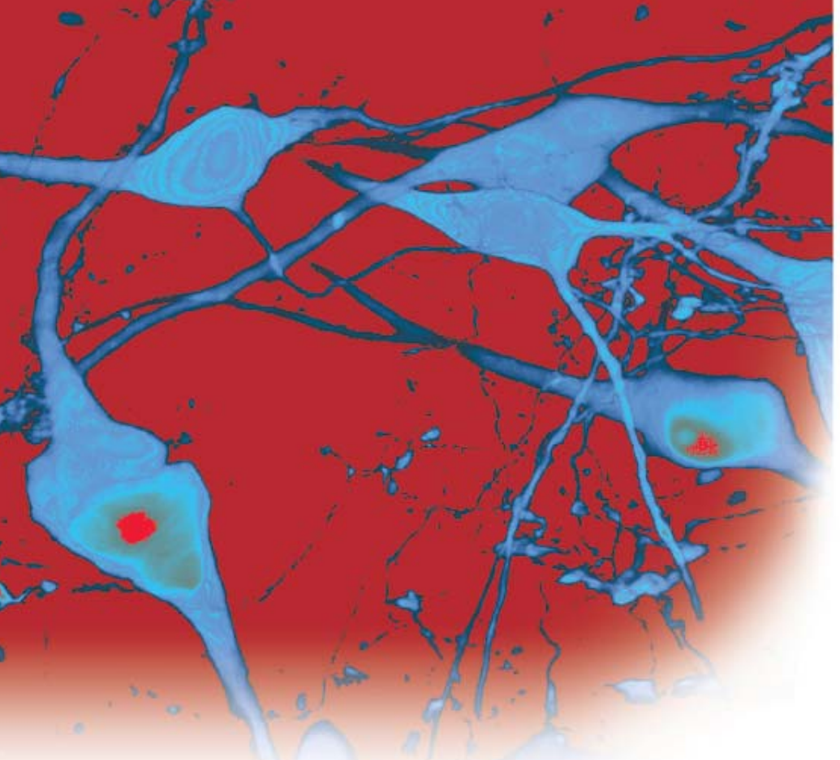


Living brain cells

Affairs of the Heart

One in three men and one in four women will die of a cardiovascular disease. It is the leading cause of illness and death in today's over-fed and smoking populations, costing health services around the world billions every year. Major grant awards will help Bristol researchers to address these problems.

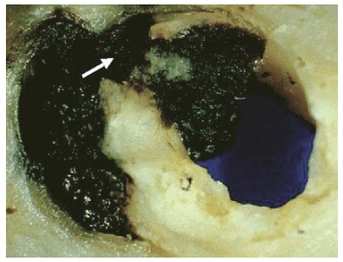
In the 19th century the average age in Britain was about 40 because infant mortality was so high. Today, however, a baby boy can expect to live until 76 and a girl until 80. Thanks largely to huge advances in medical science over the last century, this trend in people living longer and longer will undoubtedly continue as body parts become replaceable and our understanding of the big killers, such as heart disease, improves.

But most of the discoveries made today will take billions of pounds of investment and decades of further research before the results reach our shelves in the form of drugs or other treatments. Much of this research will be done in university centres such as the Bristol Heart Institute, which facilitates collaboration between the many cardiovascular research groups across the University, as well as those at the Bristol Royal Infirmary. Many members of the Institute already have active national and international collaborations, but three groups have recently been awarded major grants totalling almost £10 million for crucial research into problems of the heart and cardiovascular system.

€9 million to facilitate European science

When the European Union put out a call last year for Networks of Excellence in all the biomedical areas they attracted some 400 proposals. Only a very small number were funded, one of which, 'Genomics Applied to the Vascular System', unites 28 research groups around Europe, involves over 100 scientists, and will be co-directed by Professor Andrew Newby at Bristol.

As the arteries gradually become blocked over time there are two consequences. One is that they get smaller and smaller, which leads to a lack of blood flow that causes pain, particularly during exertion – the so-called 'stable' condition. Then there is the heart attack or stroke itself – the 'unstable' condition. The process



A fatal atherosclerotic plaque rupture (arrow) and a blood clot (black) obstructing flow in a human coronary artery

Newby's team is interested in is what causes the transition from one condition to the other? The project's focus will be on the cell biology of what is happening in the blood vessel wall. That's where the 'Genomics' in the title comes in. Finding new genes, new inflammatory genes, for example, that act as targets to receive the delivery of drugs, will be a key aspect of this research.

The total budget for all the science to be done across the 28 groups is about £50 million. The EU grant of £9 million specifically funds the networking element of the programme, facilitating collaborative science across Europe.

$4.4 million for hypertension

Hypertension, or high blood pressure, is a condition in which the heart pumps blood around the body at too high a pressure. It frequently causes no noticeable symptoms in itself, but over years it may damage various organs in the body, such as heart and blood vessels, making it more likely that the individual will have a stroke or heart attack.

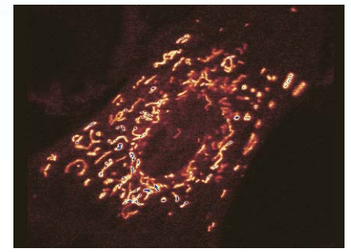
In the majority of cases the cause of hypertension is unknown, but Professor Julian Paton and Dr Sergey Kasparov, in the Department of Physiology, believe that hypertension in many patients is a disorder of the brain, similar to Alzheimer's disease. In hypertensive people there appears to be an excessive amount of activity in the nerves that connect the brain to the heart and blood vessels, causing ➜ blood pressure to rise. Paton and Kasparov are already developing a 'smart' virus that will target cells controlling blood pressure in the brain to regulate their excitability. In turn, this will reduce the excessive activity of nerves supplying the heart and vessels.

This work caught the attention of Professor Mohan Raizada's group at the University of Florida, Gainesville, USA, which has distinct, but complementary approaches to the problem. Together the two teams have been awarded a grant from the USA's National Institutes of Health (NIH) totalling $4.4 million. Their proposal was given one of the highest ratings on record, and attracted one of the few grants awarded by NIH to groups outside the USA.

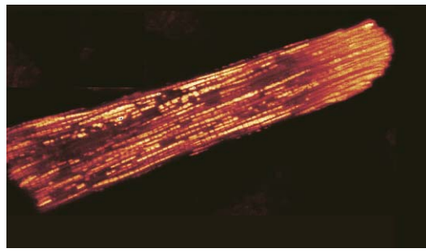
During the course of this project the team will seek new genes to target with smart viruses. These viruses will be designed to invade only the cells within the brain that are specific to the cardiovascular system. Each virus will carry a piece of engineered DNA intended to alter the cell's function, in order to control hypertension.

£670 thousand for Jekyll and Hyde in the heart

Mitochondria are the 'powerhouses' within heart cells, and burn fuels such as glucose and fats to provide the energy required to keep the heart beating and pumping blood around the body. Each heart beat is triggered by a fleeting increase in calcium concentration in the heart cell, and as the heart beats harder and faster the frequency and magnitude of these calcium 'transients' increases. Mitochondria possess a mechanism for detecting these changes in calcium concentration and responds to them by increasing the rate at which they burn fuel. This is why you need to exercise hard in order to burn off fat.



Mitochondria in heart cell of newly born rat



Mitochondria in heart cell of adult rat

However, if the heart muscle is deprived of its blood supply and hence oxygen, such as during a heart attack, the mitochondria can no longer provide the energy necessary to keep the heart beating. If the period of ischaemia is too long, restoring blood flow can cause major damage to the heart as the mitochondria that previously empowered the heart beat take on a new and sinister role that leads to the destruction of the heart muscle cells.

Professor Andrew Halestrap and Dr Elinor Griffiths from the Biochemistry Department, along with Dr Saadeh Suleiman in Clinical Sciences, have been awarded £670,000 from the British Heart Foundation to try to understand the molecular mechanisms involved in this Jekyll to Hyde conversion, and to develop drugs that prevent it. It is hoped that a better understanding of how the healthy heart matches energy supply to energy demand may help in the development of drugs that improve heart function in the undamaged part of heart after a heart attack. Already they have found ways of providing protection in experimental animal models and the intention is that these will translate into effective treatment in the clinic.

Over the next five years results from these projects will appear, greatly improving our understanding of these killer diseases and adding to the pool of knowledge that ultimately benefits us all. ■