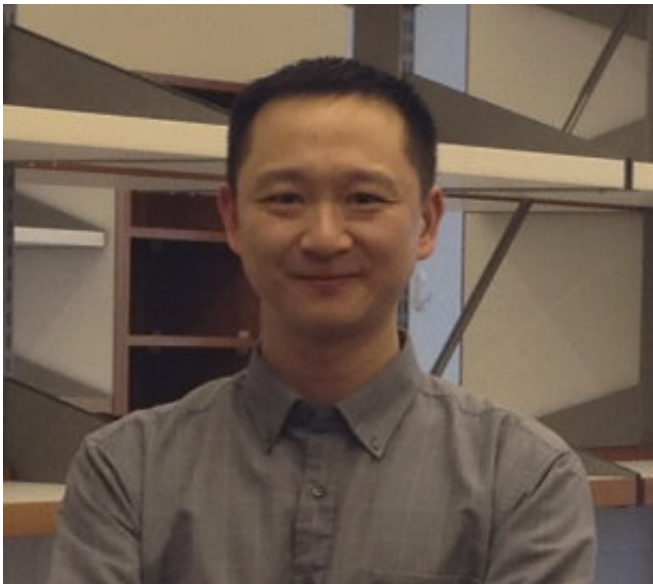


# Sequencing RNA in 20,000 Cardiac cells reveals insights into heart development and disease

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Liming Pei, Ph.D., is a molecular biologist in the Center for Mitochondrial and Epigenomic Medicine at Children's Hospital of Philadelphia. Credit: Children's Hospital of Philadelphia

Scientists using a powerful new technology that sequences RNA in 20,000 individual cell nuclei have uncovered new insights into biological events in heart disease. In animal studies, the researchers identified a broad variety of cell types in both healthy and diseased hearts, and investigated in rich detail the "transcriptional landscape," in which DNA

transfers genetic information into RNA and proteins.

"This is the first time to our knowledge that massively parallel single-nucleus RNA sequencing has been applied to postnatal mouse hearts, and it provides a wealth of detail about biological events in both normal heart development and [heart disease](#)," said study leader Liming Pei, Ph.D., a molecular biologist in the Center for Mitochondrial and Epigenomic Medicine (CMEM) at Children's Hospital of Philadelphia (CHOP) and an assistant professor in the Department of Pathology and Laboratory Medicine in the Perelman School of Medicine at the University of Pennsylvania. "Ultimately, our goal is to use this knowledge to discover new targeted treatments for heart disease. In addition, this type of large-scale sequencing may be broadly applied in many other fields of medicine."

Pei and co-study leader Hao Wu, Ph.D., also of the CMEM and an assistant professor of Genetics at Penn Medicine, published their findings online Sept. 25, 2018 in *Genes & Development*.

While massively parallel single-cell RNA sequencing (scRNA-seq) has been available to researchers in the past three years, it is technically challenging to study single cells in postnatal hearts due to the large size of [cardiac muscle cells](#).

To enable single-cell analysis of large cells such as muscle cells, or cells with complex morphology such as neurons, robust massively parallel single-nucleus sequencing (snRNA-seq) methods have been developed recently in Wu's laboratory, as well as by others in the field. To date, massively parallel snRNA-seq has been applied only to the central nervous system. Pei and colleagues are the first to adapt the technology for use in postnatal heart tissue.

The research team used the snRNA-Seq method termed sNucDrop-seq

to analyze nearly 20,000 nuclei in heart tissue from normal and diseased mice. "We are excited to further develop sNucDrop-seq and apply it to mammalian postnatal hearts, which are of critical medical relevance but difficult to study with standard scRNA-seq," said Wu.

The current study focused on cardiomyopathy, a group of diseases characterized by progressive weakening of the heart muscle, and representing a leading worldwide cause of heart failure. Pei and colleagues used mice developed to model a type of pediatric mitochondrial cardiomyopathy.

"The heart is a complex organ, with a multitude of cell types, and much still remains poorly understood about mammalian heart development and heart disease, especially during the postnatal period," said Pei. "Our study provides key insights in three areas: normal heart development, heart disease, and gene regulatory mechanisms of a heart hormone called GDF15."

The sequencing tool identified major types of heart cells, such as cardiomyocytes, fibroblasts and endothelial cells, as well as rarer cardiac [cell types](#). The study team found great variety among each cell type, as well as indications of functional changes in the heart cells during both normal and diseased conditions. For example, the researchers detected metabolic changes in fibroblasts, the fibrous [cells](#) that make the heart abnormally stiff in heart disease.

Another finding concerned gene networks that regulate production of cardiac hormones in heart disease—specifically GDF15, which slows overall body growth, presumably to reduce the energetic demands on a damaged heart. Such signaling, said Pei, could reveal more about the biological mechanisms that underlie the growth restriction commonly seen in children with [congenital heart disease](#).

Greater understanding of cardiac biology, as provided in this research, said Pei, may lead to targeted therapies aimed at key gene networks that could offer better treatments for heart patients.

"This research was a first step in defining the transcriptional landscape of normal and diseased heart at high resolution," said Pei, who added that future work in his and his collaborator's laboratory will investigate how heart disease progresses over a longer timespan than the early postnatal period. The research tool may also offer opportunities to investigate diseases in organs and systems beyond the [heart](#).

**More information:** Peng Hu et al, Single-nucleus transcriptomic survey of cell diversity and functional maturation in postnatal mammalian hearts, *Genes & Development* (2018). [DOI: 10.1101/gad.316802.118](https://doi.org/10.1101/gad.316802.118)

Provided by Children's Hospital of Philadelphia

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