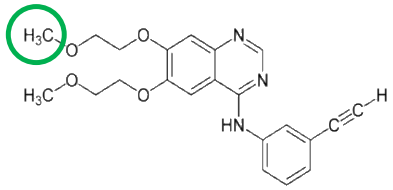


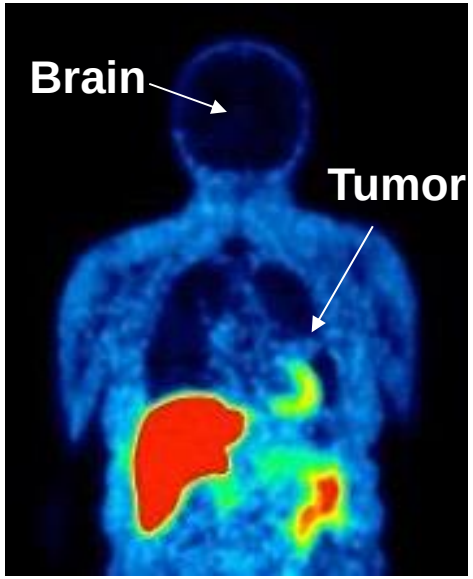
Camidge et al., Nat Rev Clin Oncol 2014

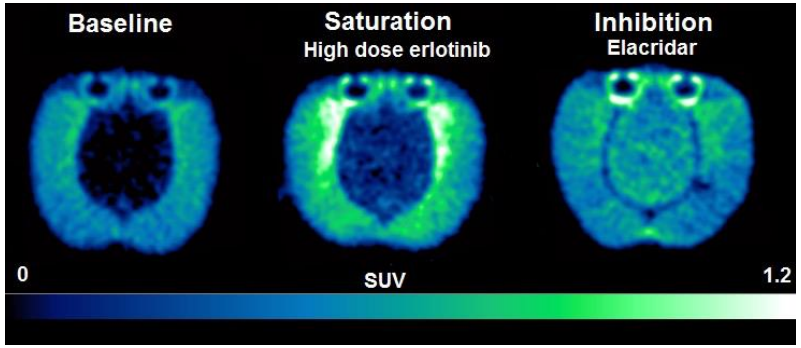


Agarwal, Drug Metab Dispos 2013

^{11}C-erlotinib PET imaging

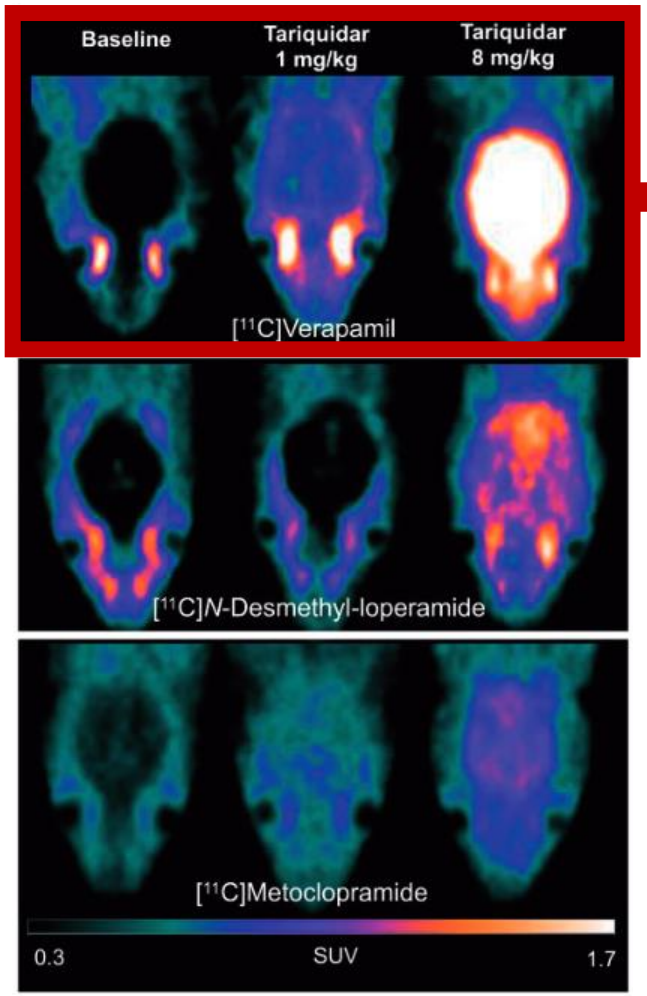




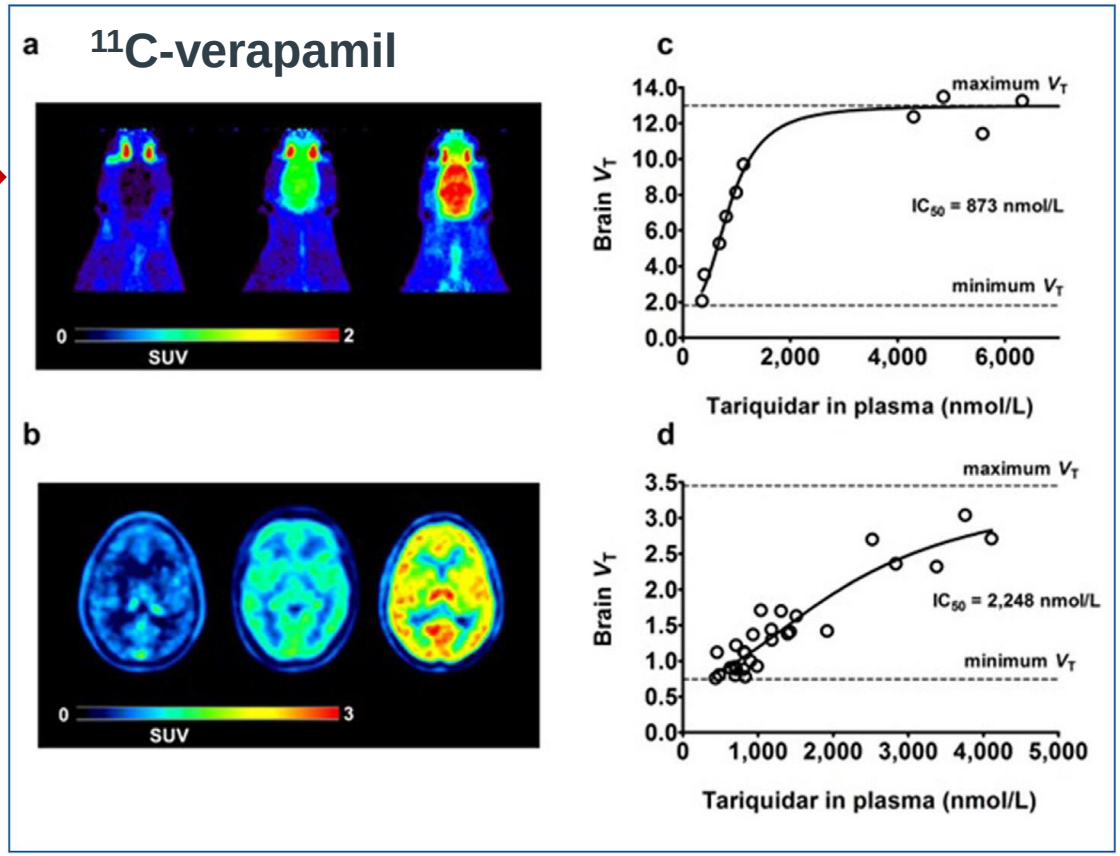


Tournier et al., J Nucl Med 2017

Translational approach



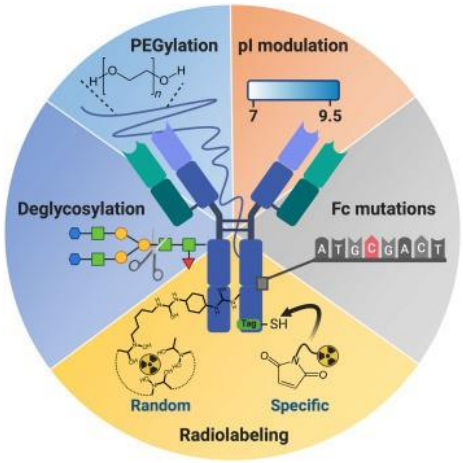
Breuil et al., J Cereb Blood Flow, 2022



Tournier et al. Pharmacol Ther, 2018

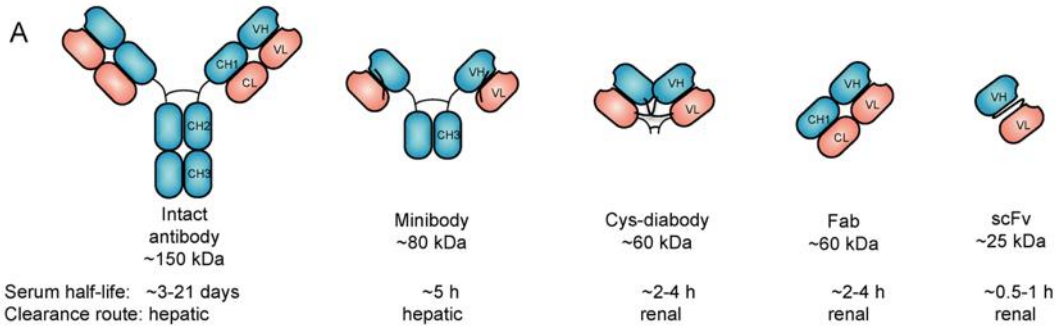
Volume of distribution **V_T = tissue-plasma concentration ratio at steady state**

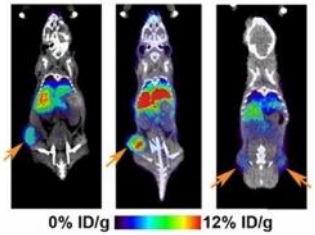
PK-ImmunoPET



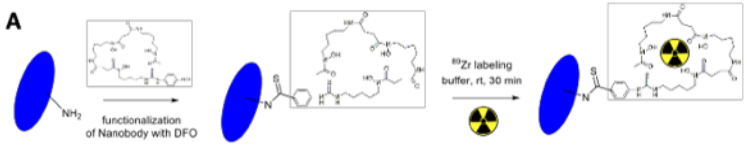
Bouleau et al., Pharmacol Ther 2021

- Long biological half-life (distribution/elimination phase)
- Target-mediated PK
- Species differences in epitopes





Truillet et al., Bioconjug chem 2018



^{89}Zr radiolabeling

$T_{1/2}$ = 3.3 days
Straighforward radiochemistry
PET acquisition days /weeks after injection
Basic PK modelling

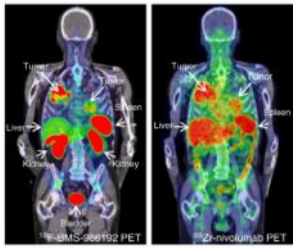
Radiation exposure
Limited translational perspectives
In patients only

^{18}F-radiolabeling

$T_{1/2}$ = 110 min
Challenging radiochemistry
PET acquisition max 4h after injection
No consensus PK model

Acceptable radiation exposure
Fully translational method
Phase 0/1 in healthy volunteers

Consistent with engineered Abs ?



Niemeijer, Nat Commun 2018

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Conclusion

- PK imaging : innovative approach to non invasively study drug PK
- Overview of drug distribution (target tissue for efficiency or non-target tissue relevant for toxicity)
- Information about drug elimination and some drug-drug interactions
- Quantification of the total tissue radioactivity → Cannot distinguish parent parent drug from radiometabolites
- Microdosing → No pharmacological or toxicological effects = Dedicated regulations

Thank you for your attention

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