Cardiovascular Research (2016) **112**, 617–618
doi:10.1093/cvr/cvw227

EDITORIAL

Innovative reporter gene imaging techniques making inroads to biology

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This editorial refers to 'Magnetic resonance imaging of infarct-induced canonical Wnt/β-catenin/TCF pathway activation, *in vivo*' by M. Matteucci *et al.*, pp. 645–655.

The post-infarct heart undergoes profound changes to repair damaged tissues and compensate for lost function.[1] The process must strike a delicate balance among complex cellular and system-level signalling activities in an orchestrated fashion to rid the myocardium of debris and support the infarct with fibrotic tissue. Much remains to be learned in the pathophysiology of the post-infarct heart in order to achieve better therapeutic intervention with improved long-term outcome. To this end, emerging non-invasive approaches, in particular mechanistic measurements on a molecular level, hold promise in characterizing the spatio-temporal dynamics of cardiac repair/remodel.

An interdisciplinary effort to unravel the intricate signalling mechanisms *in vivo* can be exemplified in a study by Matteucci et al.[2] in the current issue. It is known that the Wnt/β-catenin/T-cell factor (TCF) pathway helps modulate the repair/remodelling processes in the post-infarct heart; yet, its precise roles are controversial and remain to be fully defined.[3] The uncertainties may be attributed to the precarious nature of the ischemic myocardium, where the pathophysiological environment varies depending on the extent and evolution of cardiac injury. Such phenomena are not uncommon in the healing heart, and contribute to a cause for heightened interest in personalized care with precision medicine.

In the feasibility study by Matteucci et al.[2], an innovative reporter gene was deployed to probe for the activities of the canonical Wnt/β-catenin/TCF pathway *in vivo*. The technique uses a β-catenin-responsive TCF/Lef promoter which is activated by elevated β-catenin levels. The upregulation of the TCF/Lef promoter is coupled with the overexpression of human ferritin heavy chain (hFTH), which results in local iron accumulation, detectable by T_2/T_2*-weighted magnetic resonance imaging (MRI). The study employed the Adeno-associated virus as a widely adaptable gene delivery system. Using this non-invasive imaging tool, the investigators could observe increased canonical Wnt/β-catenin pathway activation in the peri-infarct border zone, and that this response was abolished in the presence of a small-molecule inhibitor for the Wnt/β-catenin signalling pathway. The data were a proof-of-concept that innovative molecular imaging techniques are enabling tools for non-invasive measurements that help dissect signalling pathways and determine their roles in the evolving cardiac repair/remodelling process.

The imaging of reporter genes involves a number of key technical components. The biology-of-interest is responsive at the transcriptional level, in this case under the control of a transcriptionally strong promoter. A surrogate marker in the form of a functional protein product can provide measureable changes, such as enzymes, transporters, fluorescent proteins, or other tangible physicochemical properties. In terms of imaging modalities, the use of MRI is appropriate for cardiac imaging because of its intrinsic soft tissue contrast and relatively high spatial resolution. The latter helps delineate the location and transmurality in signal changes as a result of reporter gene activation. Within the context of existing literature, alternative reporter gene systems are based on the uptake of radiopharmaceuticals or the expression of fluorescent proteins/bioluminescent enzymes.[4–6] Radionuclide imaging has superior sensitivity but often requires secondary anatomical images for co-registration. Optical imaging techniques are widely accessible, however, for studying internal organs and tissues they are limited by the depth of photon penetration. While there are a number of technical approaches and imaging modalities where each has its own advantages and shortcomings, a successful imaging study is a matter of selecting the appropriate tools for the right application.

A notable advantage for the reporter gene approach is its non-invasive nature, which forgoes the necessity to sacrifice the test subjects in order to conduct measurements on excised tissues. This confers the opportunity to perform repeated measurements to acquire dynamic data as well as follow-up functional studies. The approach enables longitudinal characterization with multi-parametric correlations in the same individual, thus providing answers in a 'personalized' fashion. In contrast, single-time point terminal studies rely on population statistics where information that reflects individuality can be obscured as deviations. When put into perspective, personalized measurements provide binary results for each individual, whereas population-based statistics offers probability.

Since the introduction of the concept of 'molecular imaging', there has been a rapid expansion in the development of novel imaging techniques for investigating biological activities in the living system. As new imaging approaches continue to emerge at the basic and proof-of-concept levels,

The opinions expressed in this article are not necessarily those of the Editors of *Cardiovascular Research* or of the European Society of Cardiology.

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increasing number of proven imaging techniques and agents are making inroads to practice.[7,8] It is well anticipated that non-invasive molecular imaging applications will increasingly make an impactful presence in modern biomedical research and clinical applications.

Conflict of interest: none declared.

Funding

The work was supported by the National Institute of Health 1R01HL131110, 5R01CA185214.

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