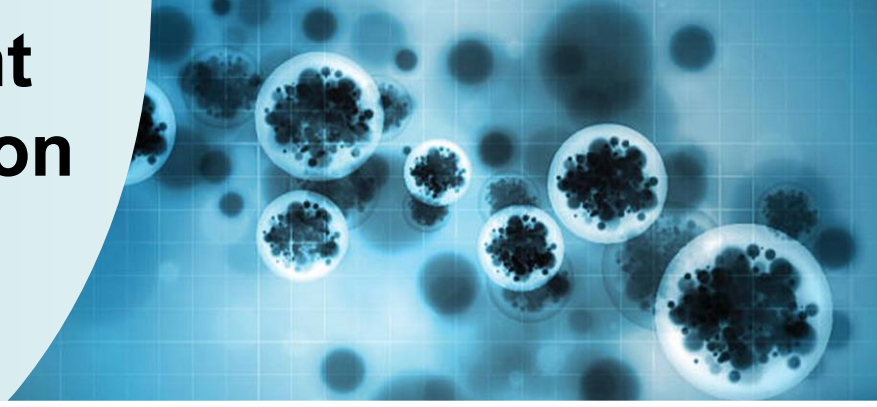
Using antibiotics scaffolds will warrant novel radiotracers for effective positron emission tomography imaging of infections: triumph or pitfall ?



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Background: The excellent features of non-invasive molecular imaging, its progressive technology (real-time, whole-body imaging and quantification), and global impact by a growing infrastructure for positron emission tomography (PET) scanners are encouraging prospects to investigate new concepts which could transform clinical care of complex infectious diseases. Researchers are aiming towards the extension beyond the routinely available radiopharmaceuticals looking for more effective tools that interact directly with causative pathogens. We were interested to investigate whether the actual use of antibiotics as PET-radiotracers can be successful or might be too much of a challenge.

Table 1: Overview of radiolabelled PET-antibiotics

	Radiotracer	Application	Target
AF	[^{11}C]trimethoprim	Imaging of Infection	Dihydrofolate Reductase – blocks Folate synthesis
	[^{18}F]FP-trimethoprim		
Fluoroquinolones	[^{18}F]F-ciprofloxacin	Imaging of Infection	Affecting Topoisomerase II DNA complex - hindering cellular RNA Translation / Transcription
	[^{18}F]FP-ciprofloxacin		
	[^{68}Ga]Ga(D-/N-OTA-SCN)-ciprofloxacin		
	[^{68}Ga]Ga-DOTA-ciprofloxacin		
	[^{18}F]F-lomefloxacin	Pharmacodynamics /Pharmacokinetics	
	[^{18}F]F-fleroxacin		
	[^{18}F]F-trovafloxacin		
Antituberculosis agents	[^{11}C]isoniazid	Pharmacodynamics /Pharmacokinetics	catalase-peroxidase causes radical molecule → trapped in the cell → NAD-adduct inhibits enoyl-acyl carrier protein reductase – blocks type II fatty acid synthase
	2-[^{18}F]F-isoniazid	Imaging of Infection	
	[^{11}C]PT70	Pharmacodynamics /Pharmacokinetics	directly inhibitors of enoyl-acyl carrier protein reductase
	[^{11}C]PT119		
	[^{18}F]F-linezolid (oxazolidinone)	Pharmacodynamics /Pharmacokinetics	Binds to RNA polymerase and inhibits DNA transcription
	[^{11}C]erythromycin (macrolide)		
	[^{11}C]rifampin		
	[^{76}Br]Br-bedaquiline		Inhibits ATP Synthase
	[^{11}C]pyrazinamide		Activation by pyrazinamidase / inhibits Co-enzyme A synthesis
	5-[^{18}F]F-pyrazinamide	Imaging of Infection	

Conclusion

- antibiotic-derived PET-radiotracer development is very scattered,
- often incoherent study designs / biases,
- reduced validity and reliability although promising results occur,
- extensive studies carbon-11/ fluoride-18-labelled trimethoprim has sparked new belief that antibiotics can become clinically relevant infection imaging agents.

Methods: Input → systematically review of PET-antibiotic-derived radiopharmaceutical development efforts aimed at infection imaging:

a) ***radiotracer development for infection imaging or***
b) ***radio-antibiotic based PET imaging (for pharmacologic drug characterization).***

Output → critical, in-depth assessment → identify challenges and pitfalls reflecting on antibiotics to benefit in better radiopharmaceutical development.

Table 2: Challenges and possible solutions for the development and testing of novel antibiotic-based radiopharmaceuticals for infection imaging

Challenge	Possible strategy /solution	Limitation
Antibiotic radiosynthesis ≠ antibiotic action	– libraries & SAR (target binding efficacy) – computational tests (aim at preserving the pharmacophore)	– radioisotope production & radiopharmaceutical key (low specific activity)
Risk of compromised tracer sensitivity	– select antibiotics that target highly active/expressed biological processes – disregard antibiotics with MoA that are not well understood – consider the mass effect of tracer formulation – radiosynthesis optimisation (formulation, dosage, carrier content); following quality guidelines – testing tracer sensitivity in non-human primate models or first-in human investigations prior to clinical trials.	– biological target expression is underwhelming – threshold B_{max}/K_d may decrease < 10 for antibiotics derivatives – radiotracer: inadequate specific activity – small animal models only acceptable for proof-of-principle investigation
Risk associated with accuracy of visualising infection	– disregard antibiotics with predisposed MOA – drug resistant pathogens: use vectors that circumvent / take advantage of defense mechanism, i.e., target over-expression or genetic redundancy	– presence of additional (cold) ligand or conflicting pathogen environment – cumbersome pro-drug activation processes – pre-treated subjects using widely prescribed antibiotics
Effects of empiric use of antibiotics	– opting for radiosynthesis of antibiotics with unique MOA is crucial	– radiotracer: inadequate specific activity
Unwanted (altered) tracer bioavailability & biodistribution	– ADME: prioritise antibiotics with rapid clearance from high-risk organ / compartments for infection – assess candidates for host enzymatic and tissue specific interactions – practice SAR-guided incorporation of a radiolabelled functional group –consideration of liposome-, nanoparticle, or microsphere-based delivery system (transfer intact tracer to target) – permit radionuclide incorporation only to non-cleavable structures	– relatively long-biological half-life of antibiotics – antibiotics sometimes associate with host inflammatory response – unforeseen shifts in physiochemical properties (lipophilicity by carbon chain spacers / polarity by metal chelator conjugation) can occur

Conflict of Interest: All authors declare no conflict of interest.

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