Impact Objectives

- Overcome severe heart failure via regenerative vascular reconstruction and cardiac regeneration
- Develop biodegradable small diameter vascular grafts

A mission to cure heart failure

***Associate Professor Kyohei Oyama** is engaged in a collaborative project seeking to help patients overcome severe heart failure and contribute to the treatment of coronary heart disease*

What inspired you to research ways to overcome severe heart failure?

The heart is the only organ that moves dynamically and has functioned as a symbol for life since time immemorial. This is what makes me believe that studying the heart is special and so working to overcome problems with the heart, including heart failure, has always just made sense to me. Coronary heart disease is one of the major causes of death around the world - once cardiac tissue is damaged, heart function irreversibly reduces and results in heart failure. While scientists have worked tirelessly to address this - and healthcare technology has dramatically improved - to date, no treatment that completely cures the problem has been established. I hope that with my current investigations on heart regeneration and biodegradable vascular grafts I can make significant contributions to the treatment of coronary heart disease and help save countless lives in Japan and other countries around the world. This is my chief inspiration and one that motivates me every day.

Can you tell us about some of the challenges you have faced in your studies?

When I started to plan my current research project on developing biodegradable small diameter vascular grafts, I had no idea what material should be used or how to prepare appropriate scaffolding to achieve our purpose - I am a molecular biologist by trade, not a biomaterials expert. Fortunately, I found collaborators who provided the necessary expertise to advance the project and overcome the challenges and limitations my team was experiencing.

You are working closely with international partner Professor Patricia Pranke, from the Hematology and Stem-cells Laboratory at the Federal University of Rio Grande do Sul. What is her involvement in this work?

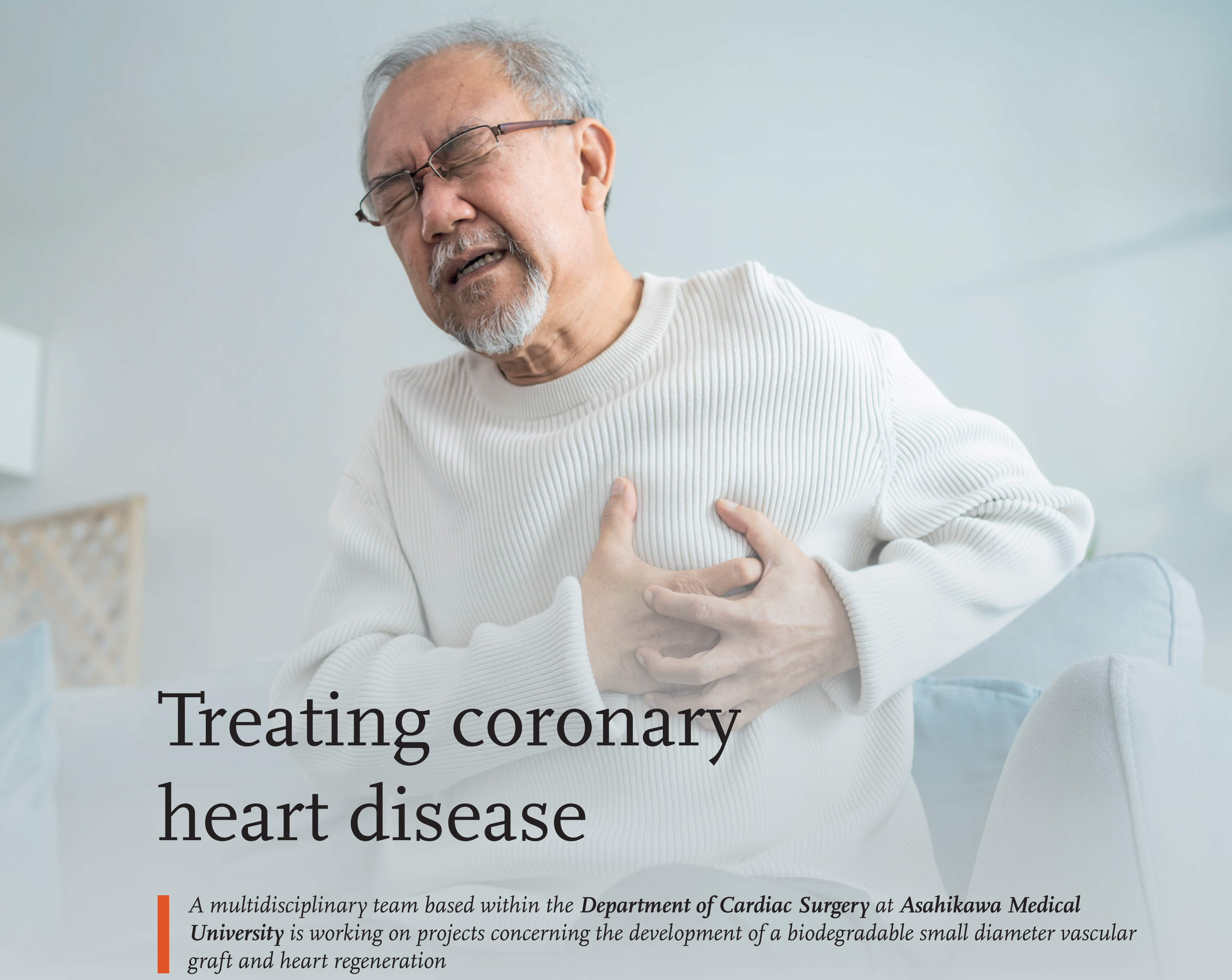
Pranke is an expert of biomaterials and regenerative medicine. Both of us attended a scientific congress called TERMIS (Tissue Engineering and Regenerative Medicine International Society) and by chance we were seated at the same table. After having a casual discussion about our respective research interests, we realised we had similar goals but different expertise. From there, we decided to combine our skills and experiences to accelerate research progress through collaboration. Given Pranke's expertise in biomaterials, her role is to create a new scaffold that is suitable for a vascular graft. This involves combining and mixing different materials, adding functional modifications and changing methodologies to make the scaffold. We then test what she has created at Asahikawa Medical University using animal models and, following feedback, work to improve the compatibility of her creation.

Can you tell us about any other collaborations you are engaged with?

For the degradable small diameter vascular graft project, we also collaborate with domestic institutions and industries: Life Materials Development Section, Human Life Technology Research Institute; Toyama Industrial Technology Research and Development Centre; and the Business Development and Quality Control Department, Iaazaj Holdings Co., Ltd. They make the nanofibre vascular graft for us following and updating protocols Pranke established. This is particularly important for us to speed up our study, since all graft preparation can be done domestically.

For the heart regeneration project, I collaborate with Dr MacLellan at the University of Washington in the US. We have different genetically modified animal models where cardiac proliferation can be activated and share the experimental skills and data obtained from both animal models to understand the mechanism of how the proliferation of cardiac myocytes is regulated. Combining data from different animal models allows us to make new hypotheses quickly.

Put simply, without these collaborations the research would not be possible.



Treating coronary heart disease

*A multidisciplinary team based within the **Department of Cardiac Surgery** at **Asahikawa Medical University** is working on projects concerning the development of a biodegradable small diameter vascular graft and heart regeneration*

Coronary heart disease (CHD) is one of the major causes of death worldwide. While improving lifestyles can make a dramatic difference to the deaths from CHD, there is clearly an ever-increasing need for researchers to find more effective means of tackling the problems associated with this disease.

Fortunately, in recent years there have been dramatic improvements in the treatment of patients with CHD, perhaps most notably in revascularisation. This is a process by which blood flow to the heart is restored after the arteries have become clogged with plaque and is typically achieved through coronary heart bypass surgery or angioplasty and stenting. However, these methods are not without their problems - to achieve a successful vascular graft, it is necessary to use one with a diameter that is less than 4mm. While this is readily achieved by utilising materials located within a patient's own body, this is not always a viable method of treatment and, as it stands, no artificial vascular graft at such a small diameter is available.

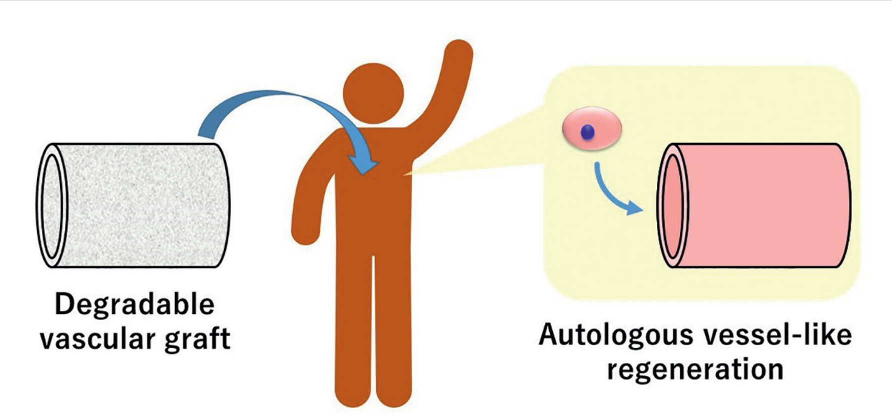
Thus, scientists around the world have turned their attention to the development of biodegradable artificial vascular grafts, which hold great potential for various reasons. Not only do they avoid issues with availability, they also resolve elastic mismatch, infection and calcification. They are therefore an attractive area of enquiry for researchers interested in overcoming many of the challenges associated with CHD.

BENEFITING PATIENTS BOTH YOUNG AND OLD

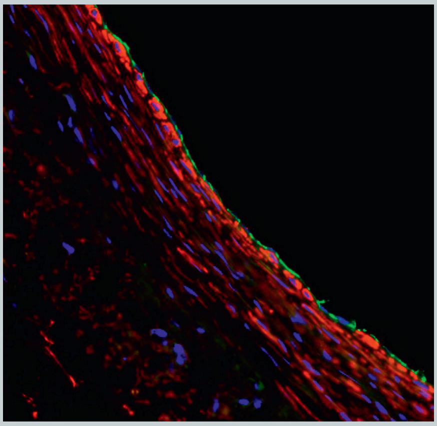
It is with the above in mind that Associate Professor Kyohei Oyama has embarked on one of his latest research projects. Based within the Department of Cardiac Surgery at Asahikawa Medical University in Japan, Oyama has long had an interest in the heart and improving treatments for those experiencing heart problems. Oyama and his team are currently engaged in two main projects: Creating a biodegradable small diameter vascular graft; and developing a heart regeneration treatment via endogenous cardiac myocyte proliferation. 'Revascularisation is the first line of treatment for patients with CHD, but there are various limitations with this procedure, including the fact that foreign materials in the body can cause severe infection and calcification, as well as being a compliance mismatch in the patient,' describes Oyama. 'Both of these problems can be overcome through the development of a vascular graft that can degrade and encourage a self-regenerative vascular graft,' he says.

If this team is able to develop a biodegradable small diameter vascular graft, it will not only benefit patients that require the revascularisation of small vessels, it will also have significant positive impacts on young patients who are still growing. Given that regenerated vascular grafts act as native vessels, it is expected that they will grow and repair as the patient does. The other

Concept for self-regenerative vascular grafts: biodegradable nanofibre vascular grafts provide a scaffold for autologous cells to attach themselves, and guide them during self-regeneration of vascular tissue. Upon degradation of the scaffold, the nanofibre grafts transform into autologous vessels.



PCL graft exhibiting autologous vessel-like regeneration inside a rat. Regenerated endothelial cells and smooth muscle cells are shown in green and red, respectively.



potential major benefit is the discoveries made through the course of this research might demonstrate suitability for other organ regeneration.

HEART TISSUE REGENERATION

While revascularisation is the current gold standard for CHD, it is only able to treat the coronary issues, rather than recover the lost cardiac tissue. Thus, in order to achieve a complete cure of heart failure, developing a strategy to replace scar tissue with functional new cardiac tissue is essential. 'The reason why cardiac tissue is unable to regenerate is that cardiac myocytes (muscle cells) have no ability to proliferate,' explains Oyama. 'I am therefore working on understanding the mechanism that limits this proliferation ability with a view to activating it.'

If Oyama proves successful in this endeavour, then it is fair to say that the treatment of CHD will be transformed and many, many lives will be saved. 'Indeed, if cardiac myocyte proliferation can be activated when performing the revascularisation of CHD, then the damaged heart can be completely cured and the possibility of heart failure removed,' he highlights. Thus, it is important for the team to study how to induce cardiac regeneration in parallel with developing an artificial vascular graft - which is where the two separate, though heavily related projects came into being.

MECHANISMS OF REGENERATION

As it stands, autologous vascular grafts are harvested from patients, which quantitatively and qualitatively limits the availability of them. In addition, harvesting these grafts is a highly invasive procedure which can lead to complications. Developing a biodegradable vascular graft will overcome these problems and improve patient outcomes. The team is currently engaged in testing their grafts in small animal models and have demonstrated that using a biodegradable nanofibre known as polycaprolactone has exhibited some regeneration ability.

While this is some way from being definitively effective, it demonstrates enough efficacy to encourage Oyama and the team to pursue this line of research.

> *'We have successfully shown that our biodegradable graft exhibits autologous vessel-like regeneration in small animal models'*

'So far, we have successfully shown that our biodegradable graft exhibits autologous vessel-like regeneration in small animal models,' observes Oyama. 'Next, we would like to demonstrate the feasibility of the graft using a clinically-relevant model such as pig coronary artery bypass surgery. To this end, we are currently addressing two challenges: improving the anticoagulation properties; and improving degradability to facilitate replacement with autologous vascular tissue,' he says.

The promise that this research has shown gives huge encouragement. However, the cellular and molecular mechanisms involved in regeneration are still unexplored and it is essential to understand these mechanisms to drive the research forward. Oyama and his team intend to address these questions in the future, in the hopes of making significant contributions to the eventual cure of heart disease. ●

Project Insights

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Associate Professor Kyohei Oyama received his doctoral degree in Pharmacy, and then worked on molecular mechanisms of cardiac growth as a postdoctoral fellow in University of California, Los Angeles and University of Washington. Currently, he is an associate professor/lecturer in the Department of Cardiac Surgery, Asahikawa Medical University. Oyama's research interest is to overcome severe heart failure via regenerative vascular reconstruction and cardiac regeneration.

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