Translational Molecular Nuclear Cardiology

James T. Thackeray, PhD*, Frank M. Bengel, MD

KEYWORDS

• PET • SPECT • Cardiovascular disease • Translational imaging

KEY POINTS

- Established translational nuclear imaging agents target critical and common molecular pathways of cardiac pathologies.
- Translational strategies are essential for effective identification and characterization of high-potential candidate tracers.
- The characterization of translational imaging compounds should strive to achieve reliable quantification, demonstrate diagnostic and/or prognostic benefit, and allow for monitoring therapeutic efficacy.

INTRODUCTION

The widespread expansion of dedicated small animal imaging systems has provided a research framework for the accelerated development of novel molecular nuclear imaging agents. Current tracers target a number of critical axes in the development and progression of cardiovascular disease, including myocardial metabolism, sympathetic neuronal activation, local and systemic inflammation, molecular biomarkers of ventricular and vascular remodeling, and monitoring of regenerative therapy. Some of these imaging agents have been approved for routine clinical application (**Box 1**). Other novel compounds remain under investigation, at variable stages of translation from lab bench to clinical evaluation (**Box 2**). There remain a number of challenges to wider clinical deployment of novel radiotracers and imaging techniques, particularly (1) absolute, reliable, and reproducible quantification; (2) demonstration of added diagnostic and/or prognostic value for risk stratification; and (3) capacity to measure disease progression and regression to therapy. Here, we discuss the current state of preclinical nuclear molecular imaging research and translation to clinical practice.

MYOCARDIAL METABOLISM

The preeminent test case of molecular imaging is the diagnostic and prognostic application of positron emission tomography (PET) with fludeoxyglucose F 18 (^{18}F-FDG) to assess myocardial glucose metabolism. More thorough metabolic analyses incorporate tracers of fatty acid metabolism, such as ^{99m}Tc-β-methyl-iodophenyl-pentadecanoic acid (^{99m}Tc-BMIPP, fatty acid transport), ^{18}F-fluoro-6-thia-heptadecanoic acid (^{18}F-FTHA, nonesterified fatty acid transport), ^{11}C-palmitate (β-oxidation), and ^{11}C-acetate (oxidative metabolism).

There remain challenges for the absolute quantification of glucose utilization in mice and rats, particularly with regard to accurate calculation of the input function.[1,2] In mice, this complication is accentuated and can contribute to suboptimal image reproducibility and high population variability. A number of hybrid analysis approaches have been proposed,[3–5] but true quantification of

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Department of Nuclear Medicine, Hannover Medical School, Carl Neuberg-Street 1, Hannover D-30625, Germany
* Corresponding author.
E-mail address: Thackeray.James@mh-hannover.de

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Box 1
Established translational radiotracers in routine clinical practice

Tracer	Target/Measurement
Myocardial metabolism	
^{18}F-FDG (fludeoxyglucose F 18)	Glucose uptake, metabolism Activated inflammatory cells, macrophages
^{99m}Tc-BMIPP (^{99m}Tc-β-methyl-iodophenylpentadecanoic acid)	Fatty acid uptake, metabolism
^{11}C-Acetate	Oxidative metabolism
Myocardial innervation	
^{123}I-MIBG (metaiodobenzylguanidine)	Norepinephrine reuptake and release
^{11}C-Hydroxyephedrine	Norepinephrine reuptake and release
^{11}C-Epinephrine	Norepinephrine reuptake, release, and metabolism
Other molecular targets	
^{18}F-Fluoride	Calcification, mineralization
^{11}C-Methionine	De novo protein synthesis
^{99m}Tc-Annexin	Apoptosis

glucose utilization in the rodent heart remains somewhat elusive.

Due in part to limited accuracy of ^{18}F-FDG kinetic quantification and complications due to continuous anesthesia, there has been a relative dearth of quantitative preclinical studies. More recent molecular metabolism imaging studies have focused on genetically modified animals,

Box 2
Novel translational radiotracers in preclinical and clinical testing

Tracer	Target/Measurement
Myocardial metabolism	
^{18}F-FTHA (^{18}F-fluoro-6-thia-heptadecanoic acid)	Fatty acid uptake
^{11}C-Palmitate	Fatty acid uptake and oxidation
Myocardial innervation	
^{11}C-Phenylephrine	Norepinephrine reuptake, release, and metabolism
^{18}F-LMI1195	Norepinephrine reuptake and release
^{11}C-MQNB	Muscarinic receptors
^{18}F-A85380	Nicotinic receptors
^{11}C-CGP12177	Beta-adrenergic receptors
^{11}C-CGP12388	Beta-adrenergic receptors
^{11}C-GB67	Alpha-adrenergic receptors
Other molecular targets	
^{68}Ga-Dotatate	Somatostatin receptor type 2, macrophages
^{18}F-Mannose	Mannose receptor, glucose uptake
^{99m}Tc-Anti-RAGE	Receptor for advanced glycation endproducts, glycation
Elastin glycoprotein	Activated elastin, matrix remodeling
99mTc-Anti-LOX-1	Oxidized lipid, atherosclerotic plaques
^{18}F-Fluorbetabir	Amyloid plaques
^{99m}Tc-RP782	Matrix metalloproteinases
^{99m}Tc-RP805	Matrix metalloproteinases
^{11}C-KR31173	Angiotensin receptor type 1 (AT_1R)
^{99m}Tc-CRIP	Arginine-glycine-aspartate (RGD) protein sequence, angiogenesis, inflammation
^{18}F-Galacto-RGD	RGD protein sequence, angiogenesis, inflammation
^{64}Cu-DOTA-vMIP-II	Chemokine receptors (nonspecific)
^{68}Ga-Pentixafor	Chemokine receptor CXCR4
^{68}Ga-SDF1	Chemokine receptor CXCR4
^{18}F-FBzBMS	Endothelin receptors
^{18}F-Fucoidan	P-selectin, thrombosis
^{18}F-FXIII	Plasma transglutaminase factor XIII