Laudation for Dr. Phong Nguyen

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Finalist of the Eppendorf Award for Young European Investigators 2024

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Everybody knows somebody who had a heart attack. Cardiovascular diseases are the leading cause of death in humans, with almost 20 million fatalities every year. Not so for zebrafish. Some fish have the enviable capability to regenerate their hearts even after severe damage. Most mammals lost this capacity in the adult stage, while they can regenerate as embryos. In zebrafish, the dead heart-tissue is simply replaced by new cells that first divide, then integrate into the existing muscle tissue and finally start beating in sync with the ensemble of other heart muscle cells. After a few weeks the heart is as good as new. How does that work? Why does it not work in humans? And can we learn from fish how to find ways to also help human hearts to recover after infarction or other damage?

This was the question Phong Nguyen tackled when he joined Jeroen Bakkers laboratory at the Hubrecht Institute. As always, everything starts with gaining a basic understanding of the biological process. We cannot even think of manipulating biology if we do not understand it. Phong knew that the tricky aspect of getting a heart to regenerate is not so much triggering the cells to proliferate – there are already successful approaches to achieve that. It is more about how to make them stop proliferating and differentiating into a fully functional heart muscle cell. As a study system, Phong managed to explant damaged heart tissue of zebrafish and followed both their proliferation and function with life cell imaging.

With this novel approach, he was the first one to follow heart regeneration in real time. The pacemaker signal for the heart is the flux of Calcium ions and it turned out that when the cells transit from their immature and proliferating state to their mature, non-dividing and functionally active state, they change the temporal pattern of their Calcium signals. When Phong then turned to the cellular structure that controls this Calcium signals, he found a protein, LRRC10, that plays a key role in switching the cells from immature to mature. Upon deletion of LRRC10, the cells do not stop proliferating and remain immature. Also, the opposite was true and after induction of LRRC10 the cells stopped dividing and took up their function.

Phong did not stop here: he went one step further and made the leap from fish to mammal. Excitingly, the mechanism was conserved and switching on LRRC10 in mammalian heart muscle cells led to their differentiation into functional muscle.

Phongs findings are not only an excellent lesson about basic developmental principals and show ontogeny and function of a cell are mechanistically intertwined. They also open a new door to controlling heart regeneration. Therapeutic efforts to foster human heart regeneration succeed when it comes to driving the cells into proliferation. But the result is usually not functional tissue but excess dysfunctional tissue, showing as cardiomegaly. Understanding which molecular pathways switch the cells to functional muscle might be the missing piece.

Phong grew up in Melbourne, Australia, where he started his career in stem cell biology. In his PhD, he already made a groundbreaking discovery. He found that muscle stem cells and hematopoietic stem cells are developmentally interlinked by their common niche. Already here, Phong demonstrated how far he is willing to go in his investigations and the mechanistic depth of his thesis work is truly remarkable. Phong clearly is afraid of nothing. He addresses the big questions, develops new technology and does not stop searching until he is at the molecular level.

Phong just arrived in Paris, where he is about to set up his own lab at Institute Curie, one of the best places to mix basic research with translational ambitions. We are excited to see what he will discover with his young team!