Molecular Imaging for Infections

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Tuberculosis Meningitis Workshop – NIH - May 22, 2017

JOHNS HOPKINS
SCHOOL of MEDICINE

Questions for TB Meningitis

1. Is there *M. tuberculosis* in the brain?
2. What is the extent of that infection?
3. Is the treatment working?

Problem - Diagnosis of Bacteria

Fundamental diagnostic: 1884

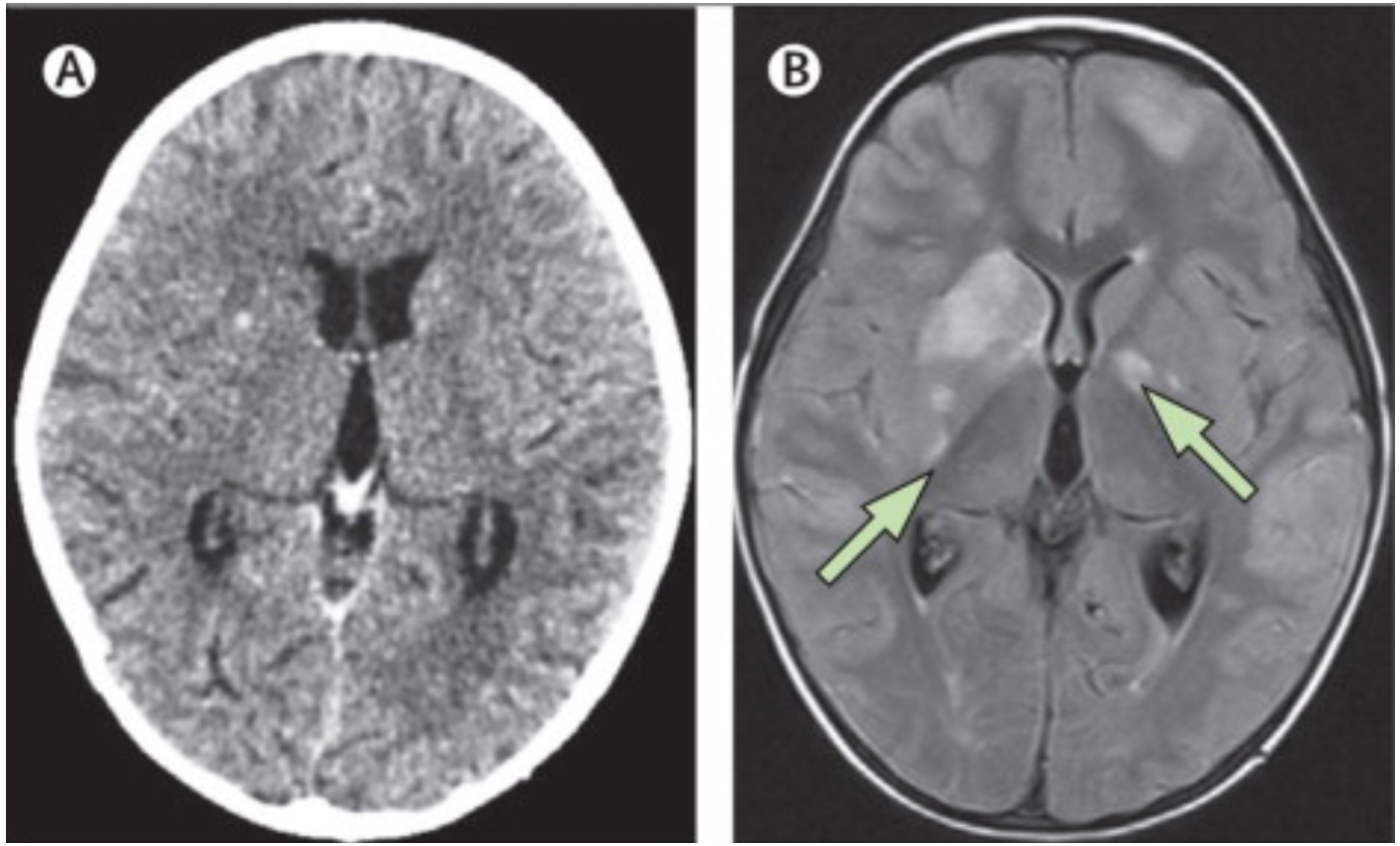
Need to isolate the bug

Fundamental diagnostic: 2017

Need to isolate the bug

Solution - Take a Picture

Normal brain CT scan of a 3-year-old child with stage 3 tuberculous meningitis

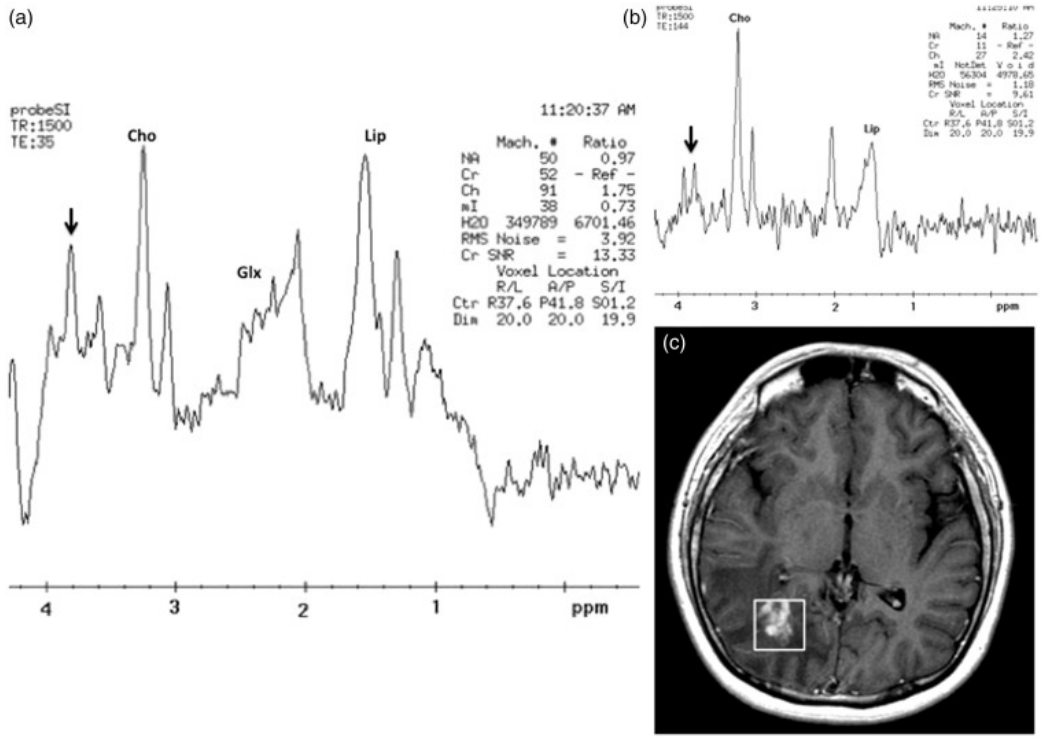


A T2-weighted, fluid–attenuated, inverse-recovery MRI image taken 5 days later showed several infarcts (arrows) in the basal ganglia.

Thwaites *et al. Lancet Neurology*, 2013.

Imaging TB Meningitis

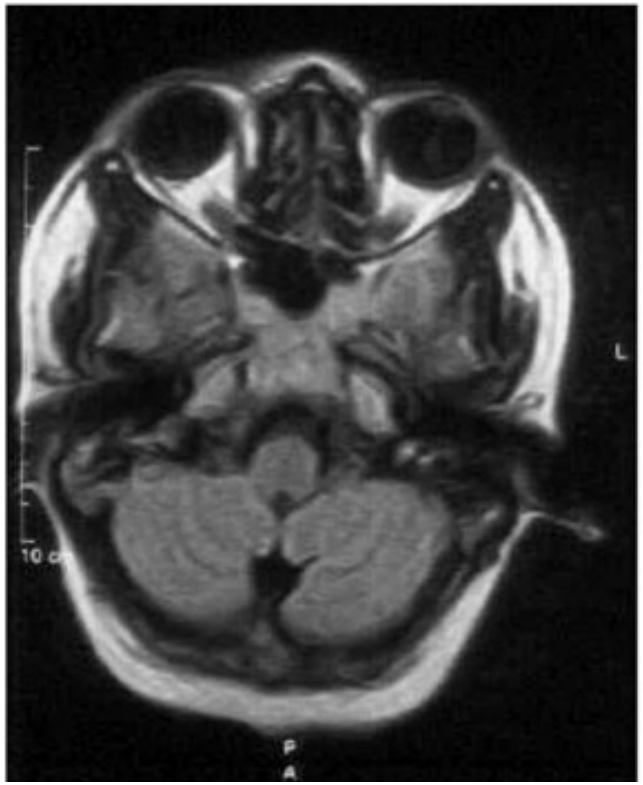
- Anatomical Imaging (CT, MRI)
  - CT useful to detect hydrocephalus and vascular complications
  - MRI is more sensitive than CT in determining the extent of meningeal and parenchymal involvement.
  - MR angiography – vascular disease
  - MR spectroscopy can be used to characterize tuberculomas and differentiate them from neoplasms
  - Problem: lack of specificity and delay in tissue changes



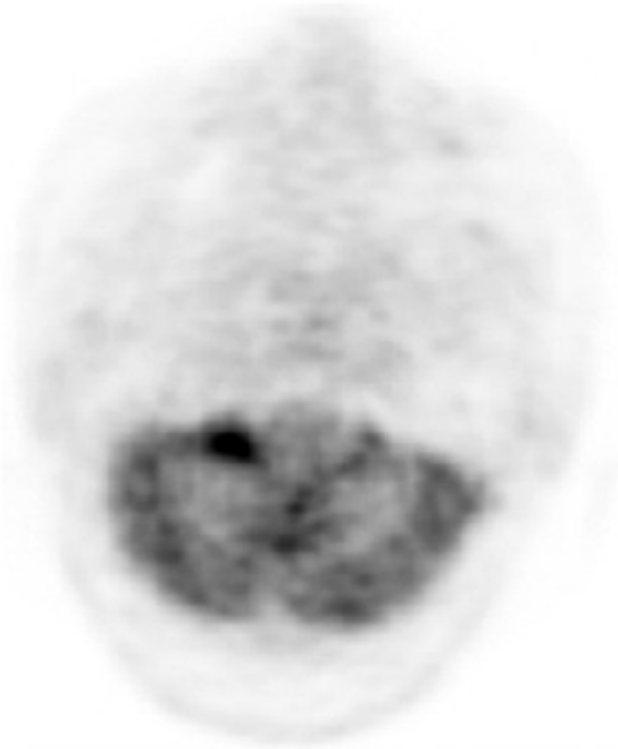
Torres *et al. Magnetic Resonance Imaging*, 2014.
Morales *et al. Neuroradiology Journal*, 2015.

Imaging TB Meningitis

- Imaging Inflammation
  - ^{18}F-FDG PET
    - Possible detection of earlier findings
    - Host dependent
    - Very sensible
    - Not specific



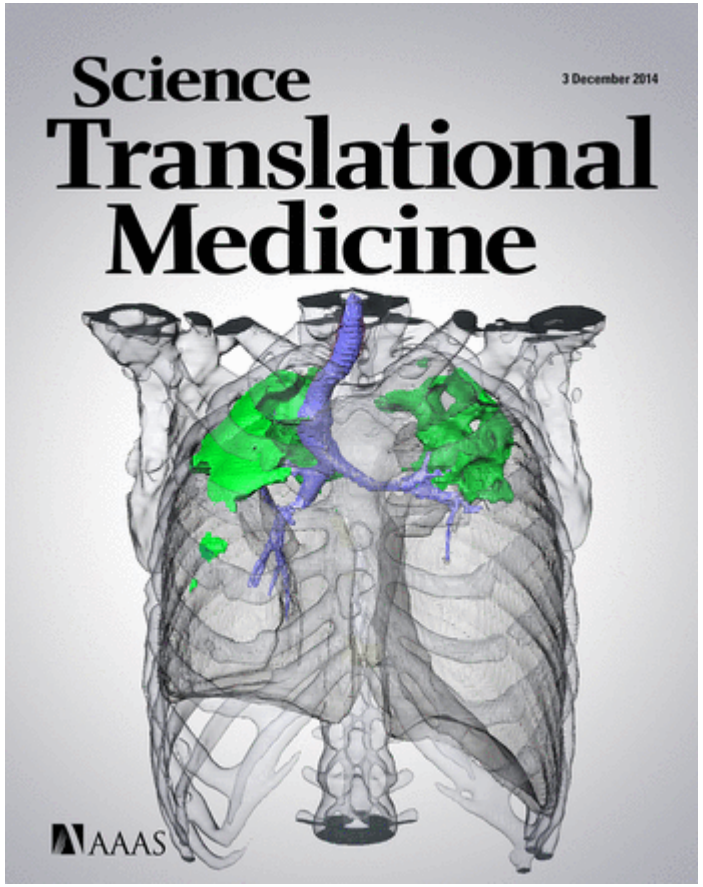
MRI



^{18}F-FDG PET

Gambhir *et al. Journal of the Neurological Sciences*, 2016.

^{18}F-FDG PET/CT correlates with treatment outcome in patients with MDR-TB



- Prospective imaged 35 adults with MDR-TB, on second-line TB treatment, using ^{18}F-FDG PET and CT at 2 and 6 months after starting treatment .
- Imaging assessed by radiologists or automated analyses.
- ^{18}F-FDG PET at 2 months and automated CT at 6 months were more sensitive than sputum smear or solid culture conversion at 2 months, these differences were not statistically significant, possibly because of the small sample size in our study.
- Automated methods were more reliable than radiologists.

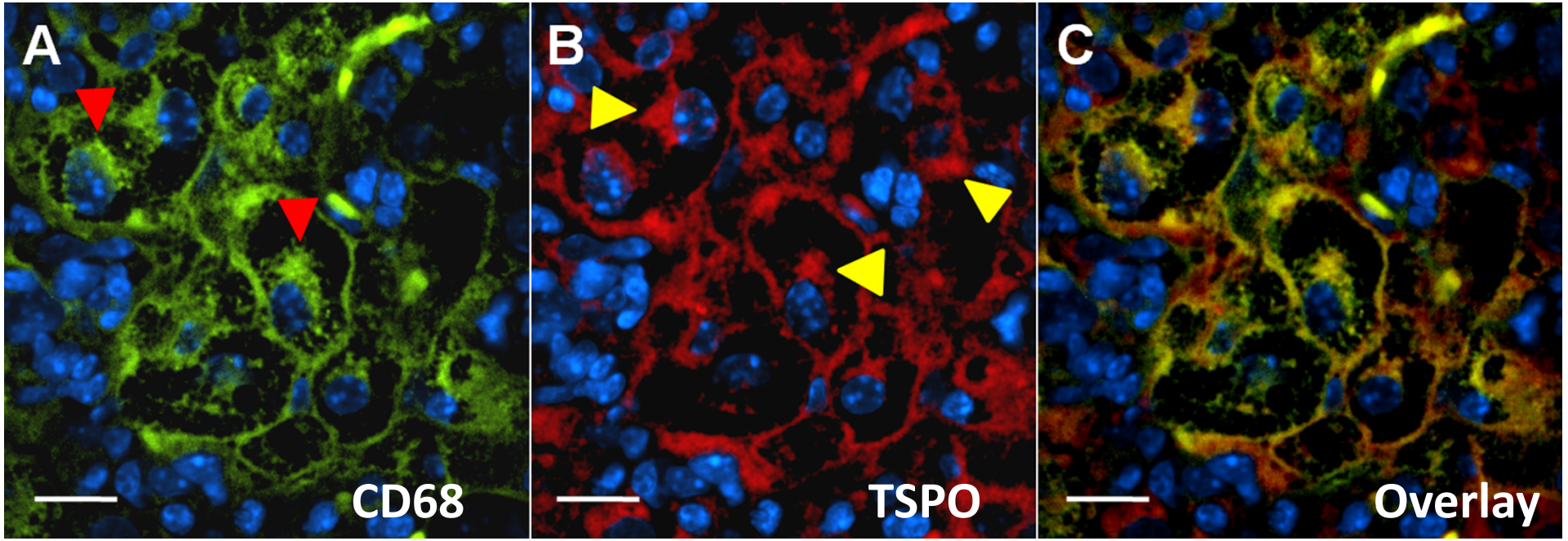
Chen *et al. Sci Transl Med.* 2014

Imaging TB-associated inflammation with iodo-DPA-713

Iodo-DPA-713 is a ligand for translocator protein (TSPO)

Up-regulated in inflamed microglia and macrophages

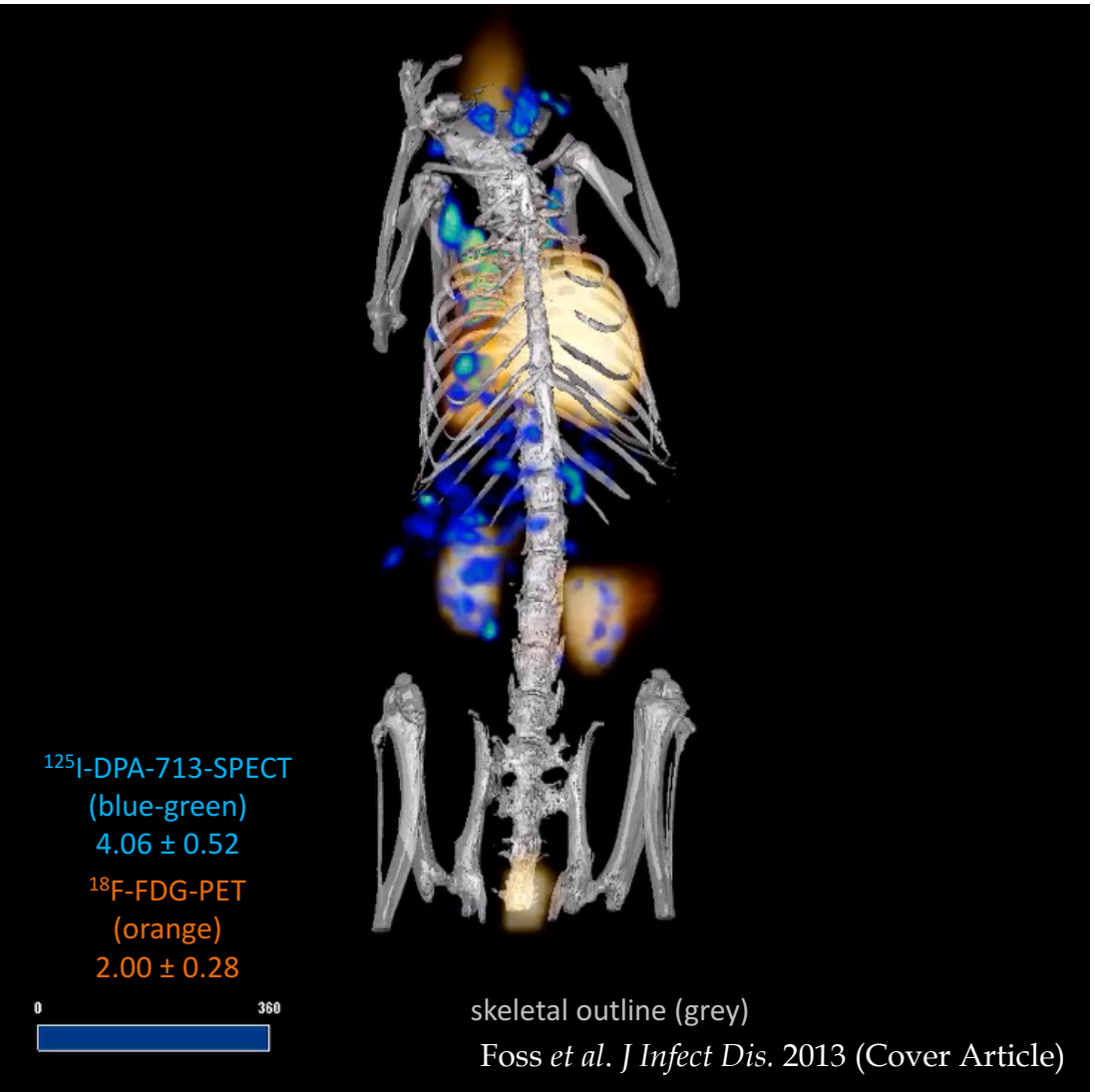
TB lesions full of activated macrophages



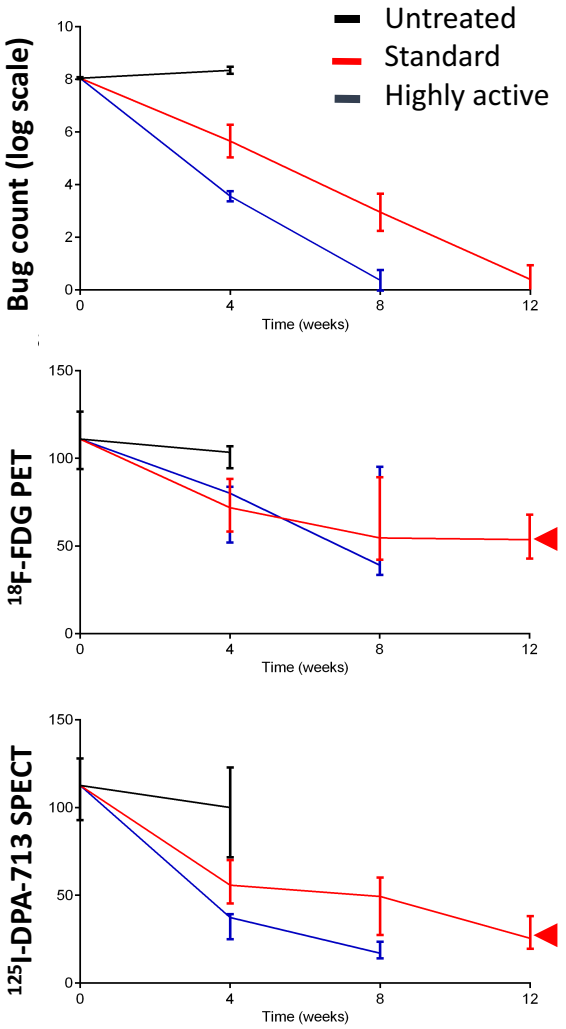
TSPO expression in macrophages within TB lesions

Foss *et al. Journal of Infectious Diseases.* 2013

^{125}I-DPA-713 vs ^{18}F-FDG: Imaging TB-inflammation to monitor treatments



Foss *et al. J Infect Dis.* 2013 (Cover Article)



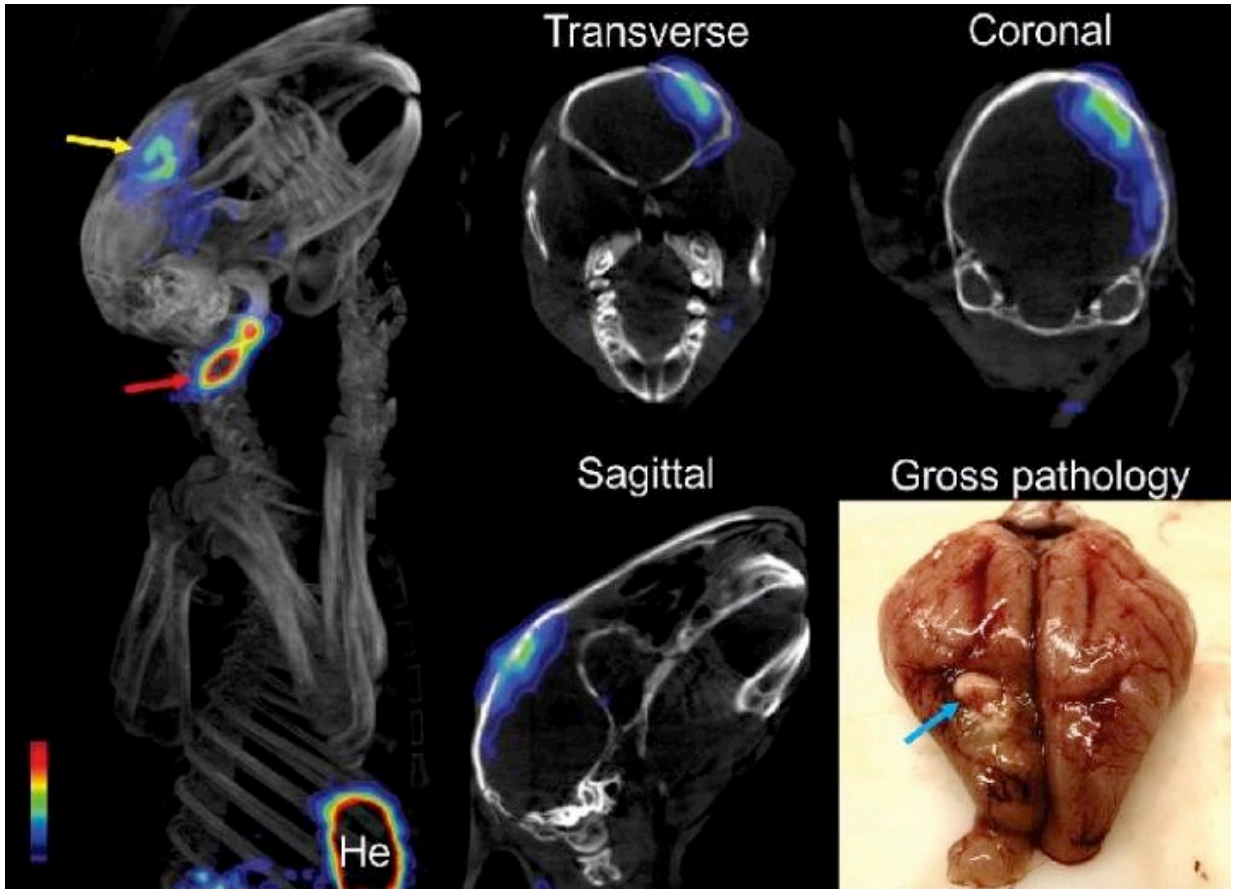
Pulmonary ^{125}I-DPA-713 SPECT, *but not ^{18}F-FDG PET*, correctly identified the bactericidal activities of the TB treatments as early as 4 weeks after starting treatment ($P < 0.03$)

Iodo-DPA-713 bound activated (CD68 $^{+}$) antigen presenting cells and imaging correlated with tissue TNF-α (Spearman's ρ = 0.94; $P < 0.01$)

Significant correlation was found between an increase in ^{125}I-DPA-713 SPECT activity (*but not with ^{18}F-FDG PET*) with bacterial burden at relapse (Spearman's ρ = 0.79; $P < 0.01$)

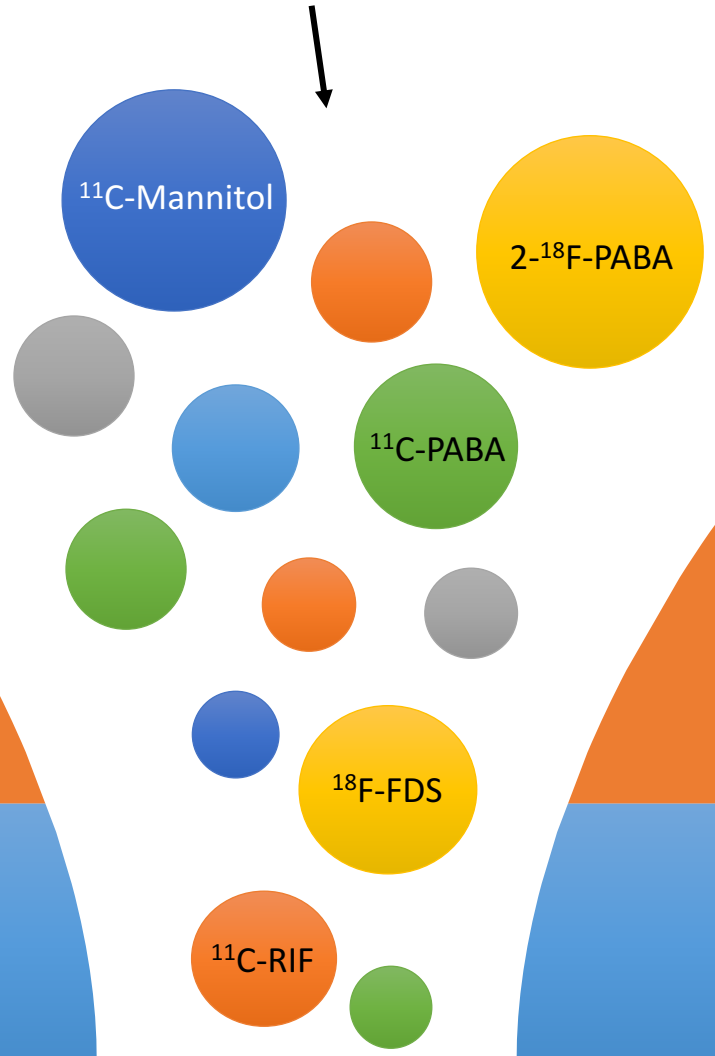
Ordonez *et al. Antimicrob Agents Chemother.* 2015

Imaging TB-inflammation using ^{124}I-DPA-713 PET in a Rabbit model of Pediatric TB meningitis



Tucker *et al*. *Disease Models and Mechanisms*. 2016

Search for small molecules metabolized by prokaryotic-specific pathways



Infection

Discriminate infection from non-infectious processes

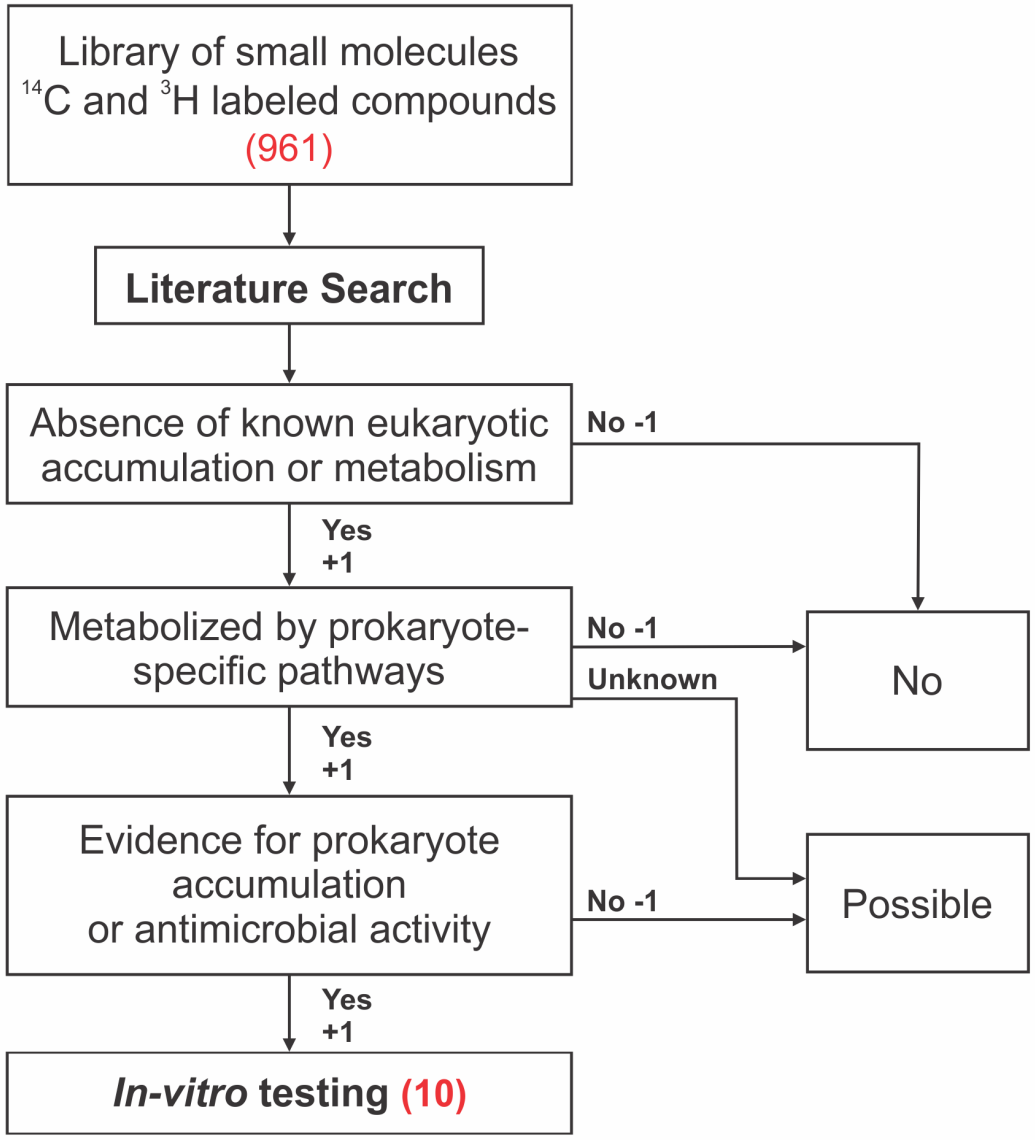
Identification

Categorize the causative bacterial species

Efficacy

Provide information on antibiotic efficacy

Searching for Bacteria-Specific tracers



Ordonez and Weinstein *et al*. *Journal of Nuclear Medicine,* 2017

Searching for Bacteria-Specific tracers

Detect the presence of bacterial infection

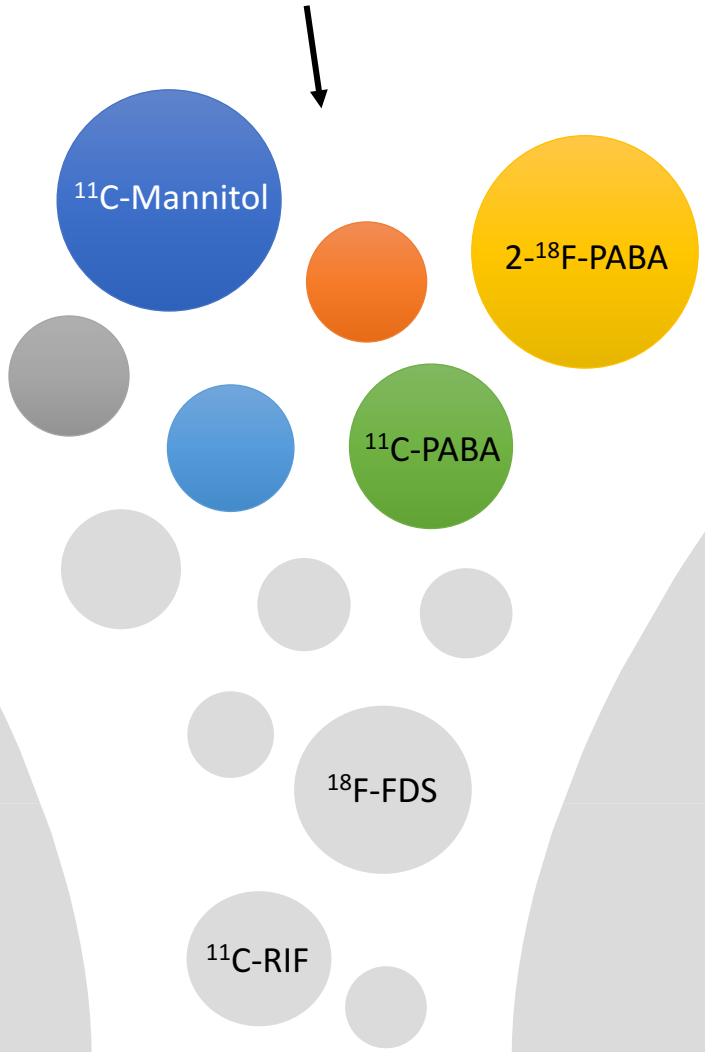
Identify the "type" of bacteria

Name	*S. aureus* (Gram-positive)	*E. coli* (Gram-negative)	*P. Aeruginosa*	Mycobacteria*	Macrophages (J774)
L-Arabinose [1-^{14}C]	0.41 ± 0.03	41.61 ± 9.91	0.21 ± 0.02	0.28 ± 0.01 (Mtb)	0.18 ± 0.01
Cellobiose [^{3}H]	1.81 ± 0.10	0.80 ± 0.05	--	0.13 ± 0.02 (Ms)	--
D-Lyxose [1-^{14}C]	0.03 ± 0.01	1.86 ± 0.14	0.12 ± 0.04	0.35 ± 0.08 (Mtb)	0.04 ± 0.01
D-Mannitol [1-^{14}C]	68.40 ± 7.39	81.80 ± 1.96	0.69 ± 0.05	0.29 ± 0.13 (Mtb)	0.12 ± 0.01
Methyl-α-D-glucopyranoside [methyl-^{14}C]	11.01 ± 0.71	26.78 ± 0.59	--	0.11 ± 0.01 (Ms)	--
PABA [3,5-^{3}H]	16.82 ± 1.03	18.99 ± 5.80	4.02 ± 1.11	32.93 ± 4.73 (Mtb)	0.11 ± 0.01
L-Rhamnose [^{3}H]	4.96 ± 0.13	4.73 ± 0.07	0.24 ± 0.04	3.82 ± 0.84 (Mtb)	0.60 ± 0.02
Shikimic acid [3-^{3}H]	7.54 ± 0.01	1.52 ± 0.02	1.31 ± 0.02	0.17 ± 0.01 (Ms)	--
D-Sorbitol [^{14}C] (^{18}F-FDS)†	0.47 ± 0.09	72.20 ± 9.09	0.52 ± 0.46	--	0.21 ± 0.01
D-Xylose [1-^{14}C]	0.31 ± 0.01	73.94 ± 2.06	0.53 ± 0.08	0.18 ± 0.02 (Mtb)	0.19 ± 0.01

**Mycobacterium smegmatis* = Ms or *Mycobacterium tuberculosis* = Mtb
† 2-[^{18}F]-fluorodeoxysorbitol (^{18}F-FDS) used for uptake assays
Data represented as mean ± SD

Ordonez and Weinstein *et al. Journal of Nuclear Medicine,* 2017

Search for small molecules metabolized by prokaryotic-specific pathways



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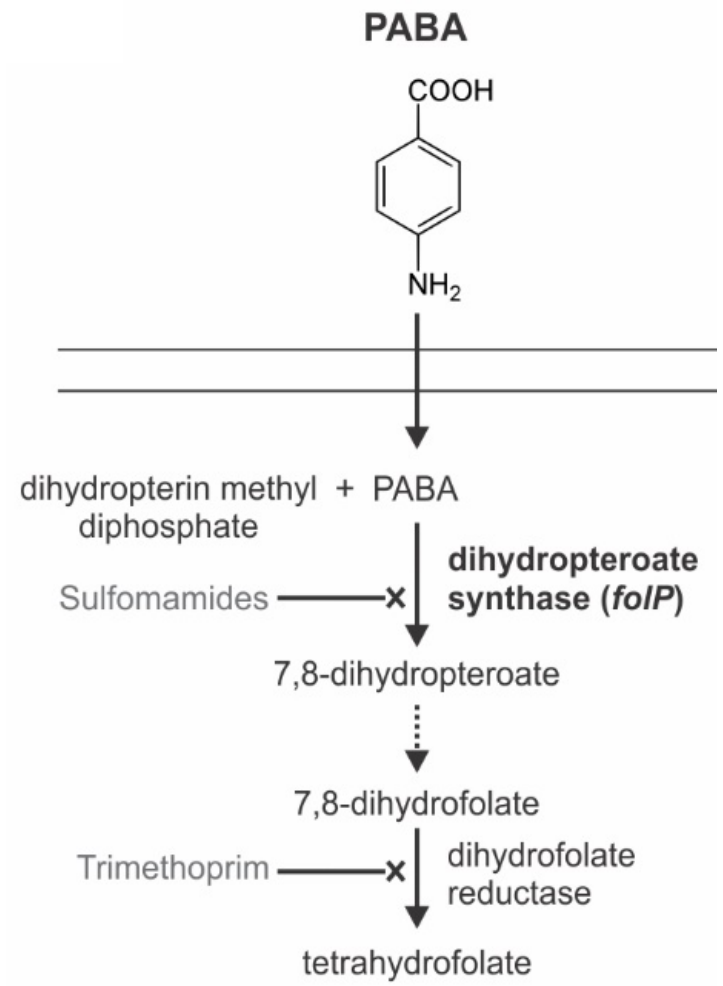
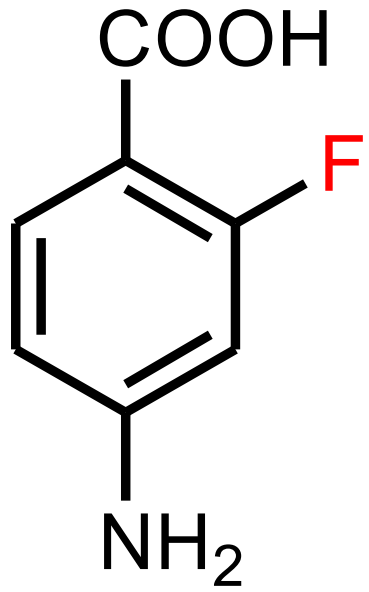
2-^{18}F-PABA for Infection Diagnosis



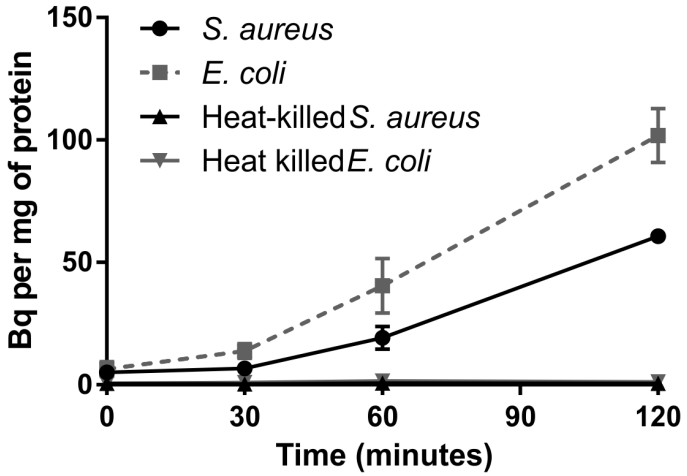


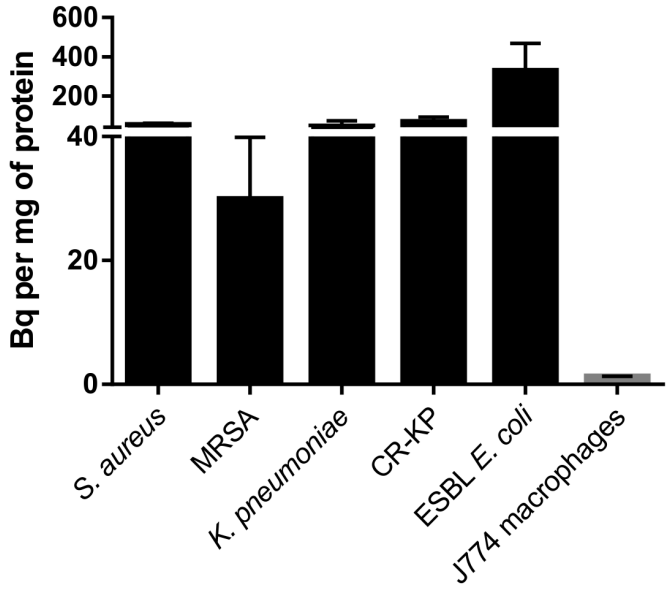
2-Fluoro-PABA

Collaboration with Stony Brook University

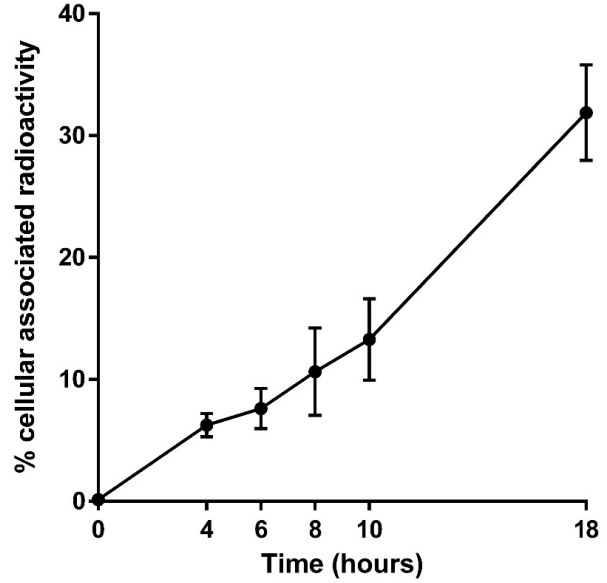
Ordonez and Weinstein *et al. Journal of Nuclear Medicine,* 2016

2-^{18}F-PABA for Infection Diagnosis





In vitro uptake in *M. tuberculosis*



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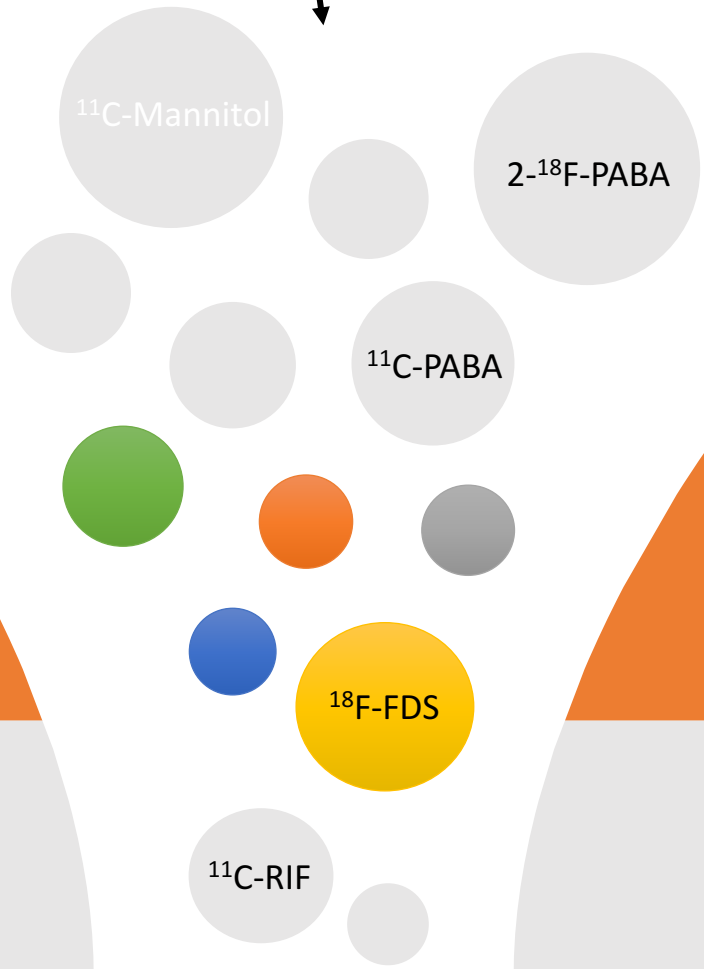
Ordonez and Weinstein *et al. Journal of Nuclear Medicine,* 2016

Search for small molecules metabolized by prokaryotic-specific pathways



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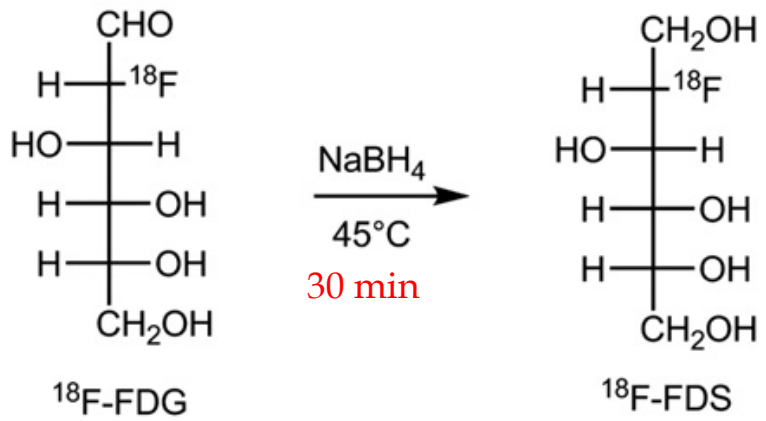
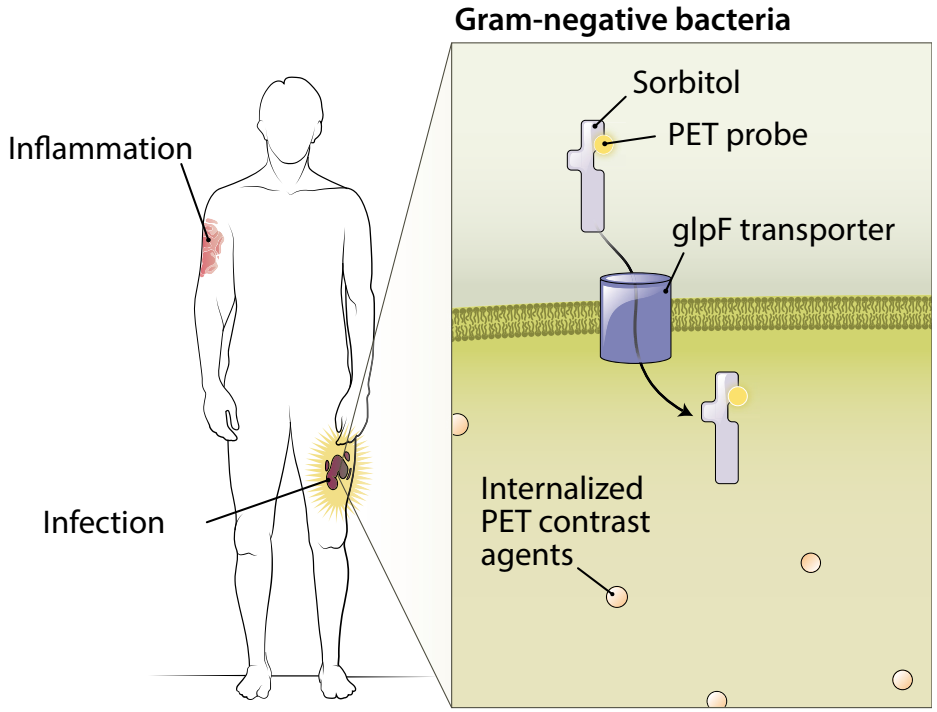
Sugar Shot for Bacteria

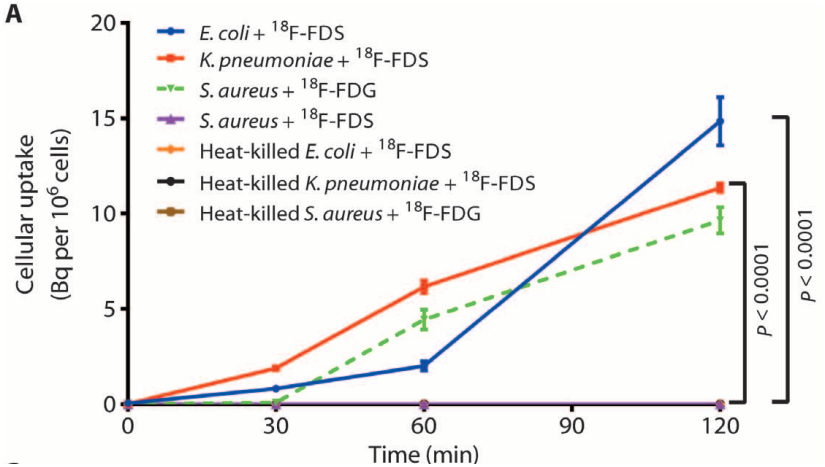
2-^{18}F-Fluorodeoxysorbitol (^{18}F-FDS)

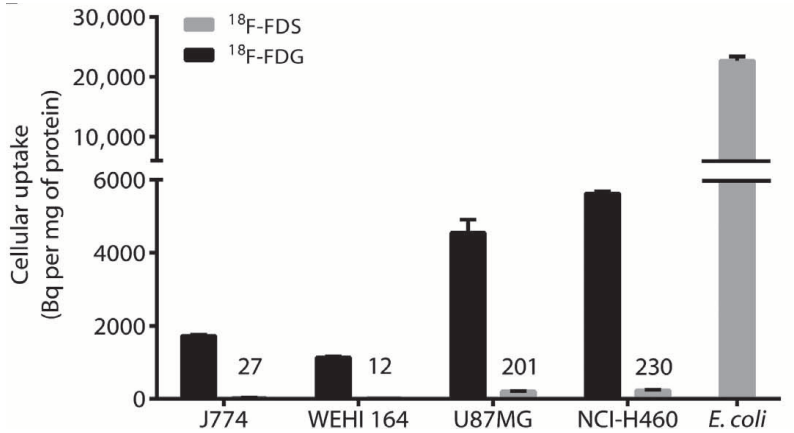


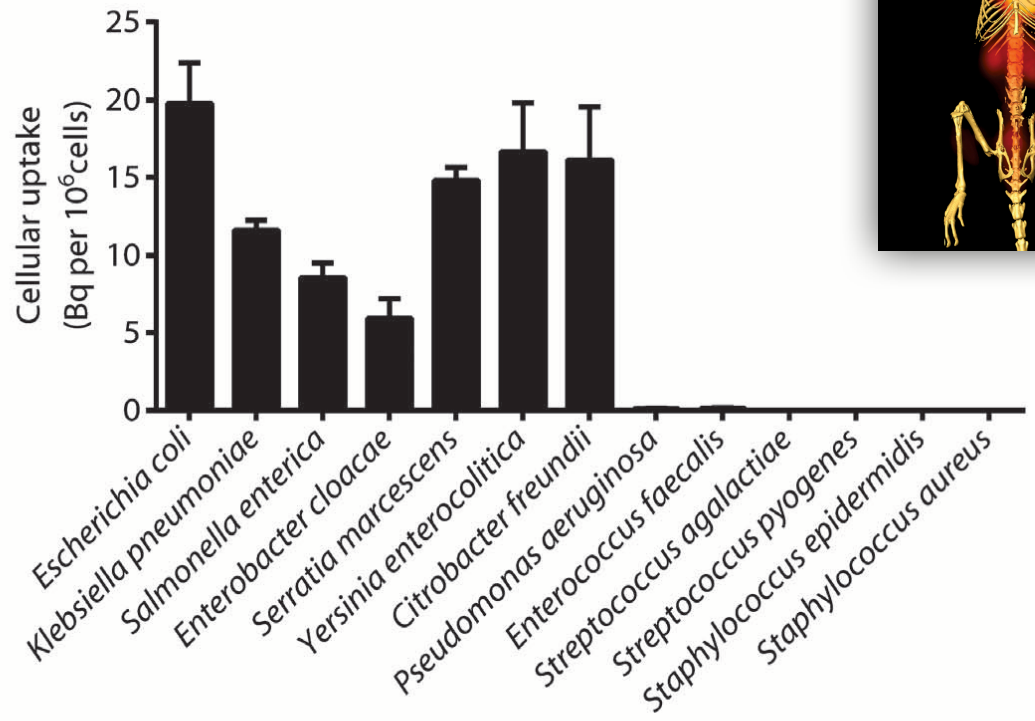


Wang X *et al.* Bacterial imaging comes of age. *Science Translational Medicine,* 2014

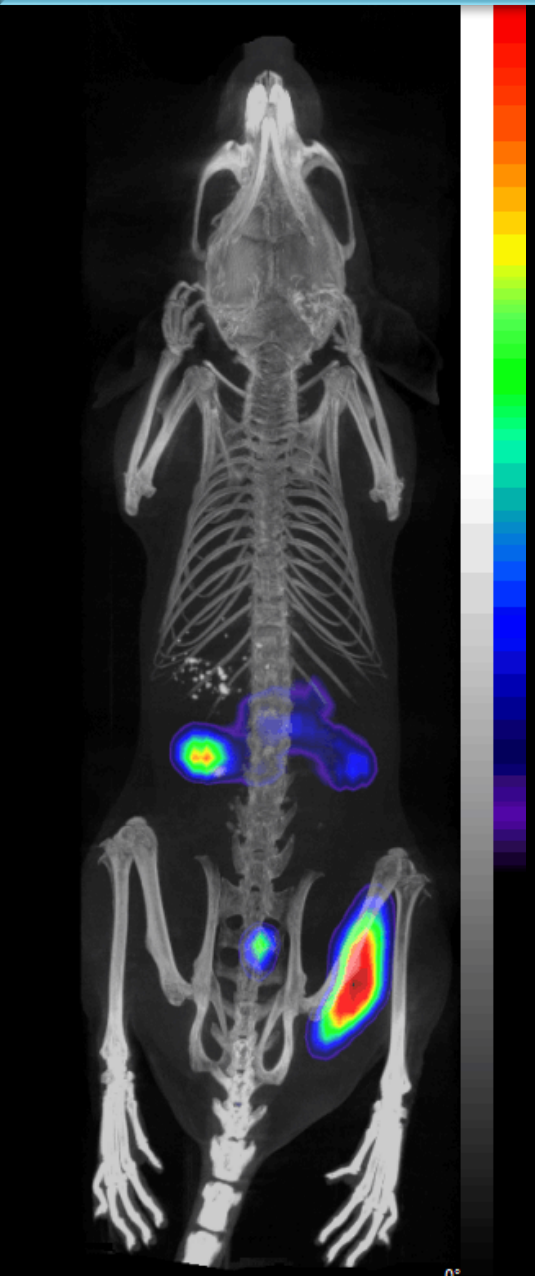
In vitro uptake of ^{18}F-FDS in Bacterial Pathogens and Mammalian cell lines



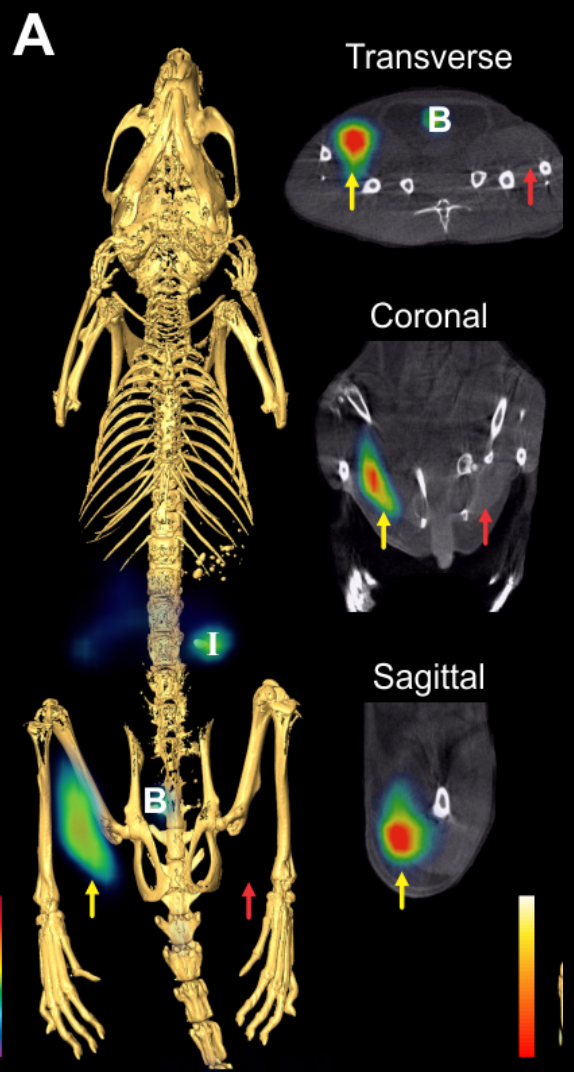


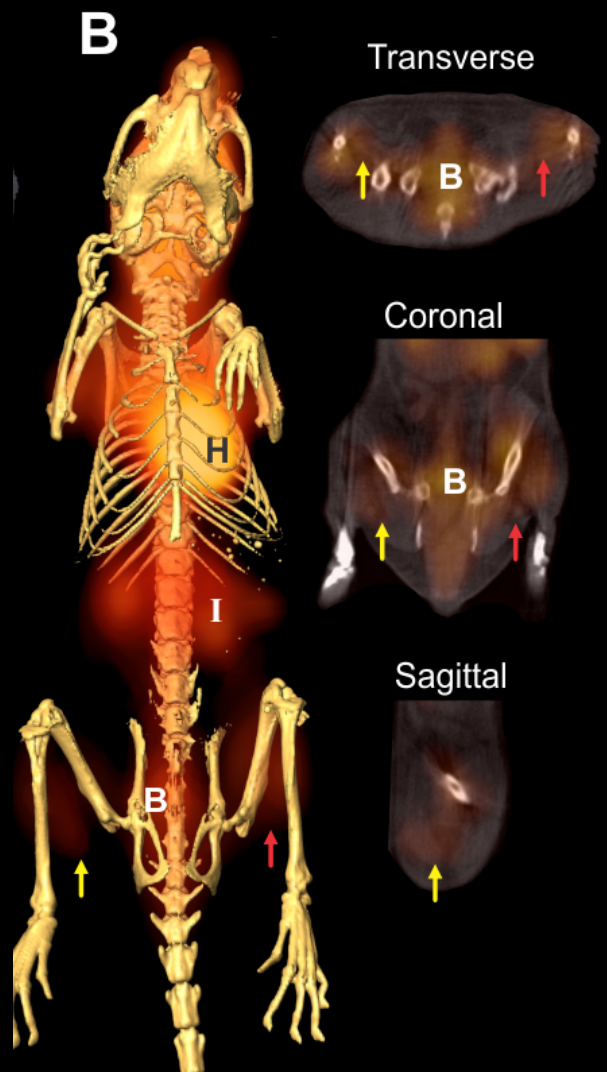


Weinstein and Ordonez *et al*. *Science Translational Medicine,* 2014.



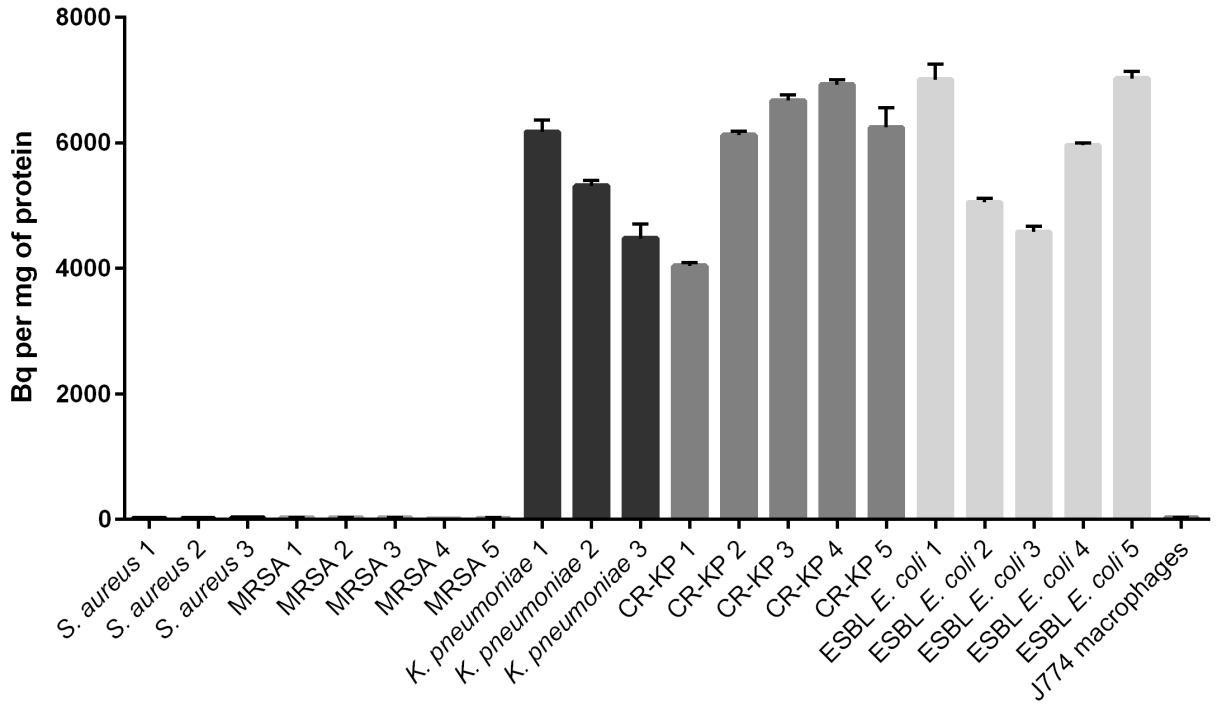
^{18}F-FDS PET can differentiate infection sites from sterile inflammation





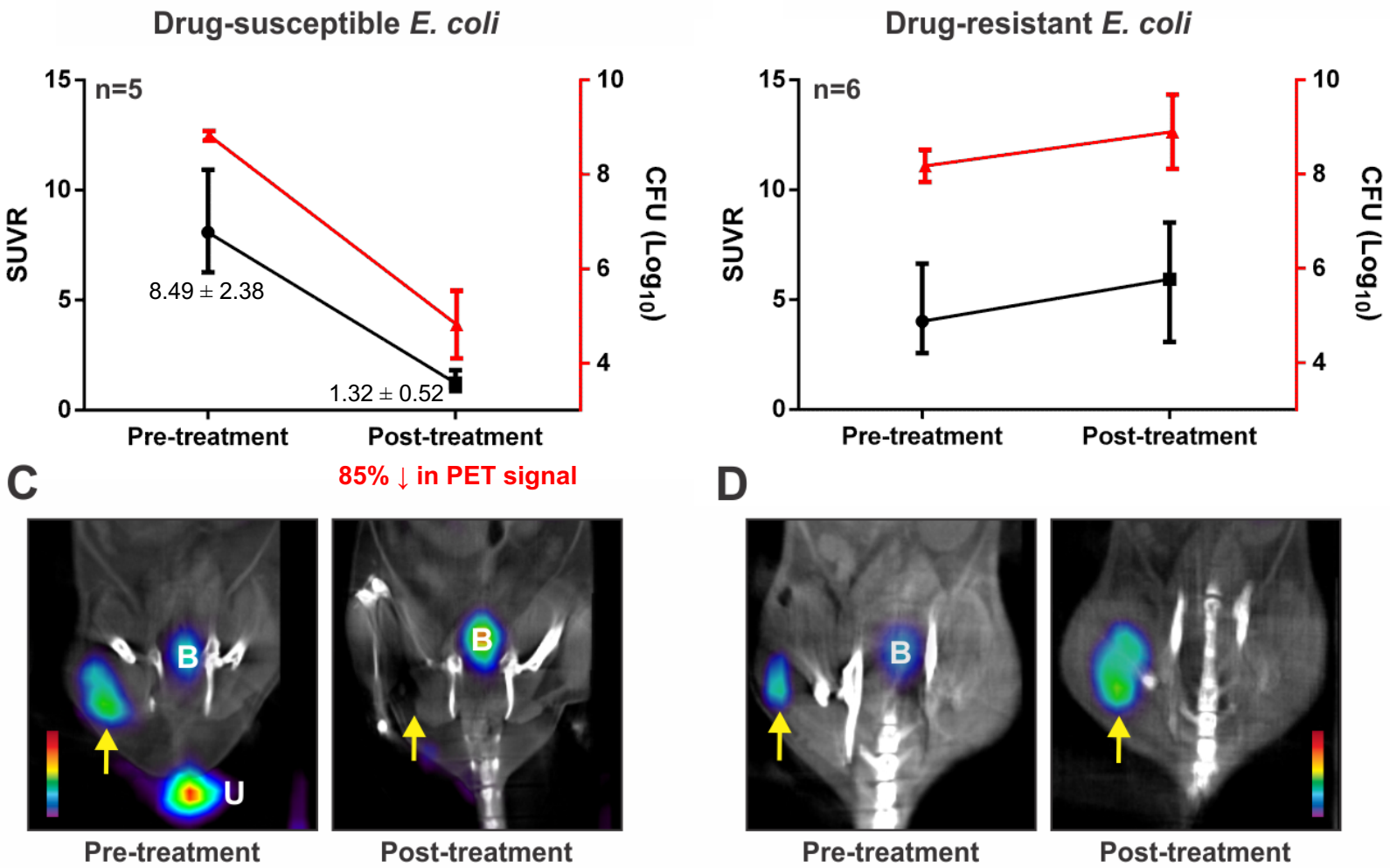
^{18}F-FDS uptake in clinical Multidrug-Resistant Enterobacteriaceae strains

- Extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae
- Carbapenem-resistant Enterobacteriaceae (CRE)



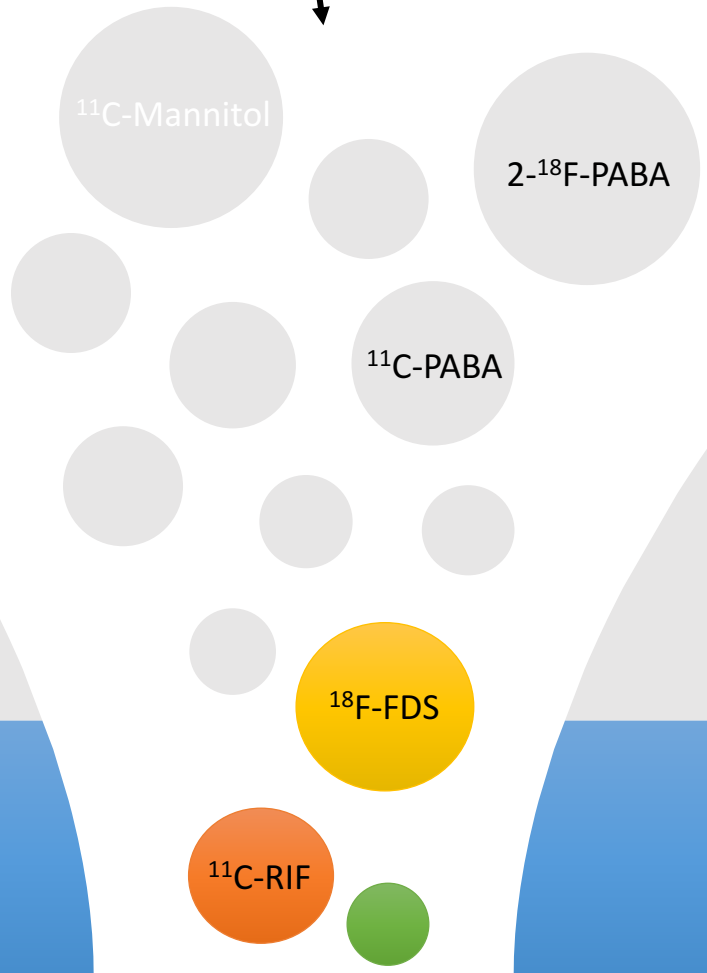
Weinstein and Ordonez *et al*. *Science Translational Medicine*, 2014.

Monitoring Antimicrobial Efficacy in Multidrug-Resistant Infections



Weinstein and Ordonez *et al*. *Science Translational Medicine,* 2014.

Search for small molecules metabolized by prokaryotic-specific pathways



Infection

Discriminate infection from non-infectious processes

Identification

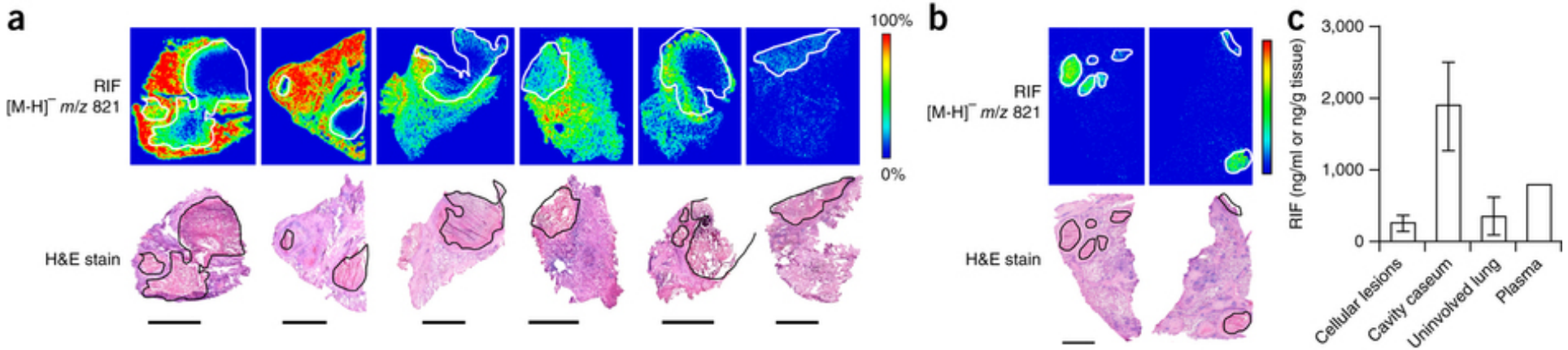
Categorize the causative bacterial species

Efficacy

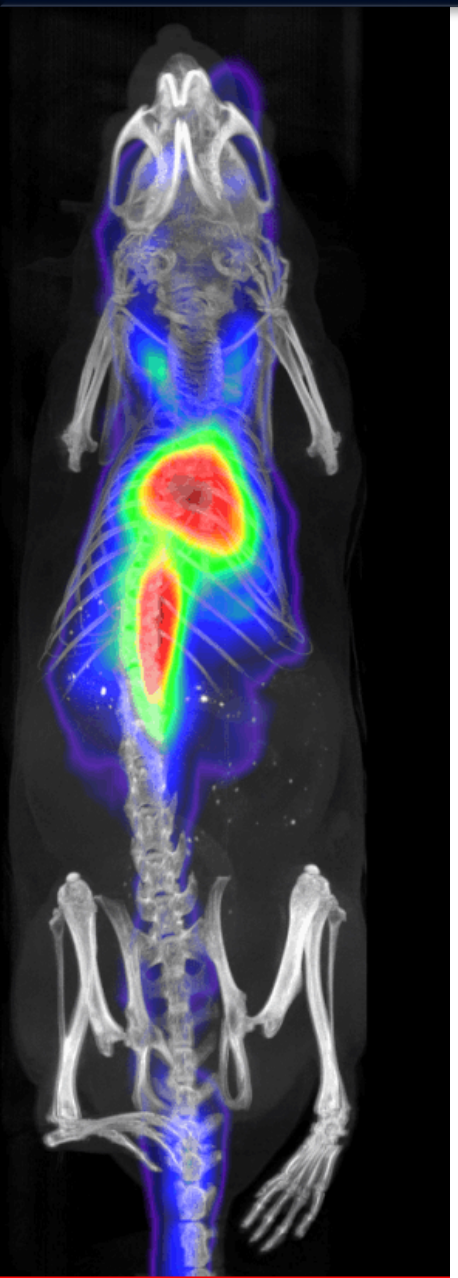
Provide information on antibiotic efficacy

Are we using the right doses of antibiotics?

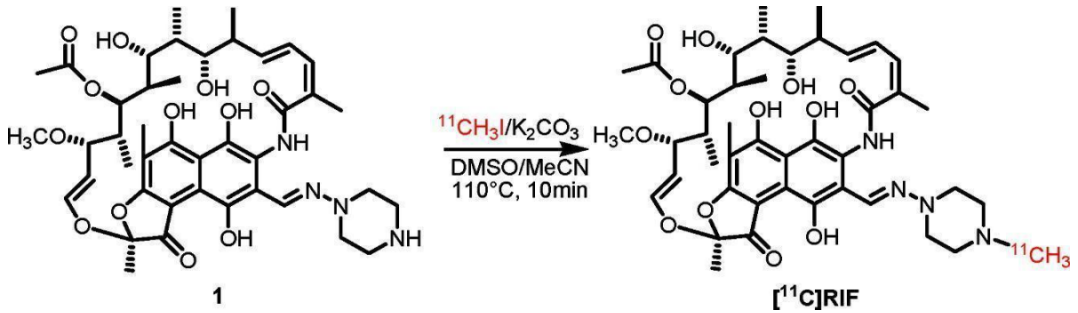
- Current doses based on blood levels and historic measures of efficacy
- Inappropriate levels in target tissues can lead to treatment failure, selection of resistant organisms, or toxicity / organ failure
- Rifampin, first line TB drug, with significant potential for shortening TB treatments

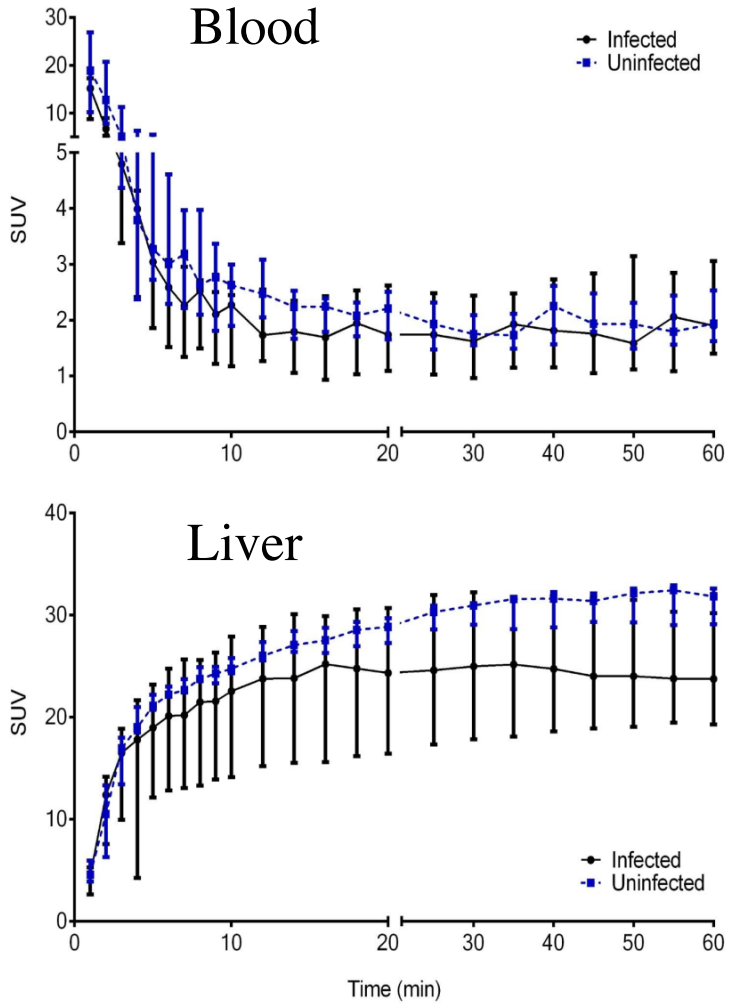


Prideaux *et al*. *Nature Medicine*, 2015.



^{11}C-Rifampin

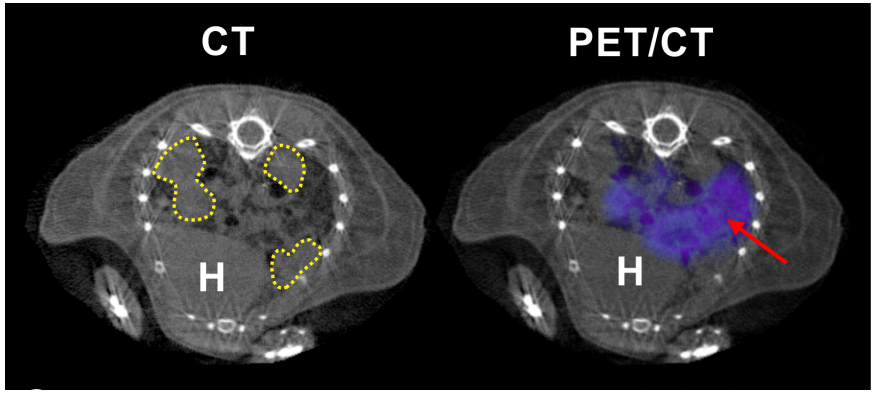


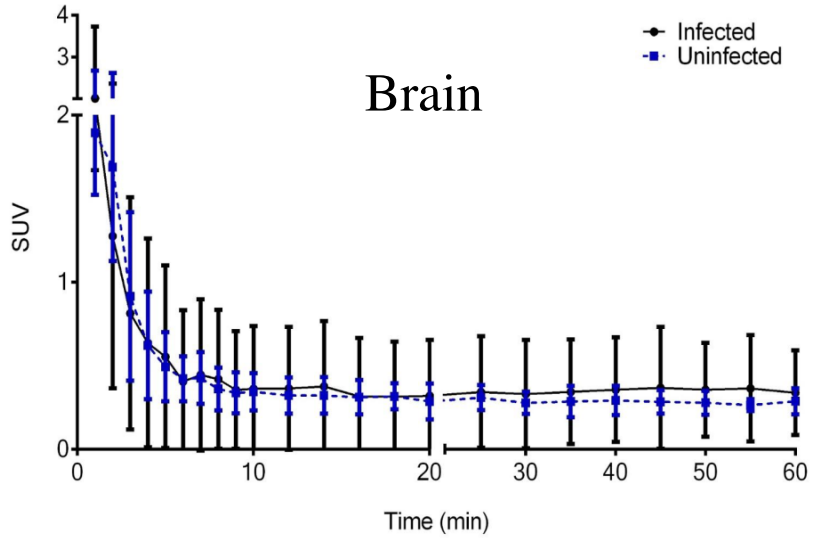


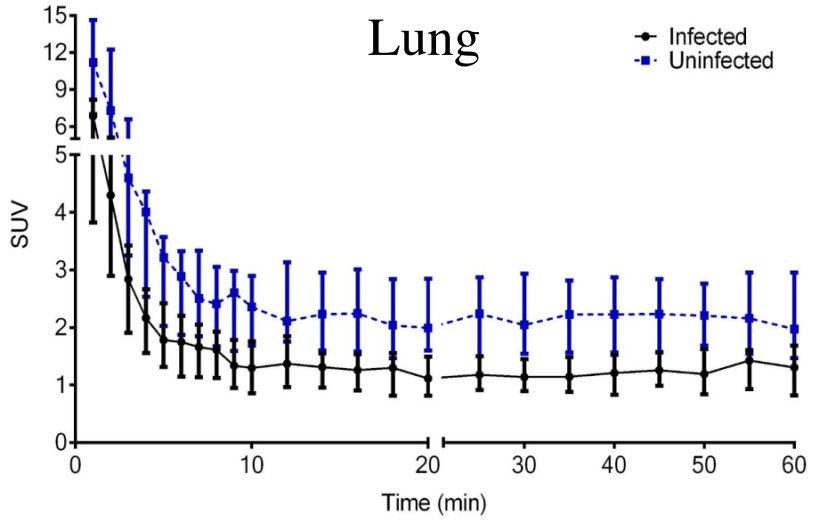
^{11}C-Rifampin PET/CT of a *M. tuberculosis*-infected mouse post IV injection

Liu *et al. Journal of Medicinal Chemistry*, 2010.
DeMarco and Ordonez *et al. Antimicrobial Agents and Chemotherapy*, 2015.

Levels in brain are 14.55 ± 1.67% of blood concentrations







Data represents Mean ± Standard Deviation (n=5)

DeMarco and Ordonez *et al. Antimicrobial Agents and Chemotherapy*, 2015.

Summary

- Noninvasive imaging can provide novel insights into disease pathogenesis, that may not be possible with conventional methods
  - Monitoring inflammation: ^{18}F-FDG and ^{124}I-DPA-713
- Need for pathogen-specific imaging
- Pipeline of bacteria-class specific imaging probes
  - 2-^{18}F-PABA – a folate precursor – promising agents for bacterial imaging (including *M. tuberculosis*)
  - ^{18}F-FDS can rapidly and specifically detect *Enterobacteriaceae*
- PET can be used as a non-invasive alternative for measuring multi-compartment drug PK *in situ* and study drug penetration (and toxicities) at the site of infection, and into privileged sites (e.g. TB meningitis)

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