

Circulation Research 2017 Best Manuscript Award Winners

Roberto Bolli

The Best Manuscript Awards are bestowed annually by the Editors of *Circulation Research* to recognize the most outstanding articles published in the journal. The 2017 Best Manuscript Awards were selected from articles published between November 2016 and October 2017 based on novelty, impact, data quality, and number of online downloads by *Circulation Research* readers. These nonmonetary awards were presented at the Editorial Board dinner in Anaheim, CA, on November 12, 2017.

As part of our new initiative to highlight first authors¹ and early career researchers,² this year we are starting a new tradition of highlighting the first authors of these award-winning articles. For each article, we have asked the first author to provide us with an interesting behind-the-scenes anecdote or insight about the research described in their article. The purpose is to give readers information that is not normally available for published articles, such as how much work the study required, how long it took, the most frustrating aspects of the project, the most gratifying aspects of the project, turning points, critical junctures, etc. We hope this initiative will help readers appreciate the difficulties inherent in performing and publishing a study as well as the human dimension of these endeavors. These things are not mentioned in the published articles and could be likened to the hidden side of the moon. There is much more to a study than what is written in published manuscripts!

Meta-Analysis of Genome-Wide Association Studies for Abdominal Aortic Aneurysm Identifies Four New Disease-Specific Risk Loci

Gregory T. Jones, Gerard Tromp, Helena Kuivaniemi et al, and Matthew J. Bown
Circ Res. 2017;120:341–353

Gregory T. Jones: This paper was a truly global collaborative effort involving over 120 authors from dozens of institutions spread across the world and took approximately 2 years to complete. For many of the contributors, it was their first time in a consortium of this type, and it was inspiring to observe the innate level of goodwill and trust that members brought to this endeavor. Coordinating such a large group was, however, not always easy, and I thank those members who endured teleconference meetings at very odd times of the day and night, and from geographical locations that were about as dispersed as one could imagine (Iceland, New Zealand, The United States, and Europe). Possibly, the most stressful time was whilst waiting to see if the results from the validation cohorts were concordant with the discovery GWAS (genome-wide association study), but the results were certainly worth

it and gave the bioinformaticians on the team plenty of interesting data to investigate. In summary, I feel honored to have had the opportunity to work with such an outstanding team of colleagues, and in particular the cohort leadership, the analysis team and the writing groups who collectively, through a healthy mix of good humor, intellect and common sense, made this complex enterprise possible.³

Myocardial Tissue Engineering With Cells Derived from Human-Induced Pluripotent Stem Cells and a Native-Like, High-Resolution, 3-Dimensionally Printed Scaffold

Ling Gao, Molly E. Kupfer, Jangwook P. Jung, Libang Yang, Patrick Zhang, Yong Da Sie, Quyen Tran, Visar Ajeti, Brian T. Freeman, Vladimir G. Fast, Paul J. Campagnola, Brenda M. Ogle, and Jianyi Zhang
Circ Res. 2017;120:1318–1325

Ling Gao: This study took around 2 years to complete. Along the way, we encountered some difficulties that we needed to overcome. The scaffold used in this project was developed by our collaborator at the University of Wisconsin. In the beginning, because of some technical limitations, we did not receive the correct number of fabricated scaffolds needed to conduct the experiment. However, we were eventually able to overcome this issue. Also, we had learned how to preserve the hiPSC (human-induced pluripotent stem cell)-derived cardiac cells in liquid nitrogen after they had been differentiated when the scaffolds are absent. When we began to transplant the cell-constructed scaffolds, known as human cardiac muscle patches (hCMPs), on the surface of the mouse heart, it was hard to identify the initial upper and lower sides of patch by the naked eye, which made suturing them difficult. To remedy this, a professional cardiac surgeon assisted us in completing the experiment by utilizing the microscope and stereoscope to suture the hCMPs onto the mouse myocardium. We now have the ability to print larger (1 cm²) scaffolds into which we will seed cells. We will then transplant them onto the swine heart for additional studies in the near future. In the interim, our lab moved from the University of Minnesota to the University of Alabama at Birmingham (UAB). Once we arrived, we realized that the new lab did not have the correct set up to resume this project. Because of this, we spent time ensuring the lab was arranged precisely to continue. I am very happy to have our work be published in *Circulation Research*. A special thank you goes to all of the colleagues in our lab, to my supervisor, and to our collaborator for their support.⁴

Single-Dose Intracardiac Injection of Pro-Regenerative MicroRNAs Improves Cardiac Function After Myocardial Infarction

Pierluigi Lesizza, Giulia Prosdocimo, Valentina Martinelli, Gianfranco Sinagra, Serena Zacchigna, and Mauro Giacca
Circ Res. 2017;120:1298–1304

Pierluigi Lesizza: I currently work as a resident fellow in clinical cardiology at the University Hospital in Trieste, which has a long-standing collaboration with the International Centre for Genetic Engineering and Biotechnology (ICGEB) in the same city. As a resident fellow, my major duties are in the clinics. In Italy—unfortunately and surprisingly—there are no officially recognized MD PhD programs. Thus, most of the work I carried out for this project was conducted at nights and on weekends. The idea behind the project was straightforward: the Giacca laboratory at the ICGEB had already shown that the expression of specific microRNAs in the mouse heart after myocardial infarction was beneficial in driving cardiac regeneration. Why not try, then, to achieve the same objective by the injection of synthetic mimics of these microRNAs? All through my work, I could benefit from the outstanding expertise of the Giacca laboratory at the ICGEB in the field of experimental cardiology, as well as count on the assistance of numerous colleagues helping me overcoming small (but sometimes very frustrating) technical issues I had to face. Thus, the work proceeded smoothly and rapidly taking more or less 1 year for its main experiments. The main problem I had to face was to break a sort of preconception in the RNA field, namely that short RNA molecules would be immediately degraded after in vivo administration. While waiting for the results of this experiment, I was very anxious, but then I was amazed to see that synthetic miRNAs injected into the heart persist for more than 10 days in a biologically active form. I believe that the main strength of this work lays in its simplicity: small nucleic acids used straightly as drugs might represent new avenues for future cardiac therapies. In closing, I must say that my personal experience as a clinical cardiologist in training and an experimental scientist has been so far quite unique and fully rewarding.⁵

Fabrication of Synthetic Mesenchymal Stem Cells for the Treatment of Acute Myocardial Infarction in Mice

Lan Luo, Junnan Tang, Kodai Nishi, Chen Yan, Phuong-Uyen Dinh, Jhon Cores, Takashi Kudo, Jinying Zhang, Tao-Sheng Li, and Ke Cheng
Circ Res. 2017;120:1768–1775

Lan Luo, Junnan Tang: A “baby formula” from stem cells? Three years ago, we were challenged by our professors to attack the major hurdles that hamper the stem cell therapy industry. Apparently, one major limitation of cell therapy is the difficulty in storing and shipping cell therapy products. As live organisms, cells need to be carefully frozen, thawed, and processed before clinical applications. How could we develop a product that can emulate the therapeutic effects of stem cells while retaining excellent storage stability? One

day, we were shopping in the grocery, and suddenly we ran into a section full of baby formula cans. The nutrient table on those cans contained the list of “good stuff” contained in the formula and apparently such composition mimicked what had been found in the human milk. That was the “aha” moment for us. We asked: could we study what was essential to the therapeutic benefits of stem cells and then package such information in “baby formula”-like powder? Luckily, such information has been available to the field. Studies from our lab and many others had shown that adult stem cells work by secreting regenerative factors. In addition, the molecules on the stem cell membranes could help the injected cells adhere to the host tissue and trigger activation of reparative pathways in the injured cells by cell–cell contact. With such knowledge, we created synthetic stem cells. Essentially, they are polymer particles which contain the secretome of stem cells and are encased in stem cell membranes. In this way, they were “inside-out” mimicking real stem cells. We created synthetic mesenchymal and cardiac stem cells and tested their regenerative potentials in rodent models of myocardial infarction.⁶

A Comprehensive TALEN-Based Knockout Library for Generating Human-Induced Pluripotent Stem Cell-Based Models for Cardiovascular Diseases

Ioannis Karakikes, Vittavat Termglinchan, Diana A. Cepeda, Jaecheol Lee, Sebastian Diecke, Ayal Hendel, Ilanit Itzhaki, Mohamed Ameen, Rajani Shrestha, Haodi Wu, Ning Ma, Ning-Yi Shao, Timon Seeger, Nicole Woo, Kitchener D. Wilson, Elena Matsa, Matthew H. Porteus, Vittorio Sebastiano, and Joseph C. Wu
Circ Res. 2017;120:1561–1571

Ioannis Karakikes: Given that the study was very technical, we reasoned that it would be feasible to complete the work within two years. Of course, things never go according to plan, and it always takes longer than expected! We made good progress in the first year mainly assembling the TALEN constructs as it was a straightforward, repetitive process. On the other hand, working with iPSCs wasn’t as straightforward as we initially anticipated. We learned that every iPSC line has a “mind of its own.” For example, trying to transfect the TALEN constructs in iPSCs was a nightmare! We tried every transfection reagent that we could get our hands on, but no luck! After numerous failed experiments and a lot of frustration, we finally had some relative success with the nucleofection system. However, we had to develop an optimized nucleofection protocol for every iPSC line used in the study and that wasn’t an easy task, as in some iPSC lines we had to test as many as thirty different protocols to get it right! Similarly, we spent a lot of time optimizing the PCR conditions to amplify the targeted loci. We tested at least 4 primer pairs for each gene with several PCR enzymes—multiply this by 88 and that’s a lot of PCR! As you understand, we ended up doing many, many optimization experiments before we could do any other experiments to demonstrate the utility of the TALEN KO constructs. Generally, there was a very steep learning curve during the first year and half of the project. Overall, there were a few setbacks and a lot of trial and error over a three-year period, but the lessons learned from this study have been very valuable.⁷

Disclosures

None.

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Anthology of Images



View of the Himalayas by airplane (Glenn Hirsch, Louisville, KY). To have your photo considered for the Anthology of Images, please email it to CircRes@circresearch.org

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