BACs to the future: new genetic models for cardiovascular discovery

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This editorial refers to ‘A transgenic mouse model for the simultaneous monitoring of ANF and BNP gene activity during heart development and disease’ by Irina A. Sergeeva et al., pp. 78–86, this issue.

One of the great challenges of modern biology is to contextualize highly detailed molecular discoveries in order to prioritize the most medically relevant events. The response to heart damage, for example, likely involves tens of thousands of cells of multiple lineages, each undergoing complex signaling cascades that trigger other equally complex molecular interactions including cell migration, lineage induction, secretion, fibrosis, and revascularization. In determining the relevance of discrete molecular events within these broader contexts, we often infer their involvement from experiments in isolated cells under somewhat artificial conditions. How do we know that these exquisitely specific events occur under realistic clinical conditions? If so, to what extent? At what point in the process do they occur (acute damage, repair, etc.)? And perhaps most importantly, are they critical to the process? In short, how do we answer as early as possible the ‘so what’ question with respect to our favorite protein–protein interaction, transcriptional induction, or other event? The response to heart damage, for example, likely involves tens of thousands of cells of multiple lineages, each undergoing complex signaling cascades that trigger other equally complex molecular interactions including cell migration, lineage induction, secretion, fibrosis, and revascularization. In determining the relevance of discrete molecular events within these broader contexts, we often infer their involvement from experiments in isolated cells under somewhat artificial conditions. How do we know that these exquisitely specific events occur under realistic clinical conditions? If so, to what extent? At what point in the process do they occur (acute damage, repair, etc.)? And perhaps most importantly, are they critical to the process? In short, how do we answer as early as possible the ‘so what’ question with respect to our favorite protein–protein interaction, transcriptional induction, or other molecular event, and thereby avoid spending years studying a potential epiphenomenon?

One approach is to do what the US NSA does—listen in. Over the past two decades, genetic sensors, beginning with simple transcriptional readouts made possible by these mice will provide a clever way to place luciferase and Katushka genes under control of the separate regulatory elements directing Nppa and Nppb expression within the Nppa–Nppb locus contained within a single BAC. As expression of the two genes is distinct, luminescence and fluorescence are observed in different regions depending on the type of cardiac injury.

The second technology is the continued enhancement of reporters and sensors. Sergeeva et al. exploit the development of the far red fluorescent protein Katushka, which can be optically distinguished from firefly luciferase. Further progress has been made in the development of dynamic sensors and effectors. Genetically encoded Ca2+ sensors are now mature tools that have been deployed in the dissection of heart development, the assessment of cell-based cardiac therapies, and endothelial control of vascular tone. Similarly, optogenetic effectors are beginning to be exploited in order to understand rhythmicity and excitability. Figure 1 shows the distribution of luciferase (blue), Katushka (red), and cellular sensors (green), all precisely targeted by BAC transgenesis.

Two enabling technologies have contributed to the development of effective reporter or sensor mice. First, bacterial artificial chromosome (BAC) transgenesis provides a simple way to express sensor genes with precise transcriptional fidelity, while not perturbing the native gene locus. By inserting sensor cDNAs within large (>150 kb) genomic DNA fragments that include all of the transcriptional control elements operating on a given gene locus and inserting this fragment at a separate point within the mouse genome, sensor expression mimics that of the endogenous gene, bypassing the necessity to understand and recapitulate the many regulatory elements contained within the segment. Several sensor mice important for cardiovascular disease have been created using this approach, and we can expect many more in the next few years. Sergeeva et al. use this technology in a clever way to place luciferase and Katushka genes under control of the separate regulatory elements directing Nppa and Nppb expression within the Nppa–Nppb locus contained within a single BAC. As expression of the two genes is distinct, luminescence and fluorescence are observed in different regions depending on the type of cardiac injury.

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If broadly available to the scientific community as they should be, the expanding palette of genetically engineered sensor mice, including detector and effector lines as well as lines with optically compatible sensors expressed on interacting lineages, will be combined in new and creative ways, allowing the cardiovascular scientific community to tap into the private conversations between and within cells that underlie complex disease processes. The mice described in this issue by Sergeeva et al. add to this growing toolbox that is increasingly empowering the study of cardiovascular biology.

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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References