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Transplant and Stem Cell Immunobiology: Translational Directions for Cardiovascular Disease Research

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Editorial

Scientists all over the world are racing to advance transplantation therapies for wide-ranging medical diseases and disorders. Our laboratory (Figure 1A) is focused on the development of new medical treatments for cardiovascular disease, the leading cause of death worldwide. Many of the current viable treatment options for cardiovascular disease rely on transplanting genetic material that does not match that of the donor recipient (i.e. allogeneic organs or tissues). Whether in response to transplantation of full organs, tissues, or cells, the recipient body's propensity to reject transplanted material is one of the greatest hurdles currently in the way of creating successful clinical treatments.

Our laboratory believes that to effectively treat the many sides of cardiovascular disease, it is important to cultivate a myriad of diverse clinical options. Our "wide angle lens" approach to disease research includes developing methods for preventing post-treatment complications, bioengineering tissue for transplantation, and promoting effective stem cell therapies (Figure 1B). By pursing these and other research directions in parallel, we hope to combat cardiovascular disease from multiple angles. Here we describe several of our recent findings, and discuss possible future research directions.

In 2014, we proposed that dichloroacetate could be used to prevent in-stent restenosis [1]. In-stent restenosis is a potentially deadly post-treatment complication, and is characterized by extreme amounts of smooth muscle cell (SMC) proliferation. In an injury model of myointima formation, SMCs displayed both a higher proliferation rate and resistance to apoptosis. Interestingly, at the same time the membrane potential of the SMC's mitochondria became hyperpolarized. We identified pyruvate dehydrogenase kinase 2 (PDK2) as a regulator of these phenomena. By blocking PDK2 function pharmacologically (with dichloroacetate) or genetically (through a lentiviral approach), the hyperpolarization of the mitochondrial membrane potential was reduced and SMCs regained their ability to enter apoptosis. Since dichloroacetate weakens the pathogenesis associated with in-stent restenosis and has a narrow range of molecular targets, it a strong candidate for future use in preventing post-treatment development of proliferative vascular diseases.

Despite significant advances in clinical research, cardiovascular disease remains the number one cause of death worldwide. Until recently, organ transplantation has been the major technique for treating heart disease, but this option faces severe difficulties since organ availability is low and often accompanied by an excruciatingly long wait. The "holy grail" of cardiovascular research would be development of an efficient method to regenerate cardiac tissue in patients. One promisingly innovative method to repair heart tissue relies on transplanting stem cells into the myocardium. While stem cell therapy has shown great potential, rejection of transplanted allogeneic stem cell material has constrained the prospective positive effects of this technique. With this in mind, it has been suggested that quick and easy generation of patient-specific pluripotent stem cells could be accomplished by somatic cell nuclear transfer (SCNT). While the creation of such cells can be successfully achieved, we have recently shown that transplanting nuclear transfer-derived embryonic stem cells (NT-ESCs) causes a strong adaptive immune response to due to their allogeneic mitochondrial DNA [2]. Mismatched-mitochondrial proteins appear to cause NT-ESCs to be readily rejected by the recipient. Further research on stem cell therapies should take into account the effects of non-autologous mitochondria on immune system rejection.

Bioengineering heart tissue is another potential method to restore non-functional myocardial tissue after ischemic heart injury. However, how the transplant recipient's immune system will react to the scaffolding of bioengineered tissue remains an open question. In our laboratory, we tested a fibrin-based matrix as the structural basis for growing transplant-ready heart tissue from autologous cells in an animal model [3]. After transplantation, although the fibrin matrix itself caused an increased immune response, it did not appear to affect the long-term retention of the transplanted syngeneic cells. This suggests the future possibility of using a fibrin-matrix scaffold to support patient-specific stem cell-derived tissue grafts.

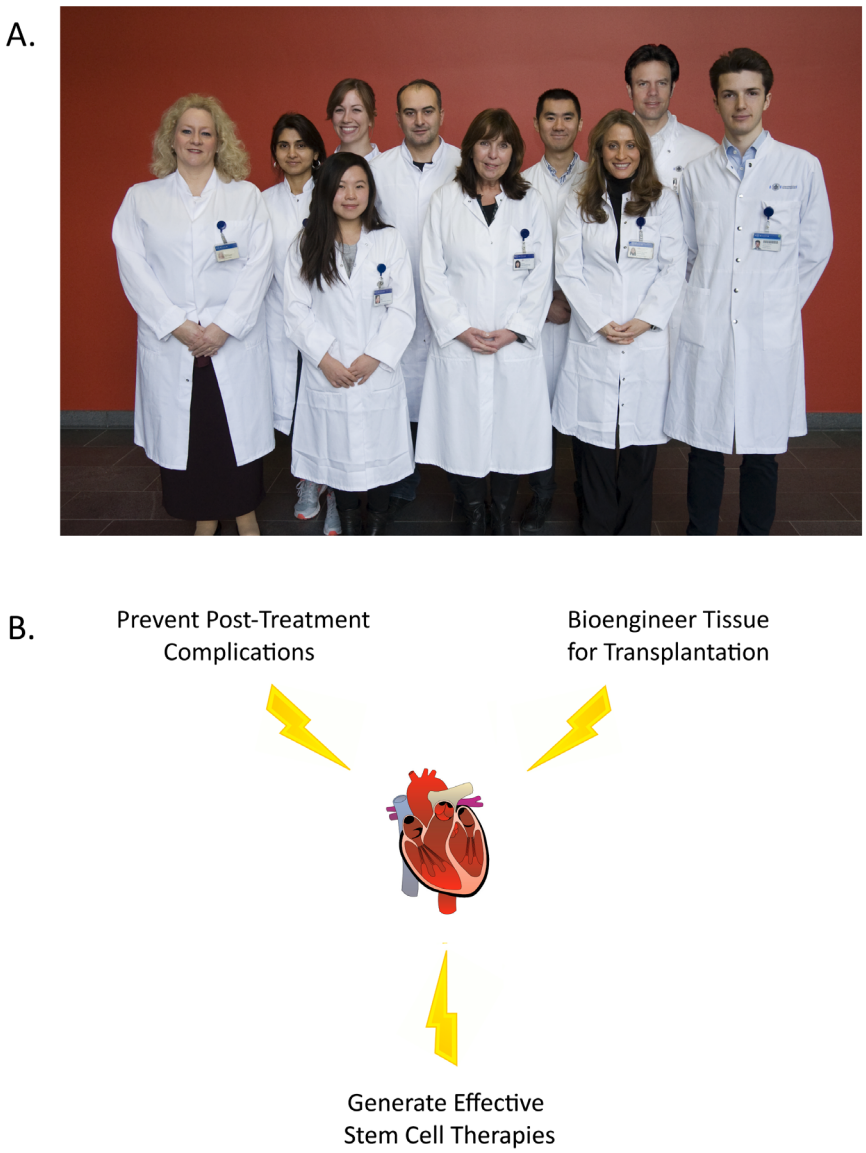

Figure 1: Worldwide, diverse treatment methods are being developed in the race to combat cardiovascular disease.
(A) Our laboratory takes a "wide angle lens" approach to disease research, pursuing a myriad of research directions in parallel.
(B) We discuss here three recent studies from our laboratory, including novel research directions for preventing post-treatment complications, bioengineering tissue for transplantation, and generating stem cell therapies.

Laboratories worldwide, including our own, continue to pursue numerous important open scientific questions with regard to transplant immunology, including how to prevent post-transplant rejection of allogeneic material. While patient-specific induced pluripotent stem cells would be one solution to this problem, generation of individual patient cell lines is extremely time, cost, and labor intensive. A more pragmatic option would be to molecularly modify the immunogenicity of a stem cell line in order to create a ready-for-use "off the shelf" cell line. Alternatively, generating a local hypo-immunogenic environment would be a novel method to prevent post- transplant rejection of allogeneic material; however, such a method has yet to be described. Successfully developing either of these technologies would be highly beneficial to both researchers and clinicians.

Over time, scientific research has moved toward specialization, with most projects focusing only on one particular area of disease treatment. We believe that specific research goals are of great importance, as they provides strong and direct insight into problems, but we also believe that diverse diseases – such as cardiovascular disease – require diverse and individualized treatment options. Simultaneously approaching numerous solutions using multiple progressive technologies is our best bet for generating effective clinical therapeutics.

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