WMIS
World Molecular Imaging Society

Imaging of Infection

A WMIS Webinar Series

TODAY'S WEBINAR

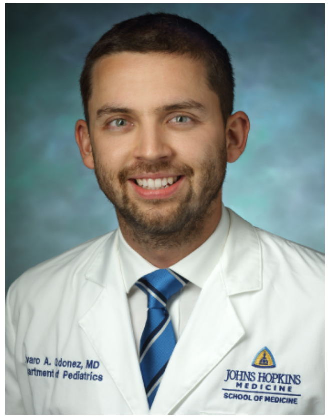
"Defining the Infectious Etiologies with Imaging"

Tuesday, April 14, 2020
11:00 AM – 12:00 PM EDT

Presenters:

Mark A Sellmyer, MD, PhD
Assistant Professor of Radiology
University of Pennsylvania

@sellmyerlab



Alvaro A. Ordonez, MD
Assistant Professor
Department of Pediatrics
Johns Hopkins University
School of Medicine

@AlvaroAOrdonez

Hosted by:

David Wilson, MD, PhD
Associate Professor
Chief of VA Neuroradiology
T32 Program Associate Director
University of California San Francisco

https://radiology.ucsf.edu/research/labs/wilson

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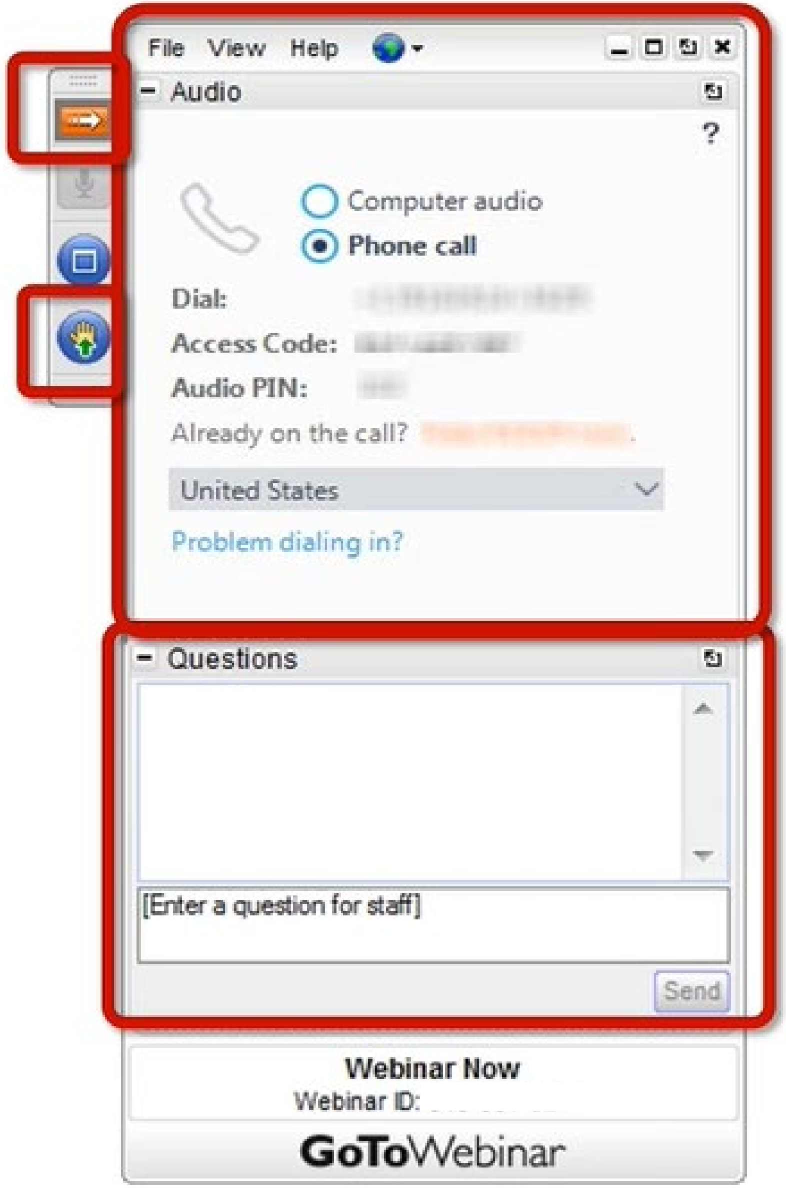
Imaging of Infections
A WMIS Interest Group



Your Participation

Join audio:

- Choose “Computer audio”
- Chose “Phone Call” and dial in using the information provided

**All participants are muted for the duration of the webinar*

Questions/Comments:

- Submit questions and comments through the question box in the side panel
- Submit questions/comments throughout the webinar, they will be addressed at the end

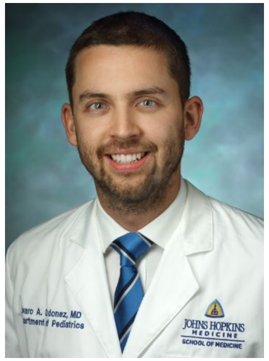
Note: Today’s presentation is being recorded and will be emailed in a follow-up email and posted on the WMIS website.

Biography:

Mark A. Sellmyer, MD PhD
Assistant Professor,
Department of Radiology
Department of Biochemistry
University of Pennsylvania
School of Medicine

- Working at interface of chemical biology and molecular imaging
- New tools for bacterial infection imaging
- Imaging gene and cell therapies including CAR T cells
- Molecular switches for controlling protein expression

@sellmyerlab



Alvaro A. Ordonez, MD
Assistant Professor,
Department of Pediatrics
Johns Hopkins University
School of Medicine

- Working in the development of bacteria-specific PET imaging agents, primarily for tuberculosis
- Development of radiolabeled antibiotics to optimize the dosing of infected patients

@AlvaroAOrdonez

David Wilson, MD PhD
Associate Professor,
Department of Radiology
Chemistry and Chemical Biology
UCSF

- Metabolism and microenvironment-targeted imaging methods
- Hyperpolarized 13C MRI and 11C PET
- Cell-wall targeted probes

https://radiology.ucsf.edu/research/labs/wilson

Defining the Infectious Etiologies with Imaging

Mark A. Sellmyer, MD, PhD

Alvaro A. Ordonez, MD

David M. Wilson, MD, PhD

UCSF
University of California
San Francisco

Penn Medicine

JOHNS HOPKINS
MEDICINE

Defining the Infectious Etiologies with Imaging

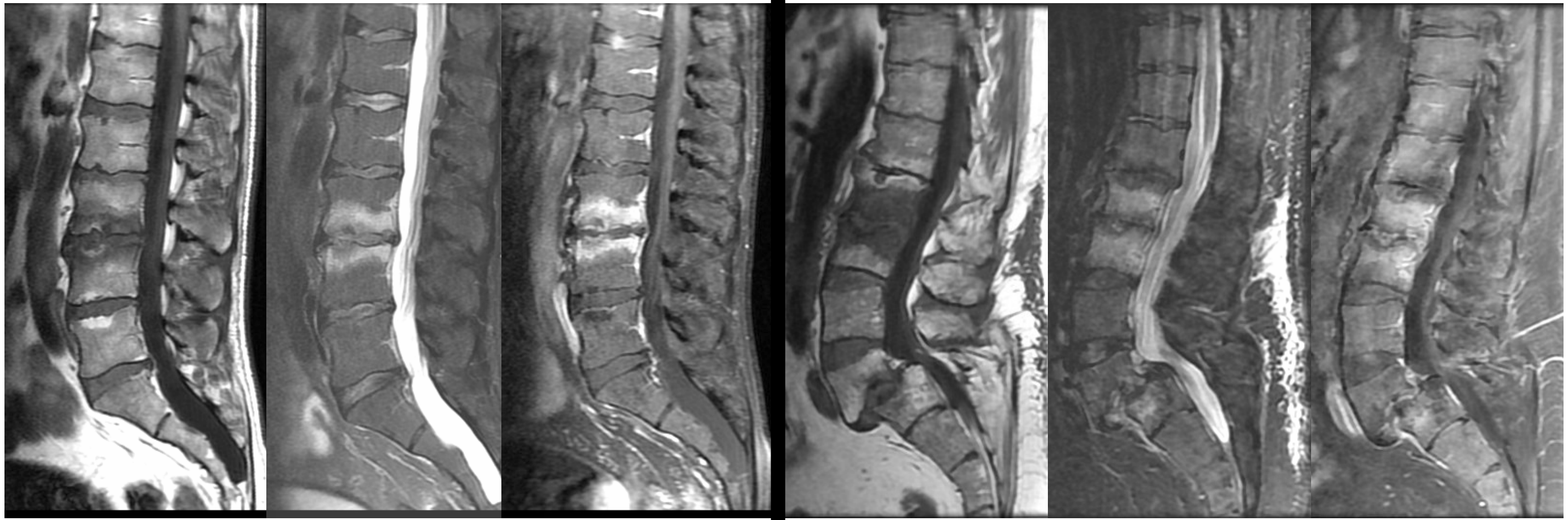
- Introduction
- Need for bacteria-specific imaging
- Bacteria-specific imaging agents
  - Metabolism based
  - Antibiotic based
- Immuno-PET
- Q & A panel discussion

Clinical motivations for Bacteria-Specific Imaging

Diagnosis: Diskitis / Osteomyelitis

- T2: Disc, marrow bright
- T1: Marrow dark
- T1 + gd: Disc, endplate enhance
- End plate destruction
- +/- rim enhancing collection

Main mimic- DJD



T1 T2 T1+ | T1 T2 T1+

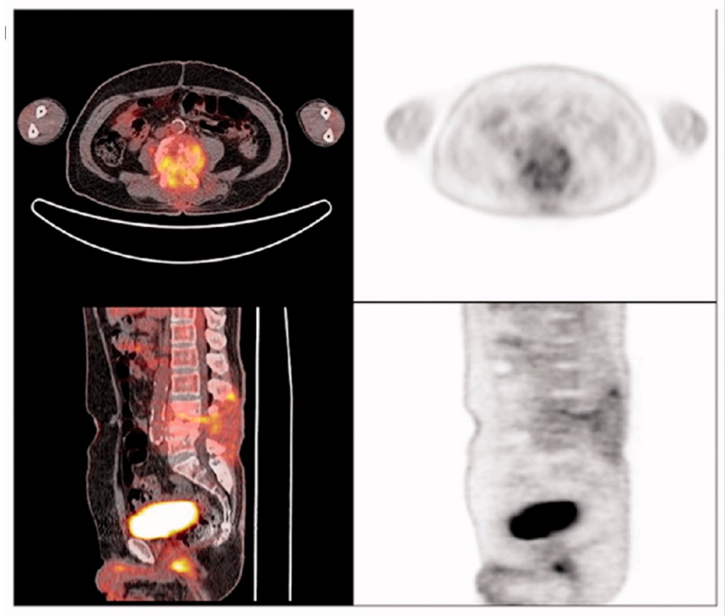
Degenerative *Infection*

- Enhancement, T2 common
- Early stage of infection
- Absence of complications- abscess

MOTIVATION

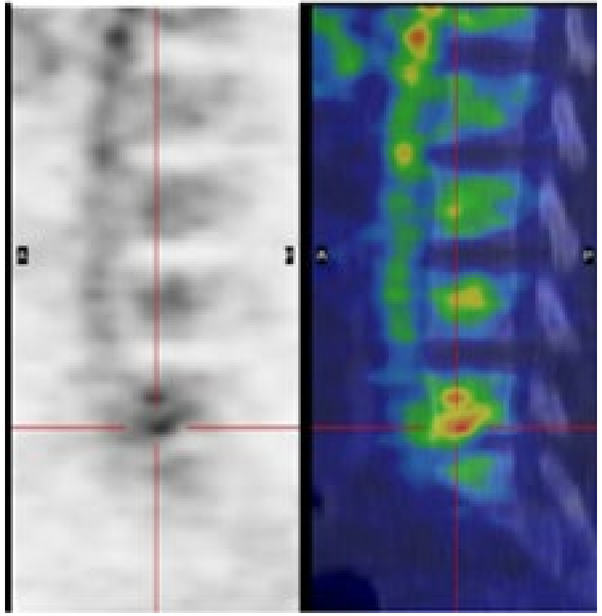
Current Imaging Tools

^{18}F-FDG



Nakahara et al. 2015

$^{67/68}$Ga-cit



Nanni et al. 2010

^{111}In-WBC

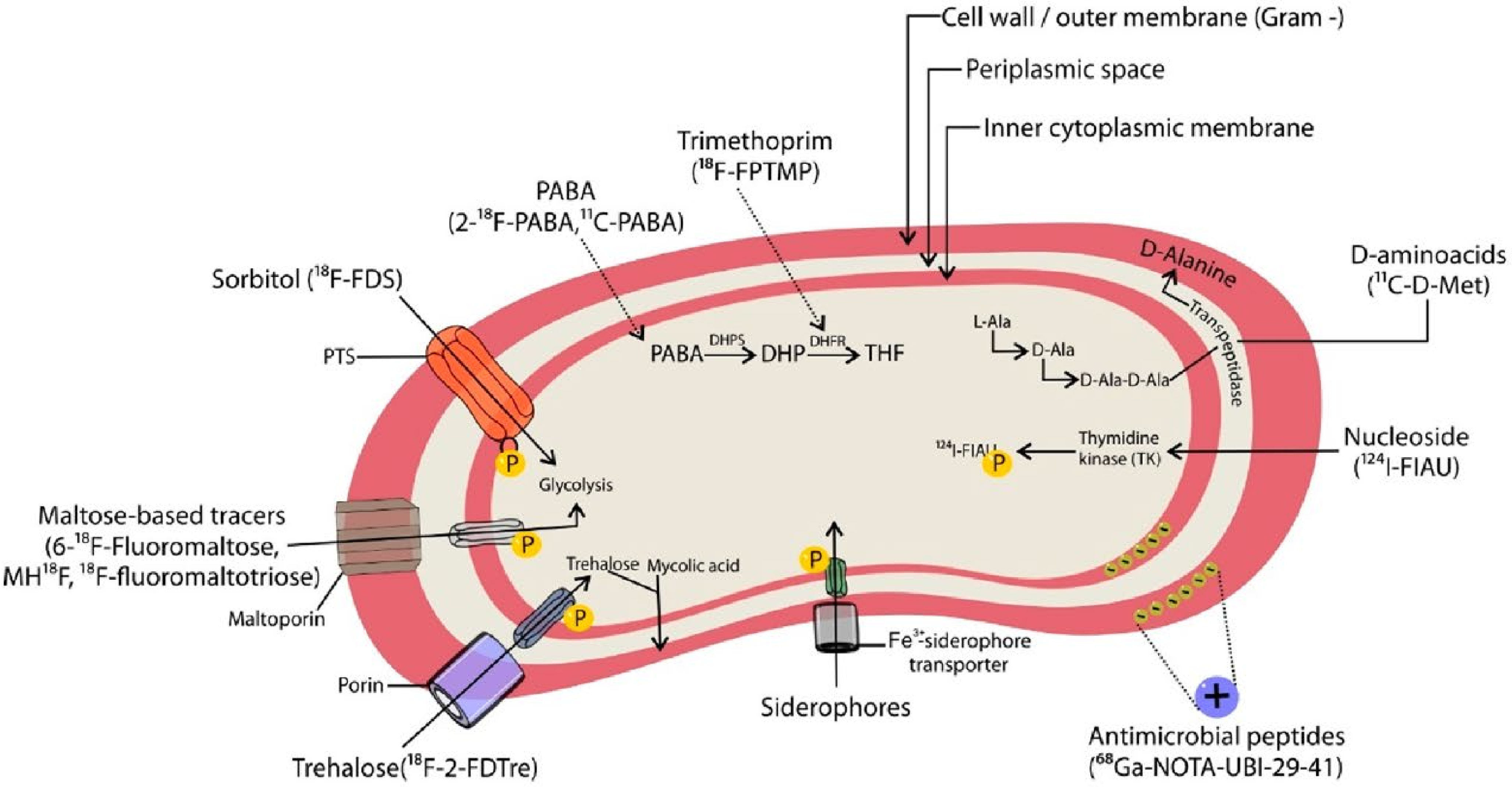
Palestro et al. 1991

- Include Iodinated and gadolinium-based contrast for CT and MR, FDG PET, Gallium, and tagged WBC scans.
- *Limitations:* Host immune response, modulation with therapy, immunocompromised patients

KEY GOALS: Bacteria-specific PET

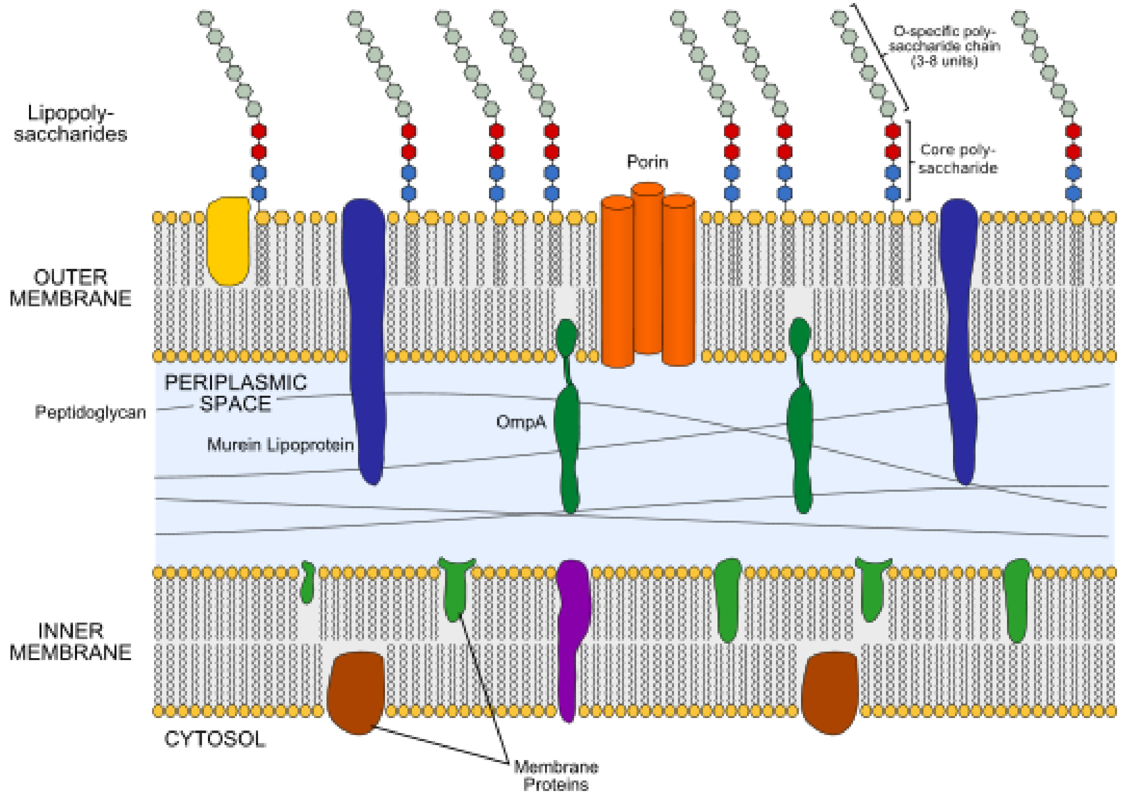
- Determine if this experiment can work
- Broad sensitivity Gram+/- ^{18}F tracer
- Specificity bacteria > human metabolism/ microbiome
- Ease of experiment
- Working together- multicenter trials, picking the right patients

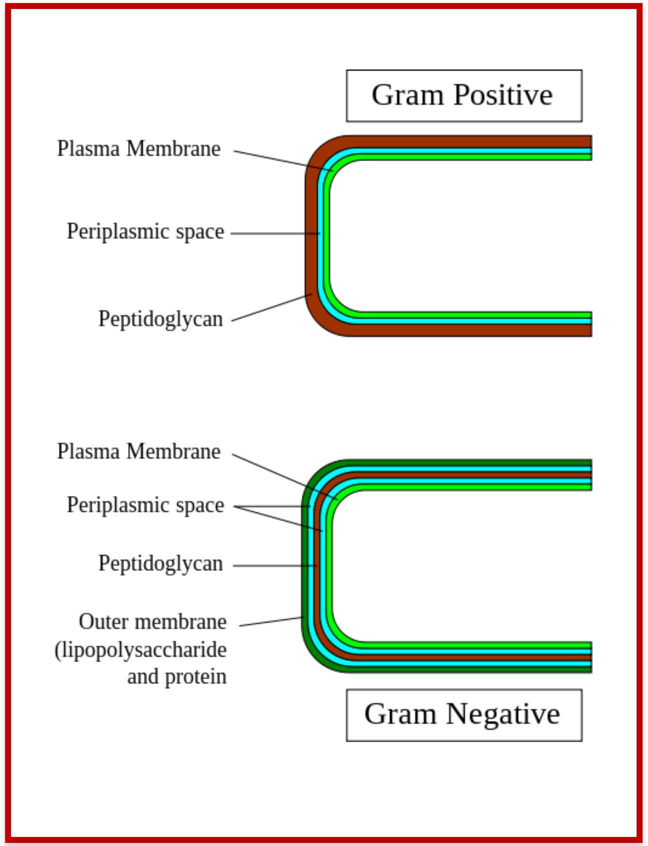
Molecular targets for Bacteria-specific PET



Mota et al. J Med Chem 2020

Bacterial cell wall structure



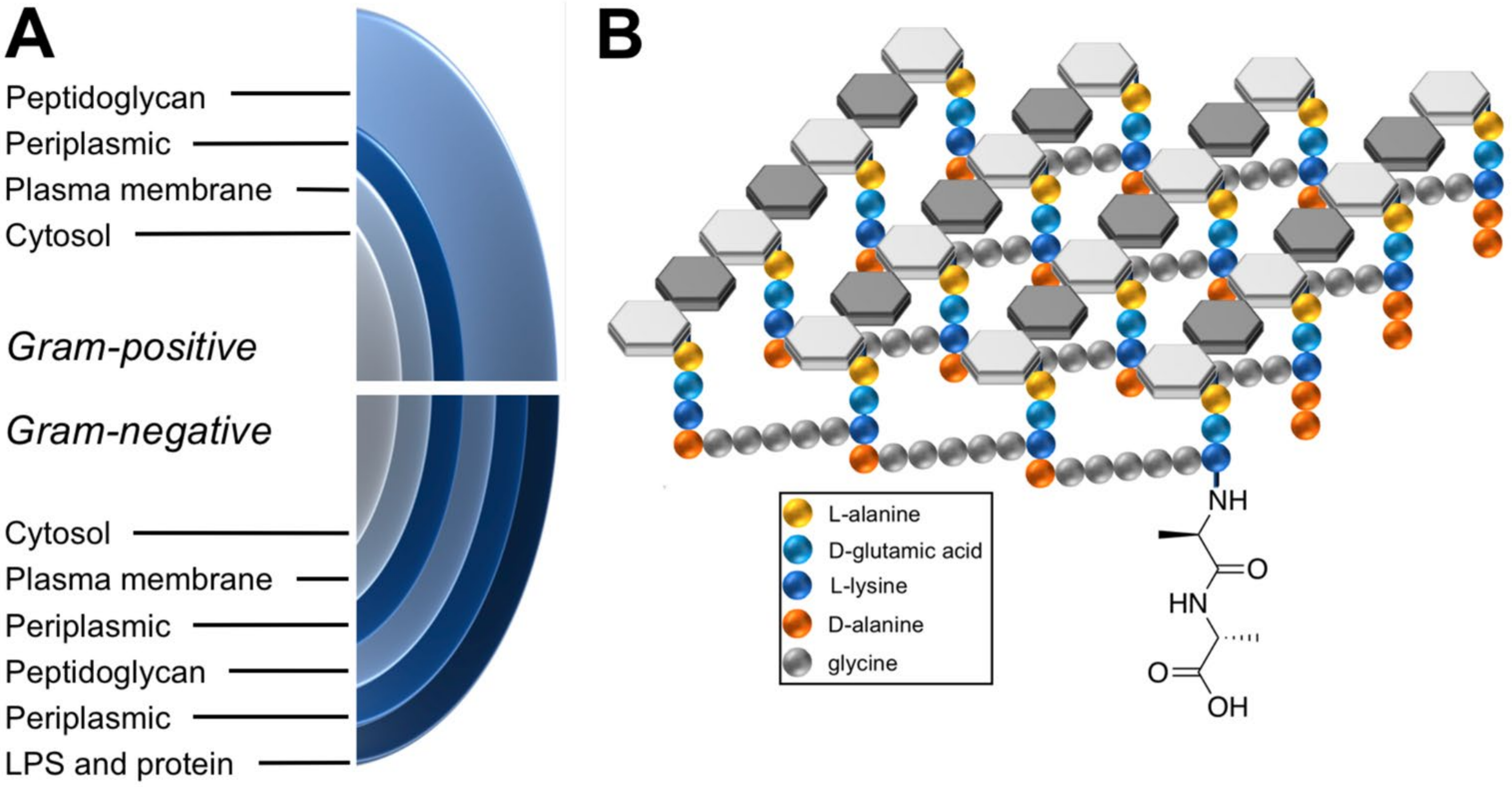


Courtesy of wikimedia.org

- Peptidoglycan- basis for “Gram staining.”
- Both gram-negatives and gram-positives have peptidoglycan
- 90% versus 10% dry-weight

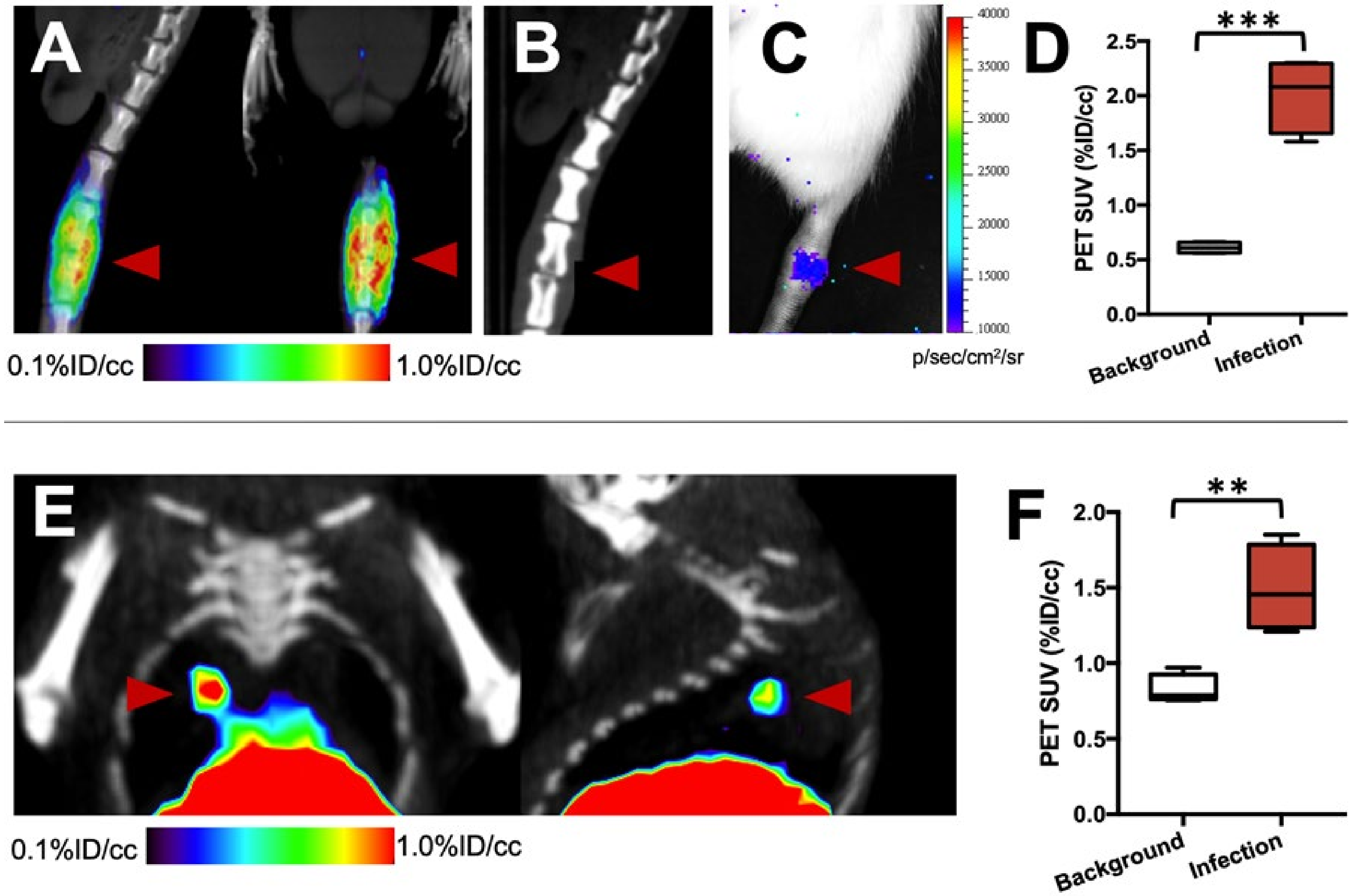
SENSITIVITY

Newer approach: D-[^{11}C]Ala



Parker et al. *ACS Cent. Sci.* 2020

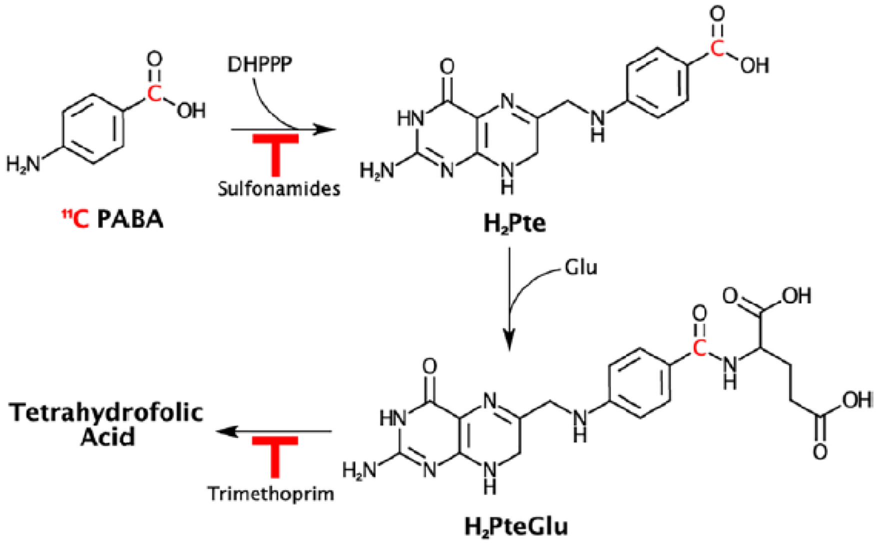
Results: D-[^{11}C]Ala

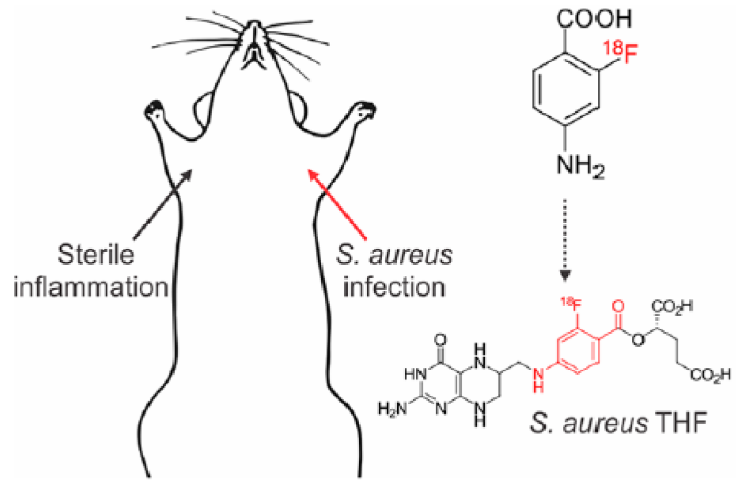


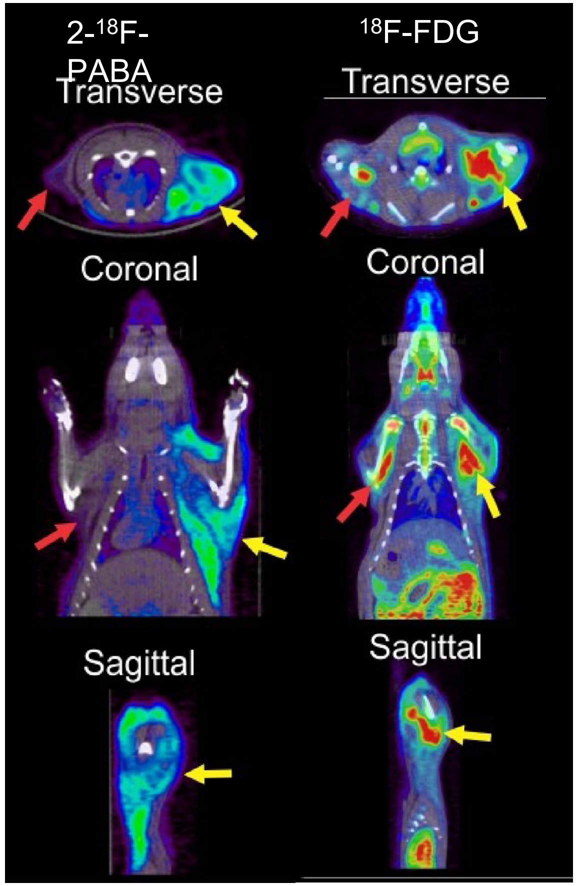
Parker et al. *ACS Cent. Sci.* 2020

Targeting the Bacterial Folate Synthesis

^{11}C-PABA and 2-^{18}F-PABA





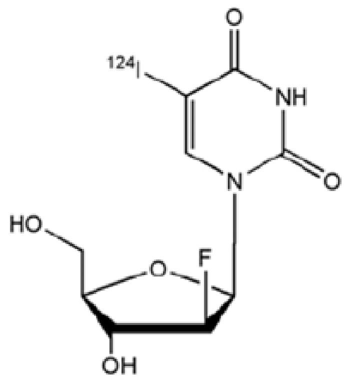


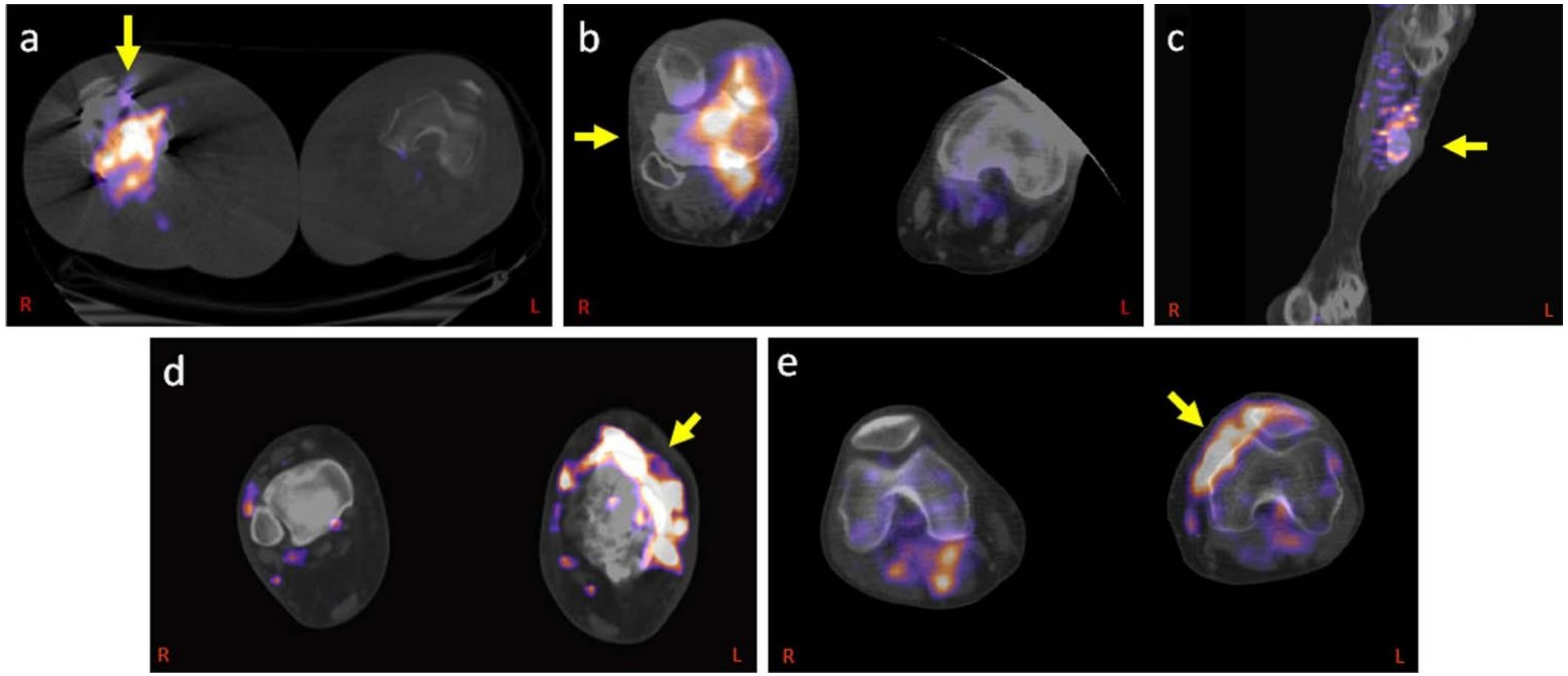
Mutch and Ordonez *et al*. ACS Inf Dis 2018

Zhang and Ordonez *et al*. ACS Inf Dis 2018

Targeting the Bacterial Metabolism

Nucleoside Analog - FIAU

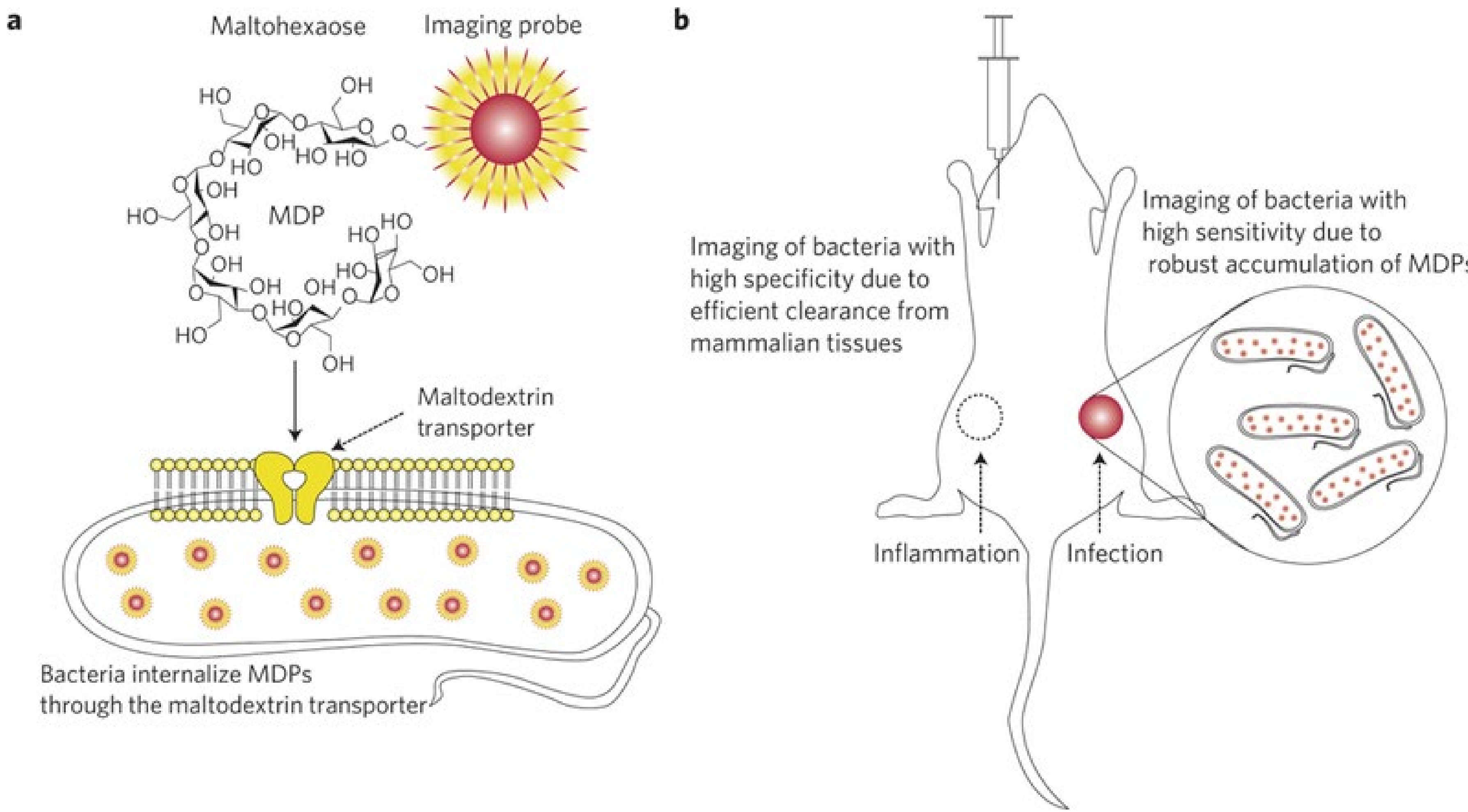




Bettegowda et al. PNAS 2005
Pullambhatla et al. Am J Nucl Med Mol Imaging 2012
Diaz Jr et al. PLoS ONE 2007

Targeting the Bacterial Metabolism

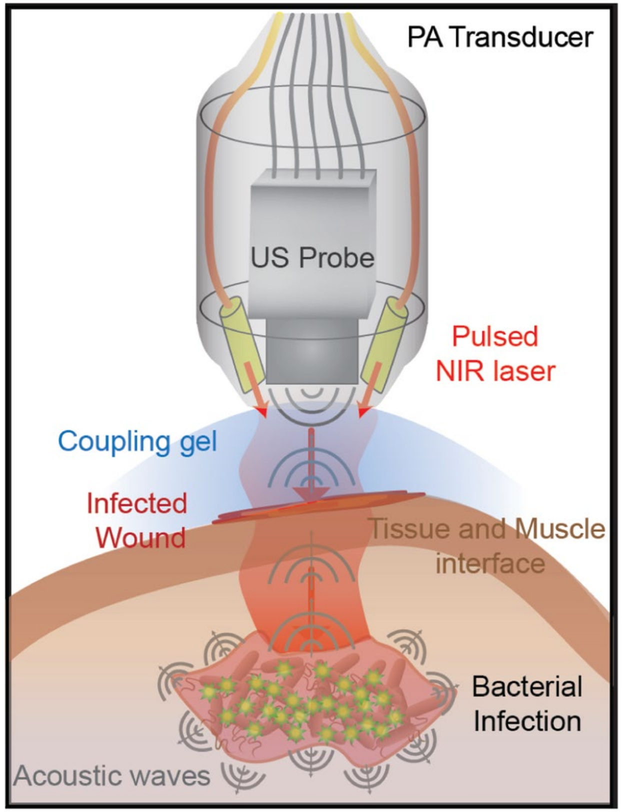
Maltodextrin-based probes

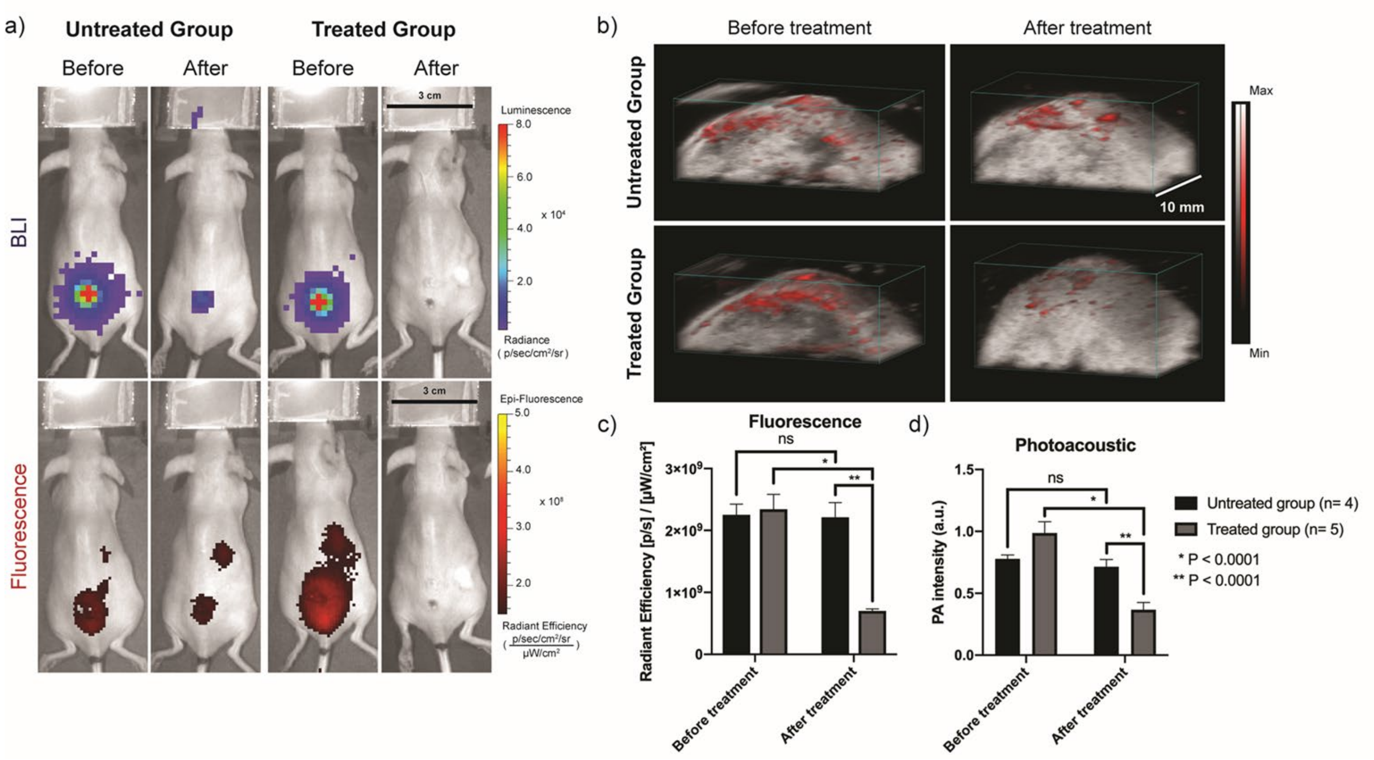


Ning X. *et al*, Nature Materials 2011

Targeting the Bacterial Metabolism

Maltodextrin-based probes – Optoacoustic Imaging



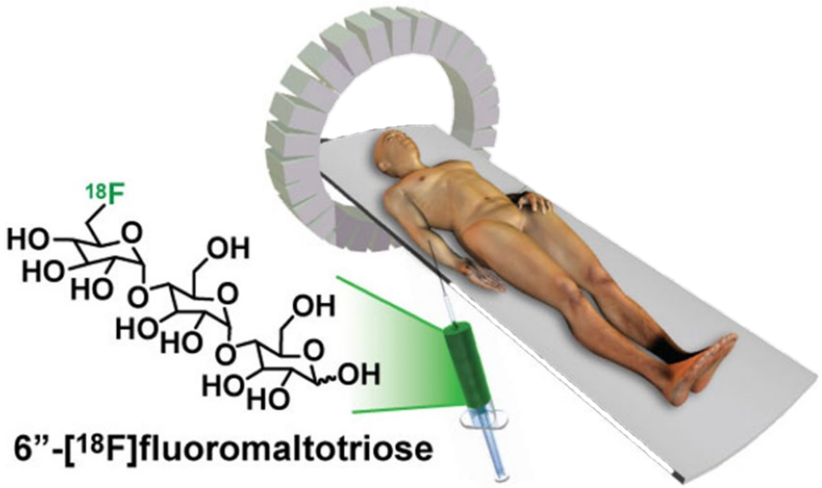


Zlitni A. *et al*, Nature Communications 2020

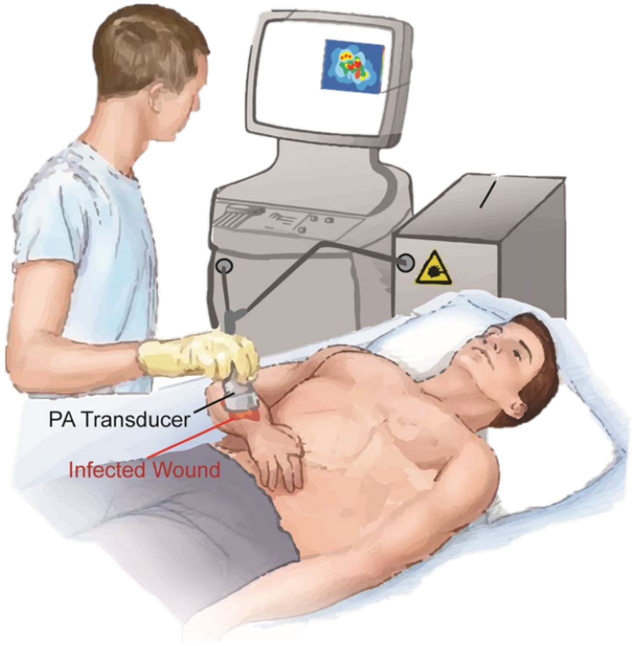
Targeting the Bacterial Metabolism

Maltodextrin-based probes – Optoacoustic Imaging

Whole Body Imaging
(PET/CT, MRI, PET/MRI)



Real Time Imaging (Ultrasound, Fluorescence and Photoacoustic Imaging)

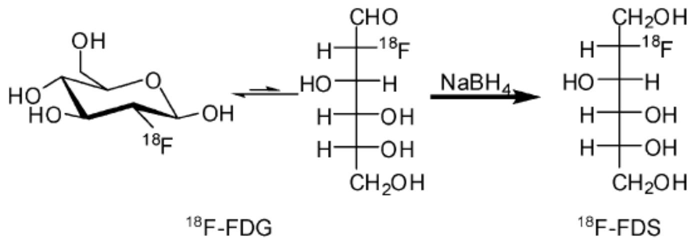


Zlitni A. *et al*, Nature Communications 2020

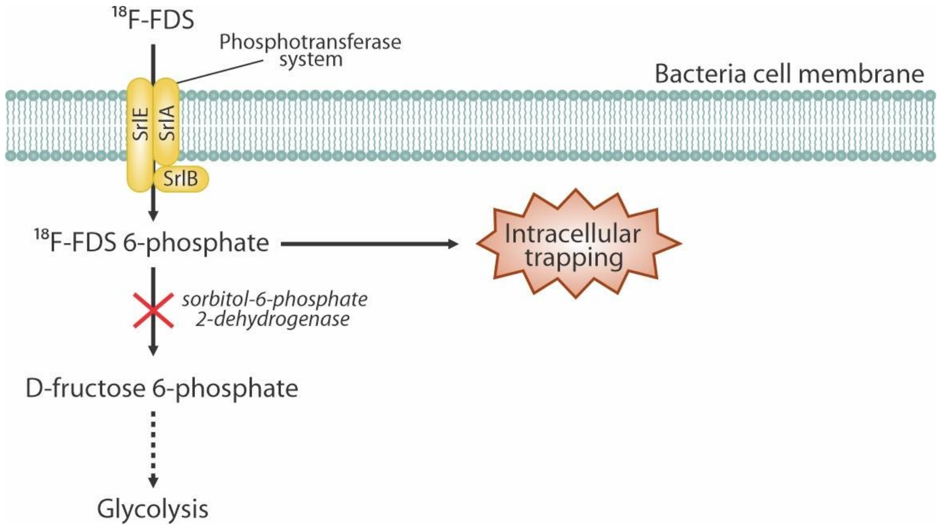
Slide from Gayatri Gowrishankar

Targeting the Bacterial Metabolism

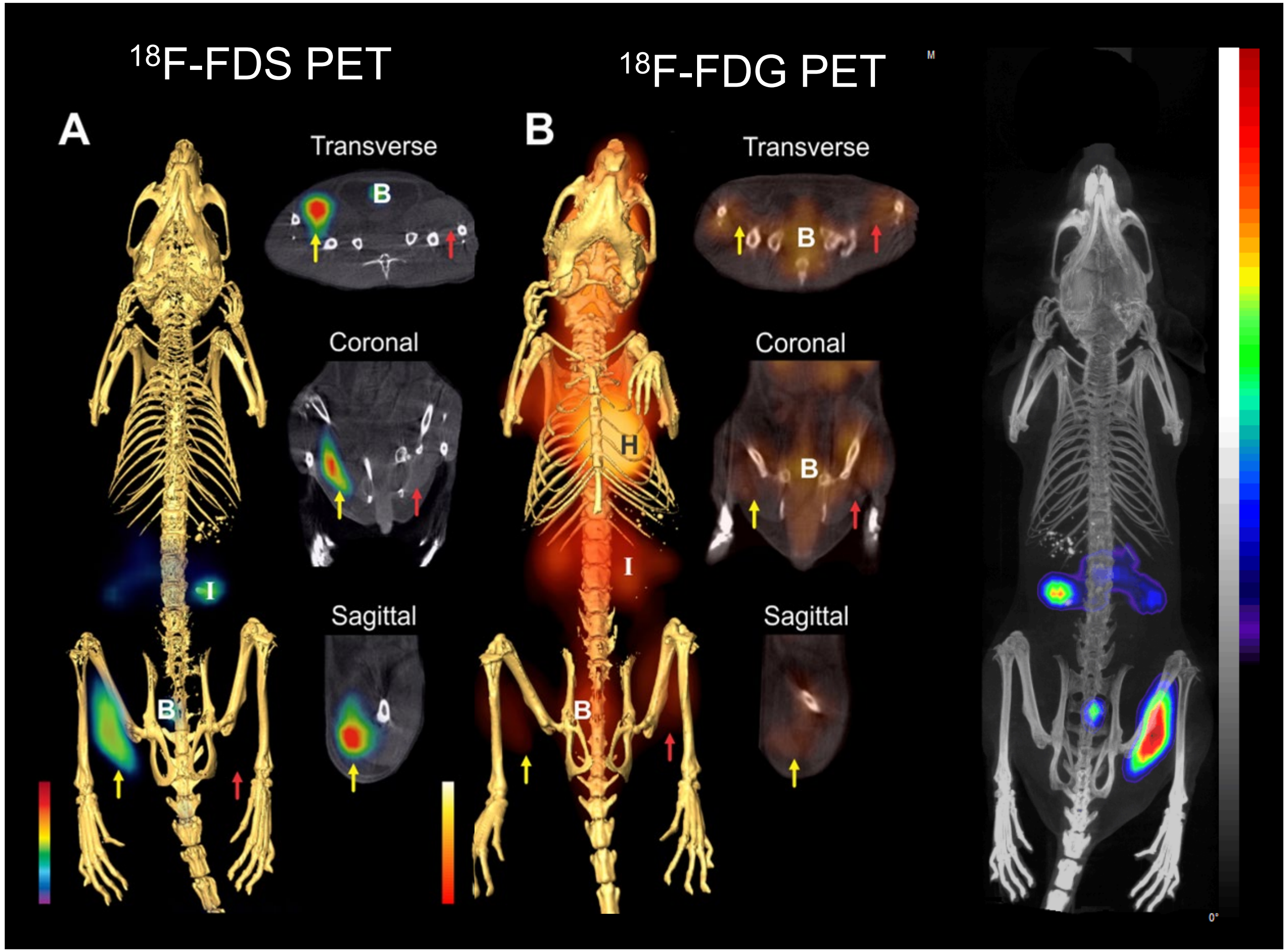
^{18}F-Fluorodeoxysorbitol (FDS)



Li *et al. Mol Imaging Biol* 2008

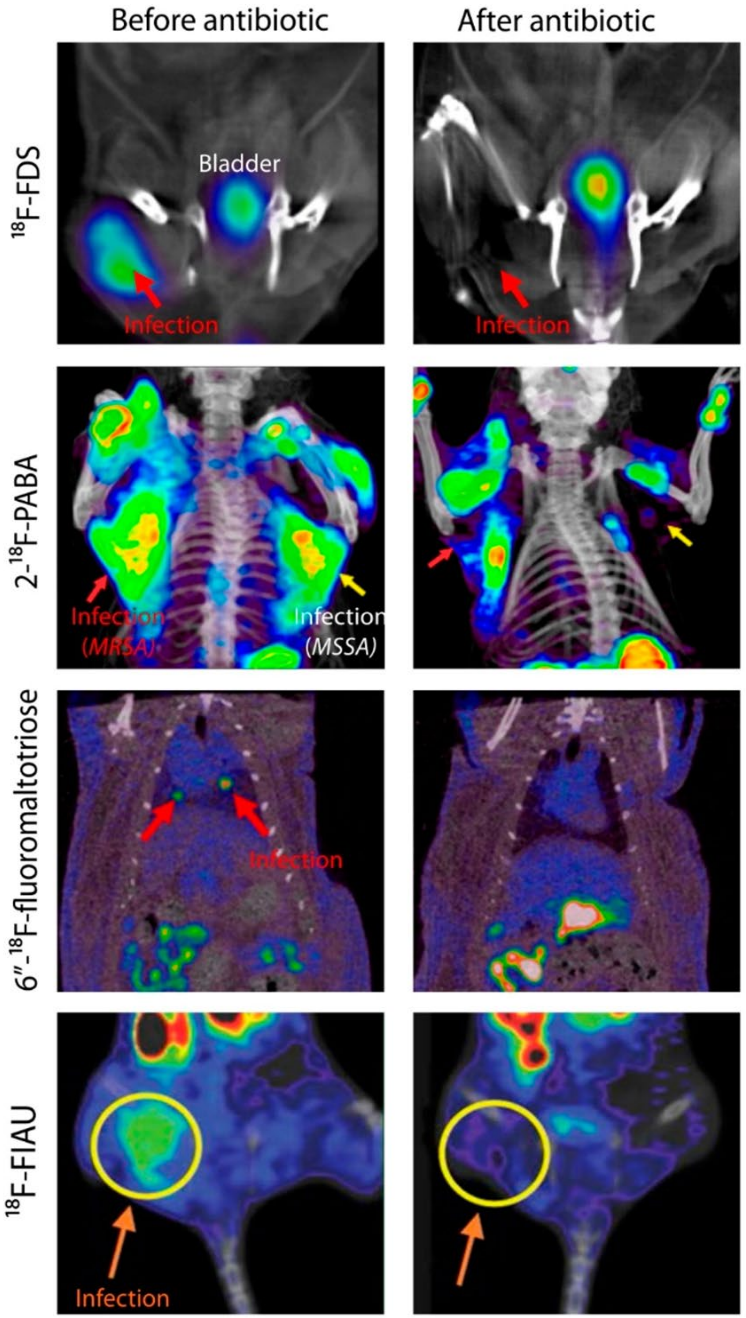


Weinstein and Ordonez et al, Sci Trans Med 2014



Monitoring Antibiotic Response with PET

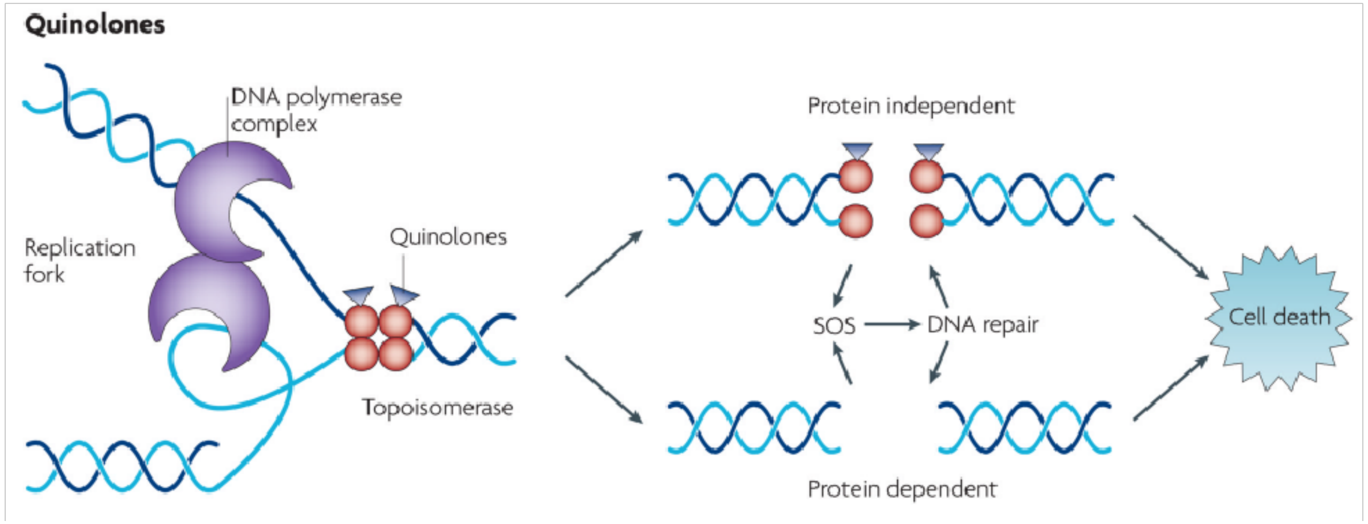
- Antibiotics are the mostly commonly used drugs
- How long do we need to treat patients?
- Could some patients get better with much shorter antibiotic courses?
- Why do some patients fail treatment even though they received appropriate antibiotics? Can we identify them early on?



Ruiz-Bedoya et al, Int J Mol Sci 2019

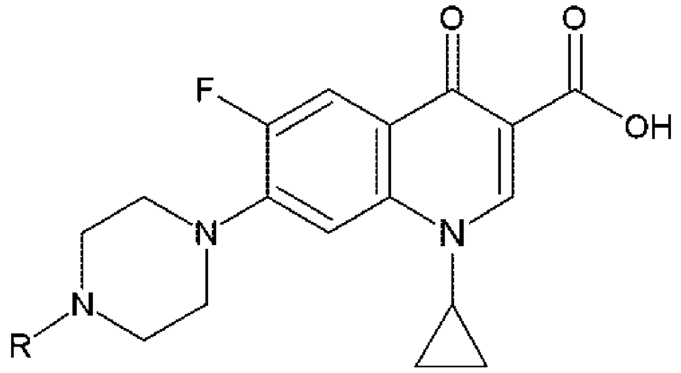
Routes to specific imaging of bacterial infection

Metabolic	Receptor Targeted/ Antibiotic	Bacterial Surface
FDS	Quinolones	Ubiquiticidin
D-Met	Cephalosporins	Mini-nanobodies
FIAU	Vancomycin	
	TMP	

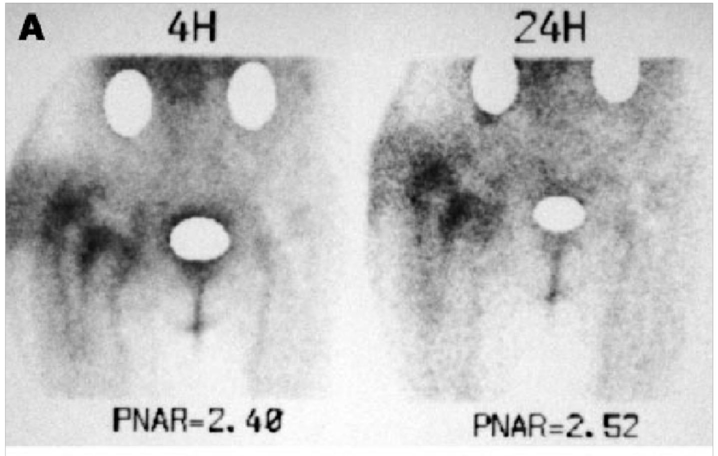


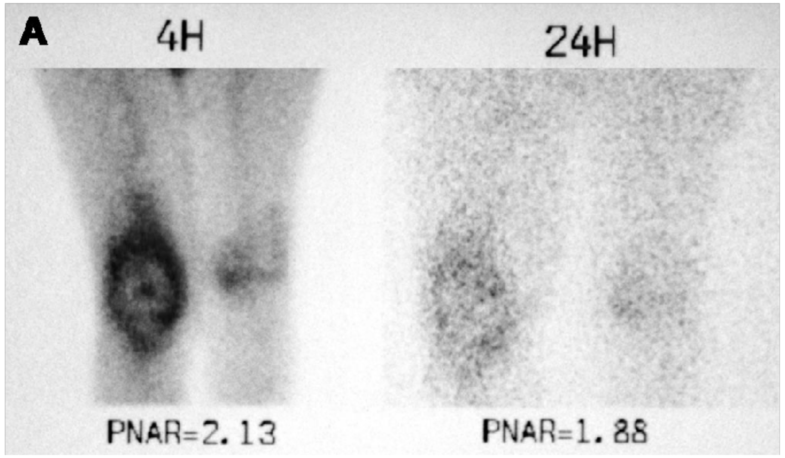
Kohanski, M. A., Dwyer, D. J. & Collins, J. J. How antibiotics kill bacteria: from targets to networks. *Nat Rev Microbiol* **8,** 423–435 (2010).

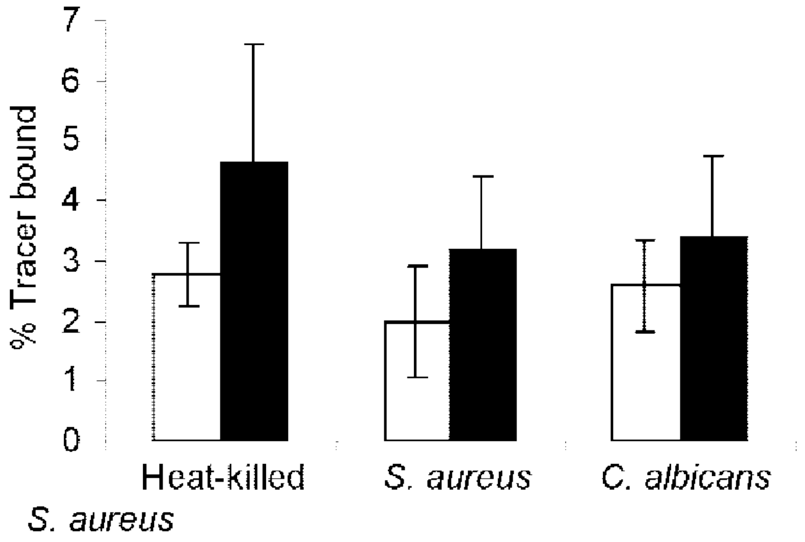
Precedent: Labeled Ciprofloxacin



Infected







Sarda, L. *et al. J. Nucl. Med.* **44,** 920–926 (2003)
Siaens, R. H., Rennen, H. J., Boerman, O. C., Dierckx, R. & Slegers, G. *J. Nucl. Med.* **45,** 2088–2094 (2004)

Precedent: technetium-99m-labeled ceftriaxone

(a)

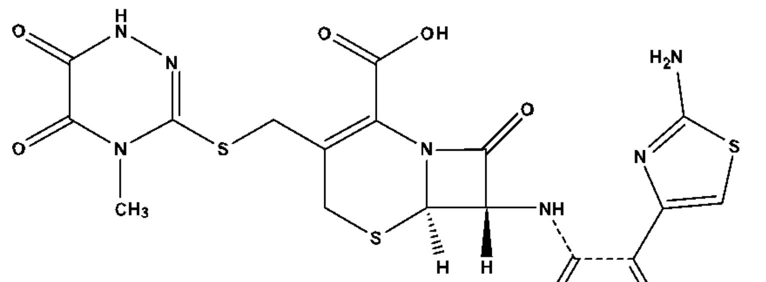
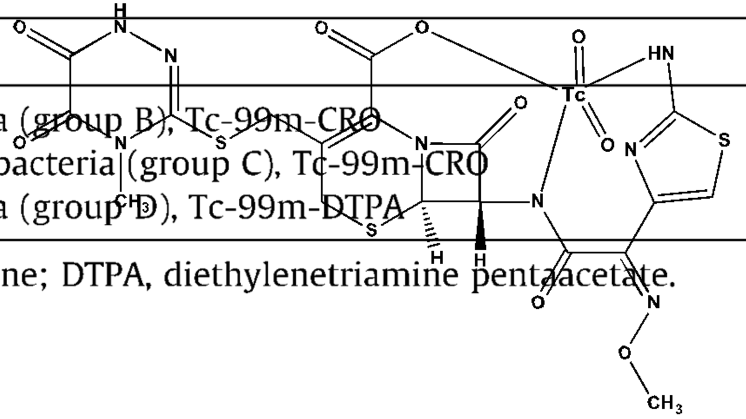


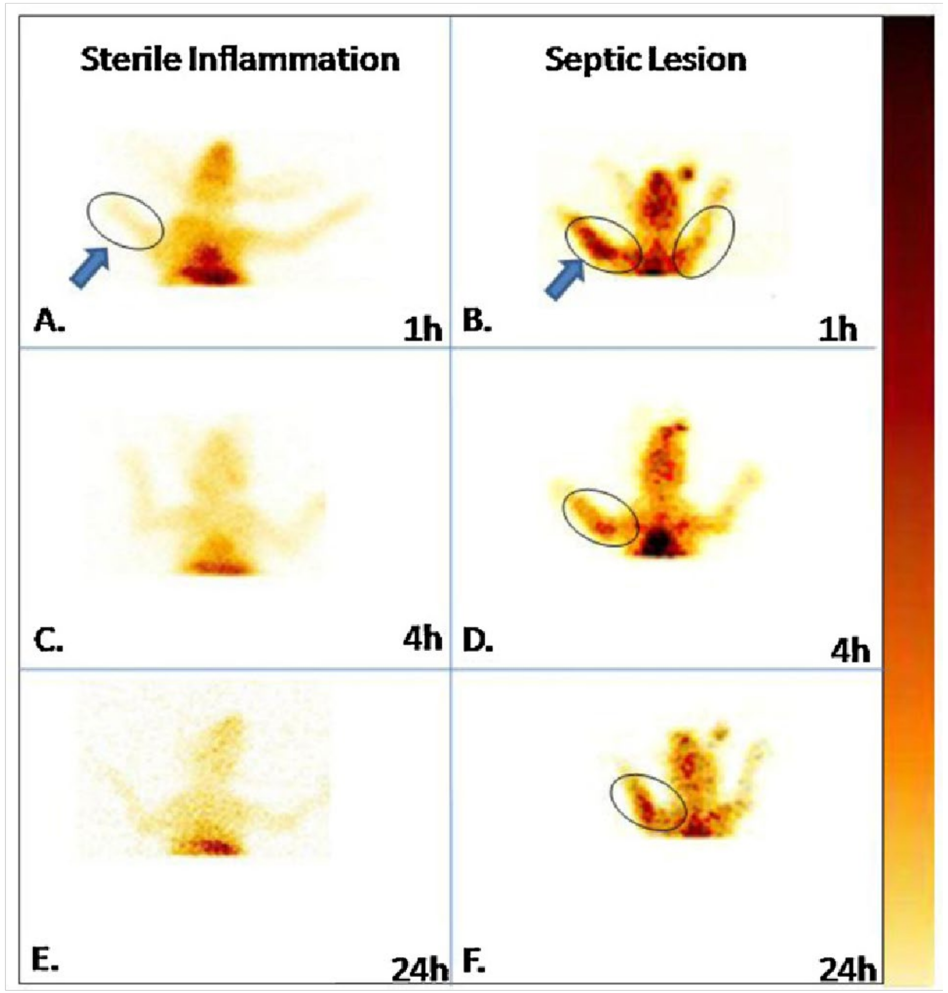
Table 2
Percentage bacterial binding after incubation with Tc-99m-ceftriaxone in groups B and C, and with Tc-99m-diethylenetriamine pentaacetate in group D (± SD of six vials in each group)

Group	% binding
Live-bacteria (group B), Tc-99m-CRO	4.35 ± 1.16
Heat-killed bacteria (group C), Tc-99m-CRO	3.31 ± 0.86
Live-bacteria (group D), Tc-99m-DTPA	0.49 ± 0.22

CRO, ceftriaxone; DTPA, diethylenetriamine pentaacetate.

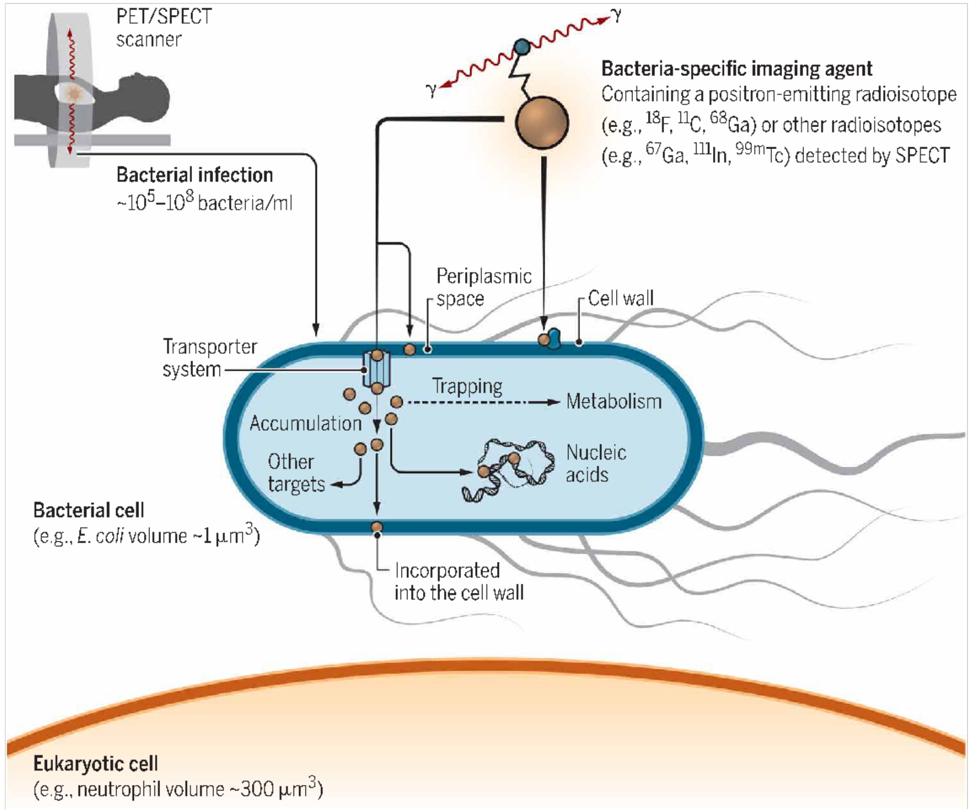
(b)



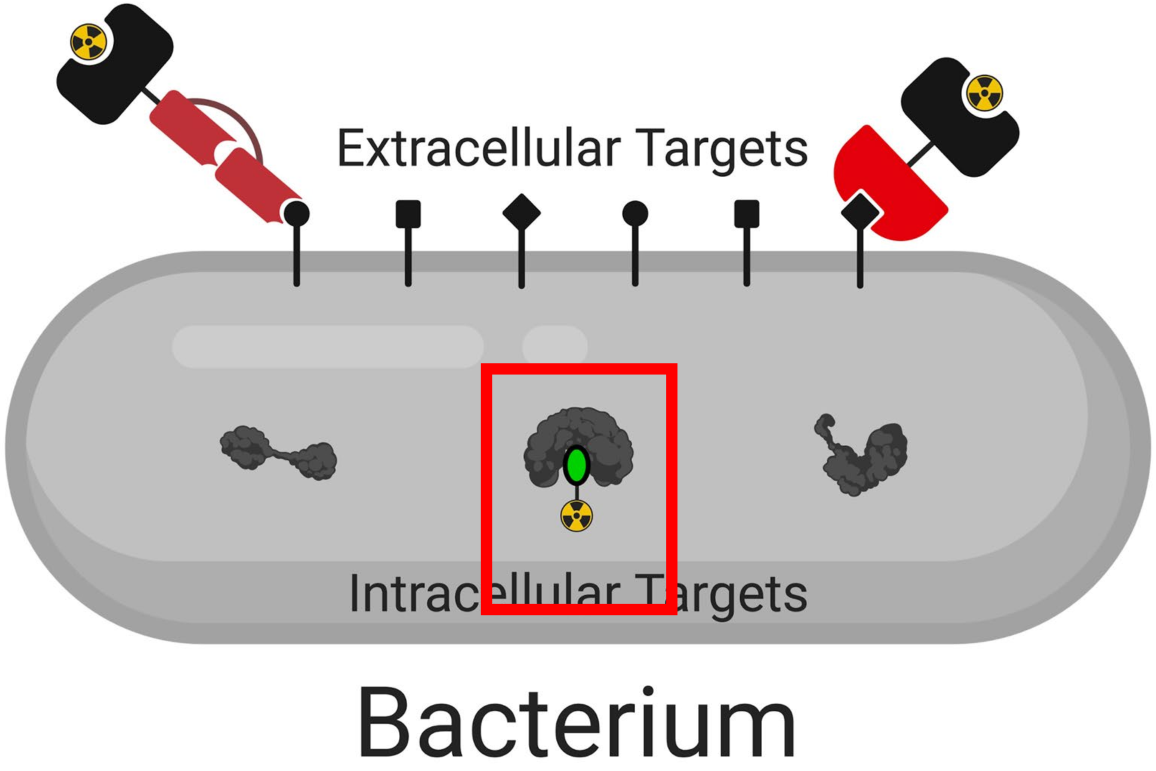


Kaul, A. *et al.* Preliminary evaluation of technetium-99m-labeled ceftriaxone: infection imaging agent for the clinical diagnosis of orthopedic infection. *Int. J. Infect. Dis.* **17,** e263–70 (2013).

Intracellular v Extracellular Targets

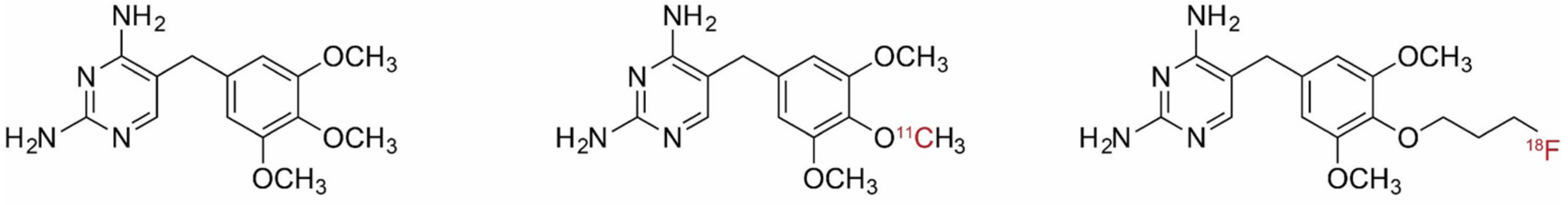


Ordonez, A., Sellmyer, M., Gowrishankar, G., Ruiz-Bedoya, C., Tucker, E., Palestro, C., Hammoud, D., Jain, S. (2019). Science Translational Medicine 11(508), eaax8251.



Northrup, J., Mach, R., Sellmyer, M. (2019). *IJMS* 20(22), 5808.

Radiotracers based on TMP for bacterial imaging

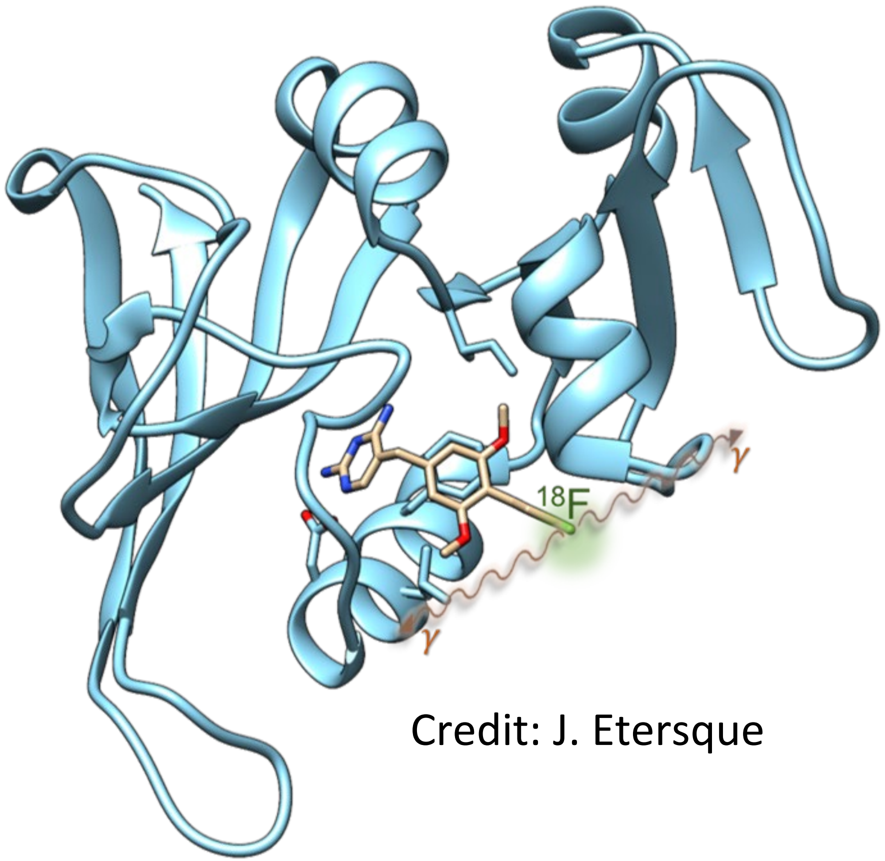


TMP [^{11}C]TMP [^{18}F]FPTMP

Stay tuned for new tracers coming out…

Sellmyer et al. *Mol Therapy* (2017) 120-126
Sellmyer et al. *PNAS* (2017) 8372-8377

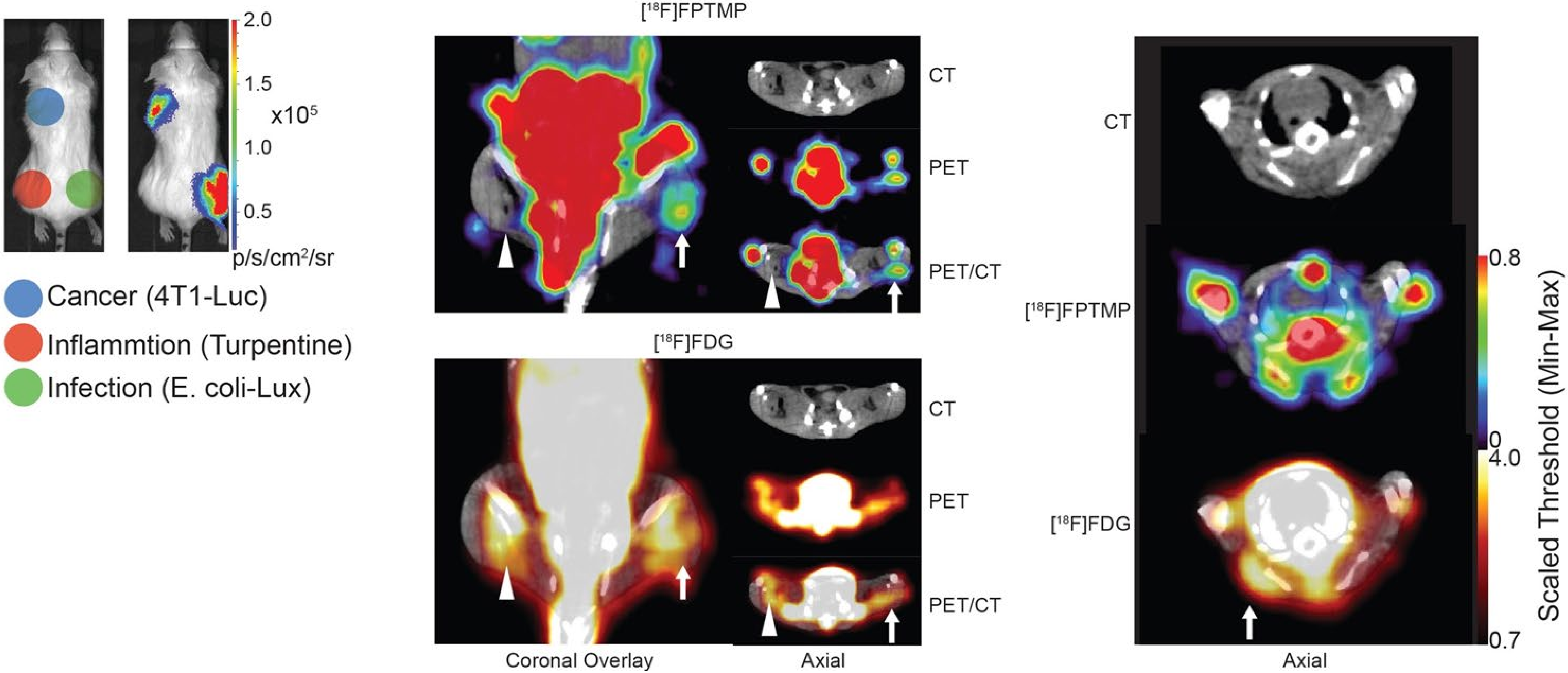
eDHFR as a target for PET imaging



Credit: J. Etersque

- Well-studied
- Small 18kDa, genetically portable (159 AA)
- Inhibitor trimethoprim (TMP) has 30,000-fold selectivity for the bacterial enzyme over human

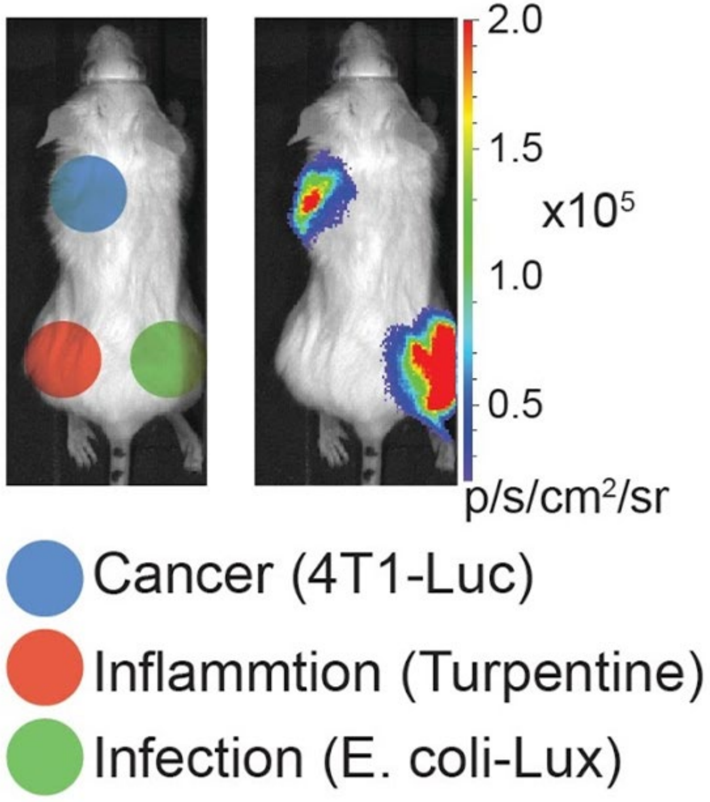
Infection v Cancer v Inflammation

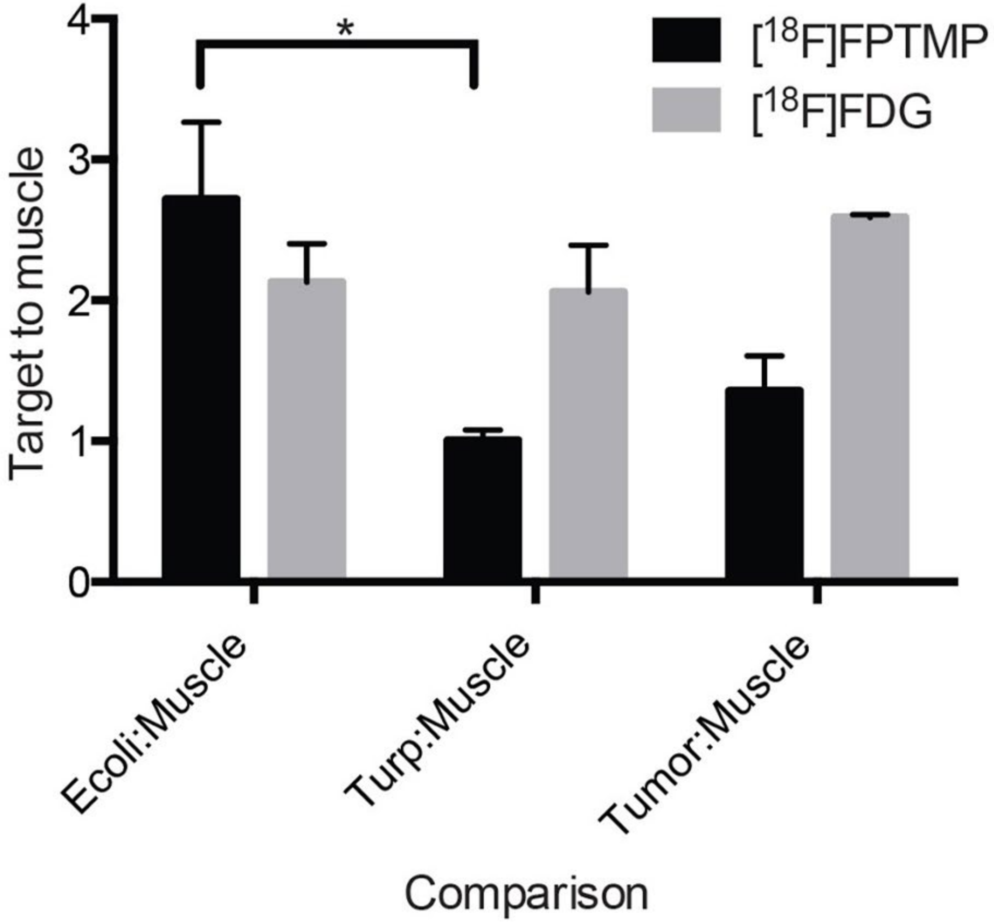


- Uptake at the site of bacterial infection and NOT inflammation or cancer

Sellmyer et al. *PNAS* (2017) 8372-8377

Infection v Cancer v Inflammation



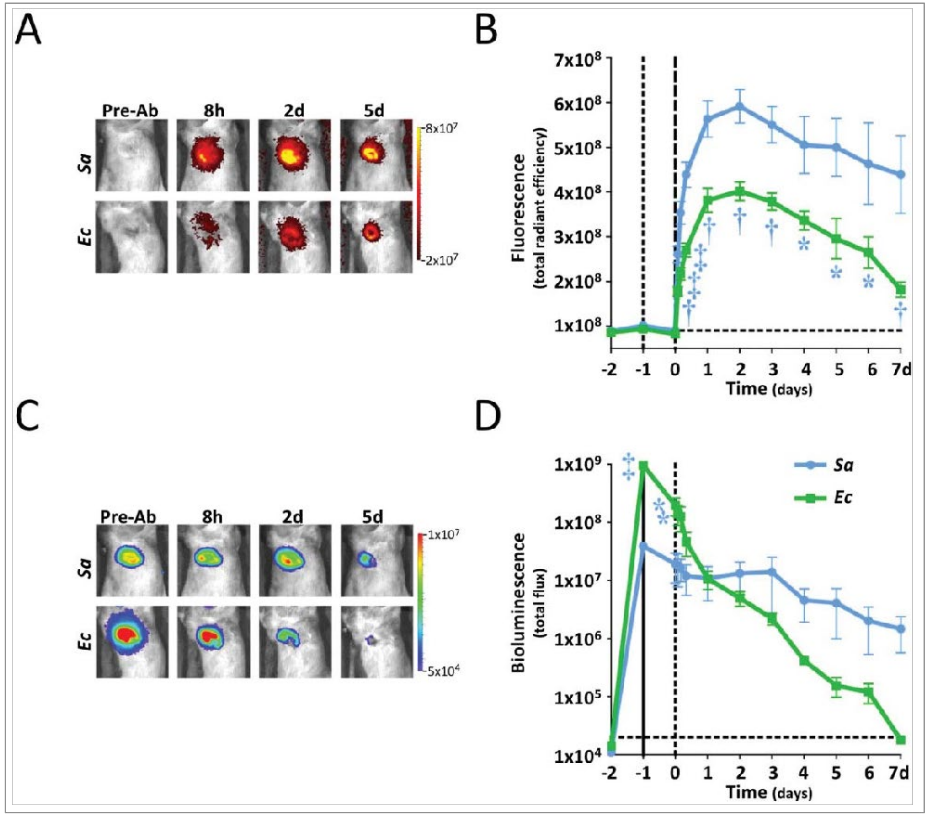


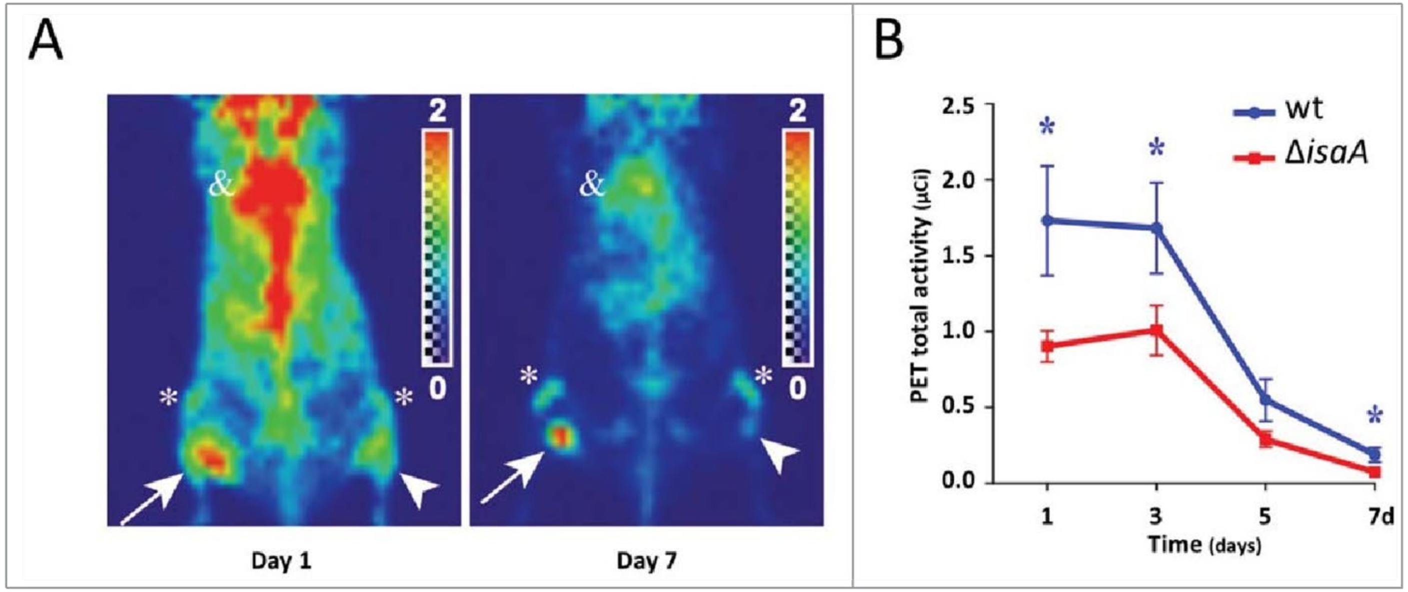
-Specificity for bacterial infection compared to FDG

Many immuno-PET approaches for cell surface markers: Bacterial and immune cell

- Rubin, R.H.; Young, L.S.; Hansen, W.P.; Nedelman, M.; Wilkinson, R.; Nelles, M.J.; Callahan, R.; Khaw, B.A.; Strauss, H.W. Specific and nonspecific imaging of localized fisher immunotype 1 pseudomonas aeruginosa infection with radiolabeled monoclonal antibody. *J. Nucl. Med.* **1988**, *29*, 651–656. [PubMed]
- Hotze, A.L.; Briele, B.; Overbeck, B.; Kropp, J.; Gruenwald, F.; Mekkawy, M.A.; Von Smekal, A.; Moeller, F.; Biersack, H.J. Tc-99m-Labeled Antigranulocyte Antibodies in Suspected Bone-Infections. *J. Nucl. Med.* **1992**, *33*, 526–531.
- Bitkover, C.Y.; Gardlund, B.; Larsson, S.A.; Aberg, B.; Jacobsson, H. Diagnosing sternal wound infections with Tc-99m-labeled monoclonal granulocyte antibody scintigraphy. *Ann. Thorac. Surg.* **1996**, *62*, 1412–1416. [CrossRef]
- ***Pastrana, F.R.; Thompson, J.M.; Heuker, M.; Hoekstra, H.; Dillen, C.A.; Ortines, R.V.; Ashbaugh, A.G.; Pickett, J.E.; Linssen, M.D.; Bernthal, N.M.; et al. Noninvasive optical and nuclear imaging of staphylococcus-specific infection with a human monoclonal antibody-based probe. Virulence 2018, 9, 1–12. [CrossRef]***
- Pickett, J.E.; Thompson, J.M.; Sadowska, A.; Tkaczyk, C.; Sellman, B.R.; Minola, A.; Corti, D.; Lanzavecchia, A.; Miller, L.S.; Thorek, D.L. Molecularly specific detection of bacterial lipoteichoic acid for diagnosis of prosthetic joint infection of the bone. *Bone Res.* **2018**, *6*, 1–8. [CrossRef]
- Welling, M.; Feitsma, H.I.J.; Calame, W.; Ensing, G.J.; Goedemans, W.; Pauwels, E.K.J. Optimized localization of bacterial infections with technetium-99m labelled human immunoglobulin after protein charge selection. *Eur. J. Nucl. Med.* **1994**, *21*, 1135–1140. [CrossRef] [PubMed]
- Calame, W.; Welling, M.; Feitsma, H.I.J.; Goedemans, W.T.; Pauwels, E.K.J. Contribution of phagocytic cells and bacteria to the accumulation of technetium-99m labelled polyclonal human immunoglobulin at sites of inflammation. *Eur. J. Nucl. Med.* **1995**, *22*, 638–644. [CrossRef] [PubMed]

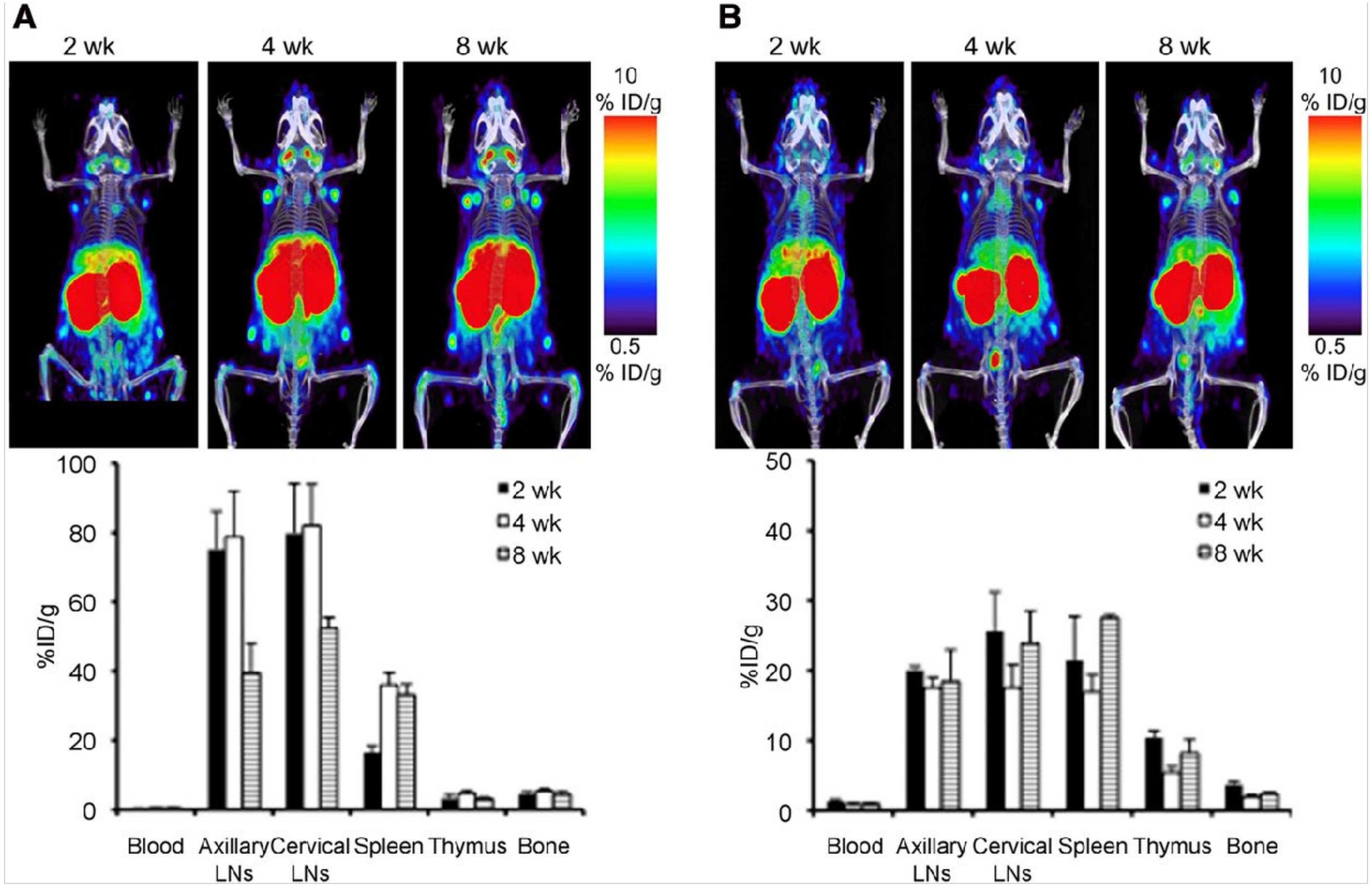
Human monoclonal *S. aureus* Immuno-PET





Romero Pastrana, F. *et al.*. *Virulence* **9,** 262–272 (2018).

CD4 and CD8 Imaging – Cis-diabody



Tavaré, R. *et al.*. *J. Nucl. Med.* **56,** 1258–1264 (2015).

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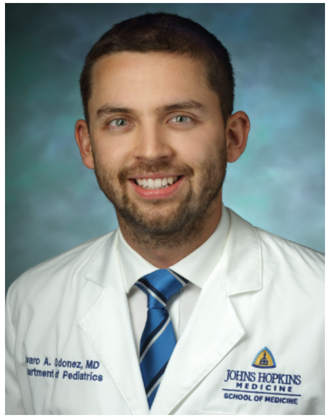
Questions? Type them into the question box

"Defining the Infectious Etiologies with Imaging"

Mark A Sellmyer, MD, PhD
Assistant Professor of Radiology
University of Pennsylvania

@sellmyerlab



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T32 Program Associate Director
University of California San Francisco

https://radiology.ucsf.edu/research/labs/wilson

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