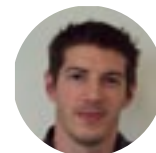


Bristol Heart Institute

Newsletter: Autumn 2021

Welcome

Professor Andy Judge, Head of Section for Cardiovascular Surgery and Vascular Biology, reflects on recent successes.



With the new academic year underway, we welcome our new cohorts of postgraduate taught master's degree students for the MSc in Perfusion Science and the MSc in Translational Cardiovascular Medicine (TCM). The teaching sessions are now back in person for the campus based TCM students and Perfusion students, and our student numbers are good.

I'm pleased to report that the labs, which closed for three months at the start of the pandemic, have been open since June 2020. Staff are gradually returning to the office at Level 7 of the BRI as the University has launched its blended working trial policy, and we are now seeing more staff in both the labs and offices.

Within our section for Cardiovascular Surgery and Vascular Biology at the University, we are delighted to have been able to appoint staff to new posts. Dr Kerry Wadey has been appointed as Lecturer in Cardiovascular Medicine on an open-ended core funded post. Francesco Paneni has been appointed as a Professor in Cardiology and Tom Johnson as an Associate Professor in Cardiology and they are expected to begin working with us at the start of 2022.

A number of staff in our section have had success following the annual University promotions procedure. Jason Johnson has been promoted to Professor of Cardiovascular Pathology, and Umberto Benedetto becomes Professor of Cardiac Surgery. Staff from the Teaching and Learning for Health Professionals (TLHP) programme have recently joined our department

of Translational Health Sciences and come under the umbrella of our cardiovascular section, where we are delighted to congratulate Andrew Blythe on being promoted to Professor of Medical Education in this year's annual promotion procedure.

Huge congratulations to all those recently promoted: we wish them continued success in their careers.

In this issue

[Blood vessel image is a winner](#)

[Pioneering stem cell therapy at Bristol Royal Hospital for Children](#)

[New research lifts lid on cardiac microvascular dysfunction](#)

[Research into new treatments for CHD boosted by funding awards](#)

[Cardiovascular researchers visit Bristol primary school for Clinical Trials Day](#)

[Remote cardiac care for patients with pacemakers](#)

[Fostering collaboration and supporting ECRs at the BHI 5th Annual Meeting](#)

[BHI Steering Group](#)

Blood vessel image is a winner

Dr Elisa Avolio wins BHF's national science image competition.



Bristol Heart Institute Research Associate Dr Elisa Avolio has won the 2021 British Heart Foundation 'Reflections of Research' image competition. The competition challenges BHF-funded scientists to showcase their state-of-the-art heart and circulatory disease research through captivating images.

Her entry 'recreating heart blood vessels' was chosen as this year's judges' winner. Although at first glance it appears to resemble a luminous jelly fish, the image shows new blood vessel-like structures – pictured in green in the centre – sprouting from a 3D gel.

Dr Avolio created the structures using a mixture of two types of heart cells – cardiac endothelial cells, which line the inside of every blood vessel, and pericytes, which 'hug' the outside of blood vessels to support the vessel and help it function.

During a heart attack, the arteries that supply blood to the heart are blocked, cutting off blood flow. The area of the heart starved of blood and oxygen dies, and it no longer functions to help the heart pump blood around the body. Dr Avolio is researching ways to encourage the formation of new blood vessels to replace those that have died, to restore blood supply to damaged areas of the heart.

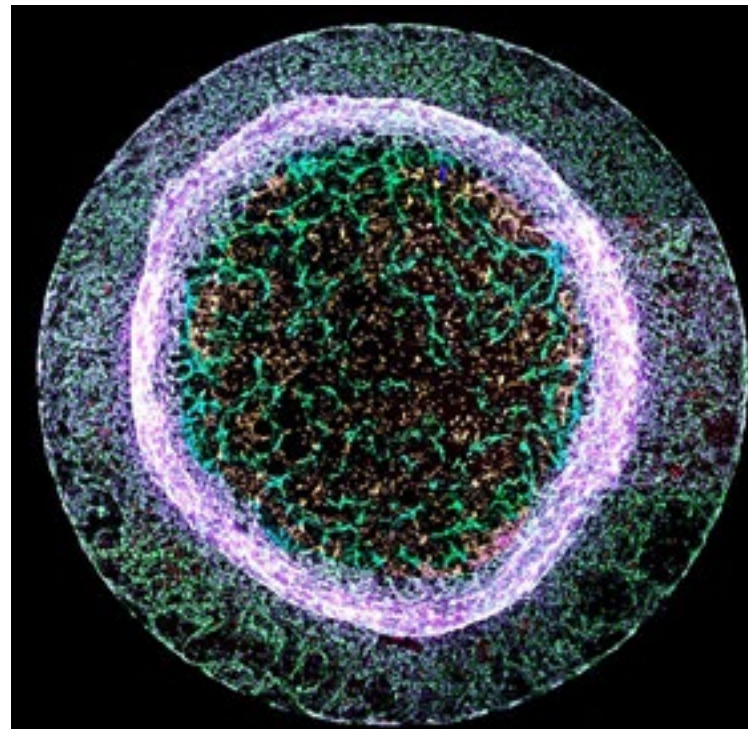
She said: "It is fantastic to have won this year's Reflections of Research competition. Each year the entries display such variety in the BHF's work to support heart and circulatory disease research. By recreating models of the heart blood vessels, we can see how the cells in blood vessel walls interact with and talk to other cells. This knowledge, along with understanding what molecules promote or block the formation of blood vessels, could be used in the future to develop new treatments for patients after a heart attack."

BHF Chief Executive and judging panel member, Dr Charmaine Griffiths, added:

"All of this year's entries beautifully capture aspects of the heart and circulatory system, bringing to life the challenges that BHF scientists work tirelessly to solve. I love the winning image not just because of its circular beauty, but also because of the hope it represents for the future of healing damaged hearts."

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Recreating heart blood vessels: Dr Elisa Avolio

Pioneering stem cell therapy at Bristol Royal Hospital for Children



Dr Filippo Rapetto discusses an innovative case using donor stem cells which offers hope for babies born with heart problems.

Filippo, can you tell us what happened?

Finley was four days old when he was diagnosed at Bristol Royal Hospital for Children with transposition of the great arteries, which affects about one in 3,000 newborns. The treatment, which is very well established, is an operation called arterial switch procedure, which includes a complex surgical step called coronary artery translocation. Unfortunately, in this case, one of the coronary arteries had an anomalous course and the translocation was not successful. This caused a significant deterioration in Finley's cardiac function.

We struggled for a couple of months with various treatments, such as extra corporeal membrane oxygenation (ECMO). After we managed to wean him off that, he was still in intensive care for many weeks, dependent on inotrope drugs to increase his heart function, which was very poor.

Because there was no conventional way to treat his condition, Professor Massimo Caputo with the Paediatric Cardiac Surgery team, the Paediatric Cardiology team and the Paediatric Intensive Care team, suggested we source donor mesenchymal stromal cells (stem cells) to inject directly into Finley's heart with a second surgical procedure. We have a collaboration with the Centre for Cell, Gene and Tissue Therapeutics (Royal Free Hospital, UCL) which provided us with the cells within a few days. Professor Caputo managed to get compassionate funding from the Trust, and he got the process going quickly.

Following the procedure, we noticed a slow but consistent improvement in the patient's clinical conditions. We then did multiple echocardiograms to monitor the cardiac function, and it got gradually and consistently better. He was able to go home about three months after the stem cell injection.

Has he made a full recovery?

He started from what we call a severe dysfunction and now his heart function is close to normal, comparable with someone who had a heart operation as a newborn.

What evidence do you have that the procedure worked?

From a scientific point of view, the only way to know whether this procedure helped would be to take some of the patient's myocardium (muscular tissue of the heart) and analyse it, which clearly we cannot do, but the clinical change after the injection was impressive.

This stem cell injection technique is not something that we invented, but this case is the first in the world that we know of, for this condition, at this age, in a patient with established cardiac dysfunction (rather than as a preventive measure), and with donor stem cells rather than previously collected cells from the patient.

How difficult is it to find a match from donor stem cells?

One of the criticisms made about this approach in the past is that there is a potential risk of triggering an immune response, but this has been shown not to be the case. No complex immunological matching is needed to utilise the cells, as they don't necessarily have to survive in the patient for a long time. The hypothesis is that they promote the recovery of the patient's own tissues by acting as modulators of the patient's healing processes.

Once we took the decision to try this procedure, then everything happened pretty quickly, and that's the beauty of it. Because he was getting worse, we didn't have the possibility of isolating their own cells and making them grow to obtain a sufficient dose – he was too unwell. *(continued on next page)*

Was there an alternative?

In desperate cases like this one, you could go to urgent transplantation, but it's very difficult to find a heart for a newborn because there are very few donors. Also, this happened in the middle of the first lockdown, when the transplantation service had pretty much stopped all over the country, for nearly all patients, so this wasn't an option.

Stem cell treatment is not the codified, recognised treatment, whereas transplantation is, so we had a discussion with several transplant centres. But I think the chances of finding a heart in time, and ultimately the chances of a good outcome, would have been minimal if we had waited longer.

What's the next step in the research?

This case is important because it demonstrates that cells that are not autologous (that come from different individuals) are safe to use. There are a lot of patients with other congenital heart conditions that could potentially benefit from this concept, so this is extra evidence that stem cell therapy has potential.

Might this technique become a standard way of treating these kinds of conditions?

With Professor Caputo's research group, we already use similar stem cells in our animal research projects, and we are trying to translate their use from animals to humans. There are several common congenital heart defects, which require some sort of surgical valve and/or vascular replacement with prosthetic materials, but these materials don't grow or repopulate with the patient's tissues. We want to reduce the rate of replacement, so we are trying to merge the currently available materials with stem cells to create a more biologically compatible tissue to be used in children.

We are delighted that Professor Caputo has been awarded a three-year BHF Translational Award to take this research to the next stage. If a subsequent clinical trial shows that the therapy is effective, this new treatment could potentially avoid repeated high risk and stressful heart operations, and significantly improve quality of life for many children living with congenital heart disease.

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Finley, pictured in autumn 2021

[Read the case report](#)

New research lifts lid on cardiac microvascular dysfunction



Findings could lead to development of new treatments.

New research has shown abnormalities in the tiny blood vessels of human hearts in regions well beyond the large arteries with atherosclerotic blockages that trigger the need for stents or bypass surgery. The findings could lead to development of new treatments for patients with angina-like symptoms without blockages or those recovering from a heart attack or unexplained heart failure.

Normal intrinsic constriction of these micro-arteries in response to changing blood pressure is called myogenic (automatic) tone. Myogenic tone controls blood flow distribution within the heart muscle, and in other parts of the human body.

Current heart scans can identify blockages in large coronary arteries, but they are unable to show these tiny, hair size micro-arteries in patients, making it impossible to diagnose poor myogenic tone, which is thought to develop independent of disease in the larger arteries. This study used tissue biopsies to study the function, structure and alterations in pathways in the micro-arteries that link to abnormalities in myogenic tone.

Professor Raimondo Ascione (Clinical Lead) at the University of Bristol and Professor Kim Dora (Basic Science Lead) at the University of Oxford led the study, which was funded by the BHF.

The research team took small heart samples, that are otherwise discarded, from 88 patients with no large coronary artery blockages and undergoing valvular cardiac surgery at the BHI. In addition, cardiac samples were obtained from three human organ donors from the Newcastle Institute of Transplantation Tissue Biobank and 45 pigs treated at the University of Bristol Translational Biomedical Research Centre (TBRC).

The research team found that 44 per cent of the micro-arteries from patients had abnormal myogenic tone despite retaining their cell viability. This abnormality was associated with an excessive presence of a molecule called caldesmon within the muscle cells in the wall of the abnormal micro-arteries and with poor alignment of these contracting cells compared to micro-arteries with normal myogenic tone from the other 66 per cent of patients, and all the organ donors and pigs.

Abnormalities in the micro-arteries affects the blood supply within the beating heart, and other organs in the body, affecting people's quality of life and life expectancy.

The findings offer new insights on coronary microvascular dysfunction that could predate the development of clinically known heart disease such as heart failure.

There is now a new area of research that confirms thousands of patients, mostly postmenopausal women, have angina-like symptoms despite their coronary angiogram showing no obvious blockages of the large epicardial arteries in the heart that are usually treated with stent or bypass. Other patients seem to develop heart failure associated with either the contraction or the relaxation of their heart for no obvious reasons.

The human coronary micro-arteries the Bristol and Oxford team has studied in the laboratory represent the microvascular area in human organs (lung, heart, brain and elsewhere) where COVID-19 has caused most of the problems during the pandemic.

[Read the paper in Cardiovascular Research](#)

Research into new treatments for CHD boosted by funding awards



Two new grants will further research into progeria and pulmonary hypertension.

MRC: Gene-inspired therapy to rescue cardiovascular disease in progeria: awarded to Paolo Madeddu

Hutchinson-Gilford progeria syndrome (HGPS), characterised by a rapidly ageing appearance, is a rare disease caused by an abnormal gene and related protein. Because there is no effective cure, children with HGPS will, on average, die of cardiovascular disease at around 14 years old.

This project proposes a new treatment where a gene - found in people who live a long and healthy life - is transferred to rescue the premature cardiovascular senescence typical of HGPS patients.

Professor Paolo Madeddu's team has discovered a beneficial variant of the BPIFB4 gene, and shown in animal models that transferring this gene reduces the suffering from a heart attack, diabetes and high blood pressure. Preliminary studies showed that the longevity BPIFB4 mutation can benefit some molecular mechanisms that are dysfunctional in children with HGPS.

Paolo says: "We will determine the efficacy of BPIFB4 gene therapy in HGPS mice, looking at the treatment's ability to preserve heart and blood vessel function. In addition, we will investigate the mechanisms underpinning this benefit, using human cells from HGPS patients. If results are positive, we will continue our research confirming the lack of toxicity, defining the best dose and timing of treatment for prolonged benefit and the advantage of adding BPIFB4 therapy to current drugs, in view of obtaining permission for a clinical study in patients."

HRUK: Targeting pericytes for halting pulmonary hypertension in infants with CHD: awarded to Paolo Madeddu, Massimo Caputo and Elisa Avolio

Some children are born with a ventricular septal defect: a hole in the wall between the two lower chambers of the heart, where blood can flow across the hole from the left side of the heart to the right. If the defect is not corrected in time, children are likely to develop pulmonary hypertension (high pressure in the blood circulation to the lung).

Surgical correction of the ventricular shunt usually allows the blood pressure in the lungs to return to normal levels. In some cases, however, the pressure may stay higher than normal after surgery.

At least five to 10 per cent of patients with congenital heart disease develop pulmonary arterial hypertension (PAH), which can lead to heart failure. The risk of developing pulmonary hypertension is higher for children living in poor countries and areas of social deprivation, because of the limited access to specialist centres where the cardiac defect can be recognised and corrected before complications arise.

Recent research indicates pericytes - multi-functional cells embedded within the walls of capillaries - could be targeted for the treatment of PAH. Paolo says: "Our research will investigate why pericytes from children with CHD constrict and block the pulmonary circulation. It will also test a new treatment to reduce the contraction of pulmonary pericytes and prevent pulmonary hypertension occurring."

Cardiovascular researchers visit Bristol primary school



Drs Lucy Culliford, Andrew Shearn and Giovanni Biglino took part in an outreach activity at Bristol's Parson Street Primary School in May 2021.

Dr Lucy Culliford organised the visit on behalf of the Bristol Trials Unit. The group explained some of their research to the Year 6 students and, as the visit happened in the same week as Clinical Trials Day, it was also an opportunity for Lucy to ask the students to think about clinical studies, the idea of randomisation and 'what is a clinical trial?'. The group showed the THERMIC 3 animation video, which was developed as part of the TRECA study exploring children's and young people's engagement with clinical trials.

Giovanni gave an overview of the technology involved in 3D printing and Andrew brought a series of heart models, including examples of babies' hearts with congenital heart disease, which sparked some stimulating conversations with the 53 students who attended.

They explained that 3D printing technology can produce models of human organs using scans taken during routine visits to the hospital. Bristol Royal Hospital for Children use this technique to create heart models from patients with congenital heart disease. Being able to hold a life-size model of the patient's heart can complement information the surgeon or cardiologist can get from medical imaging – for example, they can practice aspects of the surgery or decide the best route to access a specific part of the heart. The models are also used when explaining the details of the case to a patient or a parent.

The children asked lots of questions about 'holes in the heart', as some had had siblings with this condition. They also asked how smoking can affect the heart, and if the researchers could show them a video of a beating heart.

Lucy said: "This is the first time we've done a school visit as part of our outreach activities around Clinical Trials Day, and it was a real pleasure to talk to the children. They were very engaged and although they had only started learning about the heart the day before, they already knew lots about heart anatomy, and had more questions than we had time to answer!"

Get involved in schools outreach

If you would like to run a, outreach activity, contact your local school. Schools often have science weeks, or may be doing a topic related to cardiovascular research. Parson Street Primary School use the Cornerstones curriculum and the year 6s had just started the 'blood heart' topic - the following week they had a visitor demonstrating a heart dissection!



Remote cardiac care for patients with pacemakers

Charity appeal receives NHS Charities Together funding boost.

Bristol & Weston Hospitals Charity (formerly Above and Beyond) has been awarded £57,000 from NHS Charities Together to support its appeal to provide at-home monitoring service for BHI patients with pacemakers.

Thousands of BHI patients have a cardiac implantable electronic device (CIED) or pacemaker to help control or monitor irregular heartbeats. Having a CIED requires them to attend hospital as often as every six weeks to be checked.

However, COVID-19 restrictions have severely affected patients' ability to attend their hospital appointments. The average age of a person with a CIED in the UK is 75 years old, which puts these patients in a high-risk group.

Over lockdown, the BHI identified technology that would allow CIED patients to be monitored remotely instead. By providing patients with home monitoring equipment that they place by their bed, staff could routinely assess patients and perform essential tests without the patient leaving their home.

Remote monitoring reduces mortality in these patients as it enables the CIED clinic to detect heart failure events at an early stage and intervene before the patient develops symptoms. This includes being able to detect Atrial Fibrillation, which is the leading cause of stroke in the UK.

Following a successful trial in a cohort of complex CIED patients, Bristol & Weston Hospitals Charity

launched an [appeal this year to provide remote monitoring technology for all CIED patients at the BHI](#). This will reduce both waiting times in the clinic and the number of hospital visits overall, while providing an even more effective level of service and care.

The NHS Charities Together award, announced in September, comes as part of a package of support for 10 different health projects that will benefit more than 100,000 people in Bristol and beyond, not only those with heart conditions. [Find out more](#)



Staff at the BHI: Reproduced by kind permission of Bristol & Weston Hospitals Charity bwhospitalscharity.org.uk

Fostering collaboration and supporting early career researchers

Members shared their work at the BHI's 5th Annual Meeting.

Eighty Bristol Heart Institute researchers joined 'Fostering collaboration and supporting early career researchers', our 5th Annual Meeting, on 19 November 2021. The day was an opportunity not only to get to know some of the research taking place in the University's Specialist Research Institute, but also the researchers driving it forward.

In the first session on cardiac surgery, Massimo Caputo looked at tissue engineering, combining surgical facilities and imaging technologies in 'hybrid' theatre, cardiac 3D printing to help plan operations and how advances in VR technology are taking this to the next level.

Next, Tom Johnson, Consultant Cardiologist and recently appointed Associate Professor, examined a range of cardiovascular research priorities, from intracoronary imaging, to industry collaboration, AV Cath lab broadcasting to encourage collaboration and the potential for system-wide datasets to enhance patient outcomes.

Jules Hancox from the School of Physiology, Pharmacology and Neuroscience shared some thoughts on career progression for early career researchers, including memorable advice about choosing a research project: "Interesting is not equivalent to important" – a trap that all researchers fall into from time to time, he acknowledged!

To wrap up the morning's talks, Deborah Lawlor discussed Bristol's epidemiological research in the BHI.

For the plenary, we welcomed Professor Andrew Taylor, Director of Innovation at Great Ormond Street Hospital and Head of Cardiovascular Imaging at the UCL Institute of Cardiovascular Science, to talk about innovating in cardiovascular research. Using examples such as fast imaging

protocols and the potential for delivering precision medicine via AI, he looked at why putting innovations into clinical practice at pace remains challenging, and how ongoing interaction between researchers and clinical teams is vital.

BHI PhD students and early career researchers were invited to present their work in five minutes in three themed sessions covering epidemiology, basic science and clinical research. Attendees voted for the best presentation in each session – well done to:

- Lucy Goudswaard: "Combining Mendelian randomisation and randomised control trial study designs to determine effects of adiposity on the plasma proteome"
- Stanley Buffonge: "The battle to protect the coronary microvascular endothelial glycocalyx in diabetes"
- Monica Gamez: "Endothelial glycocalyx heparan sulfate contributes to the integrity of the blood-retina-barrier and can be therapeutically targeted in diabetes mellitus"

Thank you

Thanks to everyone who took part in the meeting and especially to the organising committee, without whom the day wouldn't have been possible: Alex Carpenter, Alba Fernandez-Sanles, Laura Pannell, Eva Sammut and Andrew Shearn, along with Giovanni Biglino and Stuart Mundell.

On behalf of the committee, Laura says: "It was a fantastic day showcasing research the BHI can be proud of, and will enable the development of collaborative relationships for many years to come."

Bristol Heart Institute Steering Group

Director

Gianni Angelini: BHF Professor of Cardiac Surgery and Cardiovascular theme lead at the NIHR Bristol Biomedical Research Centre

Deputy Director

Alastair Poole: Professor of Pharmacology and Cell Biology

Members

Dr Giovanni Biglino: Biostatistics

Dr Chiara Bucciarelli-Ducci: Imaging

Joseph Butler: Research Development Associate, Faculty of Health Sciences

Professor Massimo Caputo: Congenital heart surgery

Dr Becky Foster: Renal, diabetic and hypertensive disease

Professor Sarah George: Cardiovascular signalling

Dr Emma Hart: Cardionomics

Dr Andrew James: Cardiac biology

Professor Jason Johnson: Pathology of cardiovascular diseases

Professor Paolo Madeddu: Cardiovascular regenerative medicine

Professor Stuart Mundell: Vascular biology and atherothrombosis

Professor Ruth Newbury-Ecob: Clinical genetics

Dr Angus Nightingale: Consultant cardiologist

Dr Guido Pieleles: Sports and exercise cardiology

Professor Simon Satchell: Renal, diabetic and hypertensive disease

Professor Saadeh Suleiman: Cardiac biology

Professor Nic Timpson: Population health and epidemiology

Next edition Spring 2022

Thank you to everyone who has contributed to this edition.

If you have BHI news, events, videos or publications to share, email bcv-info@bristol.ac.uk